Medical Education Systems, Inc.

Course 708

Understanding Cancer

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Understanding Cancer

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Learning Objectives

- Explain and discuss the meaning of the term “cancer”
- Describe the basics of Oncology
- Identify and describe the role of clinical trials in cancer treatment
- List and discuss the most common types of cancer
- Describe the basics of radiation therapy
- Explain what is meant by “chemotherapy” and discuss its key elements

Introduction

The topic "Cancer" is profound and multifaceted. In reality, despite considerable advances in research and technology, it remains somewhat of an unsolved mystery to medical science. Even today, the media is full of confirmation of the "mystery" status of cancer. For example, the following article was published in the New York Times in August of 2006:

Scientists Begin to Grasp the Stealthy Spread of Cancer

The moment when a cancer begins to spread throughout the body — metastasis — has always been the most dreaded turning point of the disease.

Without metastasis, cancer would barely be a blip on the collective consciousness. Fewer than 10 percent of cancer deaths are caused by the primary tumor; the rest stem from metastasis to vital sites like the lungs, the liver, the bones and the brain.

Though chemotherapy and other treatments have lengthened the lives of people with metastasized cancer, no drugs have been specifically formulated to halt the process. That is because metastasis has remained something of a mystery until the last five years or so.

"In the last 30 years, we've learned all about identifying genes whose mutations initiate tumors," said Dr. Joan Massagué, chairman of the Cancer Biology and Genetics Program at Memorial Sloan-Kettering Cancer Center in New York. But these advances, he added, did not explain the metastatic process.

Now, knowledge of metastasis is beginning to accumulate to the point that new therapies are entering the pipeline. "In terms of milestones or breakthroughs, most of them are about to be made," said Dr. Massagué.

Dr. Patricia S. Steeg, chief of the women's cancers section of the Laboratory of Molecular Pharmacology at the National Cancer Institute, said she was optimistic for the first time. "The trickle is close, the first agents are in early clinical testing or will be soon," she said. "I'm very enthusiastic, much more than I was five years ago."

The complexity of metastasis may well have discouraged research. To metastasize, cancer cells have to acquire several dozen genetic alterations — in contrast with the handful typically necessary to initiate a primary tumor, Dr. Massagué said. Further complicating matters, each case of metastasis — breast cancer that spreads to a lung, for instance, or prostate cancer that spreads to bone — is genetically and molecularly different from the rest.

Studying metastasis is expensive and time-consuming, and it requires animal studies to track cancer cells that spread.

Dr. Danny Welch, professor of pathology at the University of Alabama at Birmingham, said scientists had avoided this area of inquiry. "There are under 100 people in the world whose labs focus on understanding more about how metastasis works," he said.

Scientists have long had a rudimentary understanding of the process. Some have estimated that a million cancer cells a day break away from a tumor roughly two-fifths of an inch in diameter and that maybe one in hundreds of millions will thrive. If it weren't so seldom, cancer would be far more deadly. More than 80 percent of cancers arise in the inside lining of organs. To metastasize, a cancer cell must break cellular bonds to dislodge itself, break down the mortar of the connective tissue, change shape and sprout "legs" that can pull it through the densely packed tissue.

After accomplishing this Houdini-like escape, the metastatic cell passes through a capillary into the blood stream, where it is tossed and tumbled and can be ripped apart by the sheer force of circulation, or attacked by white blood cells. If the malignant cell survives, it clings to a tiny capillary at another site, until it can eventually make its way out of that capillary into the tissue of a new organ.

In foreign tissue, the cancer cell, now called a micrometastasis, faces a hostile environment. The liver, for instance, is foreign territory to a breast cell. Some die immediately, others divide a few times, then die. Others stay dormant. The surviving cancer cells regenerate and colonize, becoming a macrometastasis that can be seen on diagnostic tests. As the metastasis grows, it becomes lethal by crowding out normal cells and compromising the function of the organ.

In recent years, scientists have begun to investigate each of these steps to identify the genes and their molecular products that drive the changes. Several emerging fields of study have generated excitement among cancer researchers. One focuses on the notion that the environment of the invaded organ, the microenvironment, plays a critical role in the metastatic process.

This is not an entirely novel idea. In 1889, the British pathologist Stephen Paget proposed the "seed and soil hypothesis," which suggested that the cancer cell depended on the secondary organ to thrive.

Today, it is well understood that an organ has to become somewhat receptive to the tumor. The more welcoming it is and the fewer hurdles it puts up, the easier it is for a cancer to survive. This theory partly explains why certain primary cancers prefer to spread to certain other organs. For example, breast cancers metastasize to the brain, liver, bones and lungs; prostate cancers prefer the bones, and colon carcinomas often metastasize to the liver.

"We've been focused on the seed for a long time, and we're now starting to understand more about the soil and the interaction between the seed and the soil," said Dr. Lynn M. Matrisian, chairman of cancer biology studies at Vanderbilt University. "In my mind, the real opportunity comes from understanding what makes a certain organ receptive to a metastatic cell growing there versus not receptive," Dr. Matrisian said.

Researchers are looking at a number of events that occur in the microenvironment that give a cancer cell a leg up as soon as it arrives. These changes involve both normal cells that reside in that tissue and the body's roaming immune cells. "The tumor cells co-opt these cells to act in a way that's conducive for the growth of the metastasis," Dr. Massagué said.

There is evidence, for example, that a type of white blood cell, the macrophage, may help initiate colonization. It was once thought that high numbers of macrophages found in metastatic cancer colonies were there to do battle with the cancer. Now it is believed that they somehow promote factors that help tumors progress. Other normal cells are believed to make enzymes that loosen the cellular structure of the new host organ, making room for tumor cells to proliferate.

Another example comes from the understanding of bone metastasis. Breast cancer cells are known to activate normal cells called osteoclasts that break down bone. Bone is a dynamic tissue constantly

being broken down and rebuilt. But when bone is degraded, it releases growth factors that incidentally fuel cancer.

Many people with bone metastasis are now being treated with a class of osteoporosis drugs known as bisphosphonates that inhibit osteoclasts. The idea is to prevent the breakdown of bone, and to interrupt the vicious cycle.

Taking the microenvironment theory a step further, some researchers are looking into differences in genetic makeup that can make one person more — or less — tumor-friendly than another. This could lead to a simple blood test to predict who is at risk for metastasis. The goal would be more customized treatment, and those at high risk would be treated more aggressively. Those unlikely to progress would avoid unnecessary and toxic treatments.

Dr. Kent Hunter, an investigator at the Laboratory of Population Genetics at the National Cancer Institute, recently performed a breakthrough study in mice, which provided evidence that the DNA of an organism plays an important role in determining the risk of cancer spreading. Dr. Hunter bred a strain of mice susceptible to metastasis with about 30 other strains of mice, and found that the offspring had varying rates of metastasis.

“Since these animals are all getting the same oncogene by breeding, the most likely explanation is that the changes are due to the differences in the genotype or genetic background of the mouse,” Dr. Hunter said.

In an epidemiological study of 300 women with breast cancer from Orange County, Calif., Dr. Hunter identified two genes that were associated with an increased risk of metastasis, though a large number of genes are probably involved in a person’s risk.

Another camp of researchers is looking at cancer cells for genes that can set off a whole set of steps, the so-called master regulators. A major question is how cancer cells seem clever enough to succeed in the many steps necessary to metastasize. Dr. Robert Weinberg, a professor of biology at the Massachusetts Institute of Technology, is a leading proponent of a contested theory suggesting that a tumor cell turns on an embryonic program that allows a cancer cell to relocate. “Over the last five years, it has become apparent that cancer cells don’t cobble together all these different talents, but they resurrect a previously latent behavioral program,” Dr. Weinberg said.

He argues that a program, called the epithelial-mesenchymal transition, or E.M.T, is turned on in embryonic cells, allowing them to move to different parts of the body where they set up camp and build different types of tissue. According to Dr. Weinberg, these programs are turned off after embryonic development, but they are sometimes briefly turned on in wound-healing to build new tissue.

“Cancer cells opportunistically resort to turning on these programs, and in so doing, acquire all the traits that permit them to disseminate through the body,” Dr. Weinberg said. “What remains unclear is whether or not all malignant carcinoma cells must undergo an E.M.T. in order to invade and metastasize.”

Dr. Welch of Alabama added, “The problem is experimentally proving there is a turning on of E.M.T. and then a turning off of E.M.T. when the cell lands at the distant site.”

Others are looking at cancer stem cells. Adult stem cells have the ability to renew themselves and generate new cells, but they can also become cancerous. Some experts believe that cancer stem cells

are at the core of every metastasis. This would help explain why millions of cells can reach distant organs, but only a select few — presumably those with stem cell capacities — can initiate a tumor and colonize.

To date, cancer stem cells have been isolated from a small number of tumor types, and more research is needed to elucidate whether stem cells initiate metastases and where and how they acquire their renewal capacities. Most experts are looking at smaller pieces of the puzzle, many of them involving colonization, the final stage of metastasis. Upon diagnosis of cancer, experts suspect that many people already have micrometastases throughout their body. “The horse is out of the barn,” Dr. Welch said.

Because colonization is the least efficient step in the spread of cancer, it seems like the Achilles’ heel. A vast majority of cells that land in a distant tissue never succeed in growing and forming a macroscopic metastasis, Dr. Weinberg emphasized.

A number of laboratories have identified more than a dozen metastatic suppressor genes, which prevent micrometastases from colonizing but do not affect primary tumors. In metastatic cells, these genes — including NM23, Kiss1, MKK4, and RhoGDI2 — are either defective or inactive.

In several studies of mice, researchers have repaired defective metastatic suppressor genes and found that the tumor cells spread but did not colonize. In epidemiological studies, some of these genes that have been identified have been shown to be predictive of patient survival and metastasis, Dr. Welch said. Labs are now beginning to test agents that can activate the gene or repair it.

Other researchers are focusing on trying to halt the development of blood vessels that feed the micrometastasis in the process of angiogenesis. One of the first things a micrometastatic cell must do to thrive is call in new blood vessels, said Dr. Matrisian of Vanderbilt.

Drugs that inhibit angiogenesis have not proved that successful when used alone, but they appear to have lengthened some lives when combined with chemotherapy, said Dr. Lee M. Ellis, professor of surgery and cancer biology at the M. D. Anderson Cancer Center in Houston.Underlying these advances has been the shift in the understanding of metastasis — as many different processes rather than one simple mechanism, and different in each type of cancer. Each metastasis needs to be addressed separately.

“There are commonalities, from tissue to tissue, but what we’re finding, unfortunately, is that we need to develop therapies for each specific site,” said Dr. Steeg, of the cancer institute’s Center for Cancer Research. “We used to think we only needed one pipeline to metastasis,” she said. “Pharmaceutical companies now realize that they have to look at subsets of cancer, rather than at all of breast cancer.”

“One advance can save many lives, but it’s only one bite,” Dr. Massagué, the Sloan-Kettering researcher, added, “because the next tumor type forming metastasis in the next organ needs to be addressed.”

Cancer: Background and Basics

Cancer is the second among fatal diseases, next to cardiovascular diseases, in the industrialized countries and third fatal disease in India. It is estimated that in the next quarter of a century the

number of new cancer cases globally is going to double, half of them in the developing countries. World Health Organization (WHO) has launched a campaign against cancer, with a three-fold strategy: prevent all the preventable cancers, cure all that can be cured, and reduce pain and discomfort where cure is not possible. In this context it may be worthwhile to examine the basic cellular changes leading to cancer development and to discuss some of the areas where strategies for prevention can be implemented.

Cancer is a broad term used for identifying a large number of diseases. Perhaps the only common feature of these diseases is the ability of uncontrolled cell proliferation that cannot be checked by the normal cell kinetics regulators. A normal cell suddenly turns into a rogue cell and start dividing continuously without check, leading to the development of solid lumps (tumors) or an abnormal rise in the number of dispersed cells like the blood corpuscles.

Cancer can occur in any part of the body and in any organ or tissue. Even though most of the cancers are generally associated with old age, no age group is immune to his disease. Cancer originates in our own cells, but several factors, both intrinsic and external to the body, which influence our daily life, can add to the life time cancer risk. While cancer, as such, is not infectious, some infections can act as a stimulus to induce and promote cancer development. In addition, environmental pollutants like many chemicals, industrial effluents, some therapeutic drugs, and mutagenic agents, including ionizing radiation, can increase the incidence of cancer. About 50% of all cancers are attributed to life style, e.g.. diet, tobacco habits and alcohol consumption, and exposure to industrial toxins.

The Process of Carcinogenesis

Cancer development is understood to be a multistep process. The concept of multi-stage carcinogenesis was first proposed in 1948 and supported by later studies. Present day oncology recognizes three main phases: initiation, promotion and progression. Initiation: Neoplasia initiation is essentially irreversible changes in appropriate target somatic cells. In the simplest terms, initiation involves one or more stable cellular changes arising spontaneously or induced by exposure to a carcinogen. This is considered to be the first step in carcinogenesis, where the cellular genome undergoes mutations, creating the potential for neoplastic development, which predisposes the affected cell and its progeny to subsequent neoplastic transformation. The human DNA sequences responsible for transformation are called oncogenes. Many of the active oncogenes have been isolated by molecular cloning, e.g.. human bladder carcinoma, Burkitt's lymphoma, lung carcinoma, carcinoma of the breast and several others.

Although the activation of more than one oncogene appears to be necessary for neoplastic transformation, the data imply that initiation may be induced with one hit kinetics. For example, in the human bladder carcinoma, a single point mutation converting the Ha-ras proto-oncogene into a potent oncogene was the first identified mutation in a human oncogene. Such tumor gene mutations can have profound effects on cellular behavior and response, and can lead to dysregulation of genes involved in biochemical signaling pathways associated with control of cell proliferation and/or disruption of the natural processes of cellular communication, development and differentiation.

Normal cells may bear the seeds of their own destruction in the form of cancer genes. The activities of these genes may represent the final common pathway by which many carcinogens act. Cancer genes may not be unwanted guests but essential constituents of the cell's genetic apparatus, betraying the cell only when their structure or control is distributed by carcinogens.

However, the full expression of such neoplasia initiating mutations invariably requires interaction with other later arising gene mutations and/or changes to the cellular environment, but the initiating mutation creates the stable potential for pre-neoplastic cellular development in cells with proliferative capacity .

The transformed cell undergoes continuous division with fidelity to the transformed karyotype and, possibly, with further mutations, before a malignant lesion is manifested.

Mechanisms of Oncogene Activation

Each oncogene is closely associated with a normal DNA sequence present in the cellular genome, the proto-oncogene. At least five different mechanisms are considered for the conversion of proto-oncogenes to active oncogenes: (1) Overexpression of proto-oncogene following acquisition of a novel transcriptional promoter. The oncogene then acquires activity because their transcripts are produced at much higher levels than those of the related normal proto-oncogene. (2) Over-expression due to amplification of the proto-oncogene or oncogene.

The increased gene copies cause corresponding increases in transcript and gene product. (3) Influences on the levels of transcription and, in turn, the amount of gene product. (4)Juxtaposition of the oncogene and immunoglobulin domains, following chromosomal translocations, that appears to result in deregulation of the gene. (5) Alteration in the structure of the oncogene protein. This is the most well documented mechanism in the case of the oncogene proteins encoded by the ras genes. The fourth and fifth mechanisms seem to be inter-related.

A translocation can disturb the regulation of an oncogene by:
a) providing a new promoter region or some other control element that would activate the oncogene; or
b) altering the coding sequence of a gene, changing its protein product from a benign to a malignant form.

A close association between specific chromosomal translocations and certain human neoplasms has been demonstrated. Promotion: The transformed (initiated) cell can remain harmless, unless and until it is stimulated to undergo further proliferation, upsetting the cellular balance. The subsequent changes of an initiated cell leading to neoplastic transformation may involve more than one step and requires repeated and prolonged exposures to promoting stimuli.

Thus, in contrast to initiation which is induced at a rate of 0.1-1.0 per cell/Gy of radiation, the subsequent transforming event in the initiated cells occurs at a rate of only 10-6 to 10-7 per cell generation. Neoplastic development is influenced by the intra- and extracellular environment. Expression of the initial mutation will depend not only on interaction with other oncogenic mutations but also on factors that may temporarily change the patterns of specific gene expression, e.g.. cytokines, lipid metabolites, and certain phorbol esters. This may result in an enhancement of cellular growth potential and/or an uncoupling of the intercellular communication processes that restrict cellular autonomy and thereby coordinate tissue maintenance and development.

Progression: is the process through which successive changes in the neoplasm give rise to increasingly malignant sub-populations. Molecular mechanisms of tumor progression are not fully understood, but mutations and chromosomal aberrations are thought to be involved. The process may be accelerated by repeated exposures to carcinogenic stimuli or by selection pressures favoring the autonomous clonal derivatives. The initiated cells proliferate causing a fast increase in the tumor size. As the tumor grows in size, the cells may undergo further mutations, leading to increasing heterogeneity of the cell population.

In the first phase of progression, sometimes referred to as neoplastic conversion, the pre-neoplastic cells are transformed to a state in which they are more committed to malignant development. This may involve further gene mutations accumulating within the expanding pre-neoplastic cell clone. The dynamic cellular

heterogeneity, a feature of malignant development, may, in many instances, be a consequence of the early acquisition of gene-specific mutations that destabilize the genome. Examples are mutations of the p53 gene or DNA mismatch repair gene. Many tumor types develop transforming sequences in their DNA during their progression from the normal to the cancerous state.

An elevated mutation rate established relatively early in tumor development may, therefore, provide for the
high-frequency generation of variant cells within a premalignant cell population. Such variant cells, having the capacity to evade the constraints that act to restrict proliferation of aberrant cells, will tend to be selected
during tumorigenesis.

Tumor metastasis: As the tumor progression advances, the cells lose their adherence property, detach from the tumor mass and invade the neighboring tissues. The detached cells also enter the circulating blood and lymph and are transported to other organs/tissues away from the site of the primary growth and develop into secondary tumors at the new sites. These form the distant metastases, resulting in widely spread cancers.

Cancer metastasis consists of a number of steps; the main steps are common for all tumors. The progress of the neoplastic disease depends on metastatic changes that facilitate: (a) invasion of local normal tissues, (b) entry and transit of neoplastic cells in the blood and lymphatic systems, and (c) the subsequent establishment of secondary tumor growth at distant sites. Many of the steps in tumor metastasis involve cell -cell and cell-matrix interactions, involving specific cell surface molecules. Malignant cells are thought to have reduced ability to adhere to each other, so that they detach from the primary tumor and invade the surrounding tissues.

The behavior of tumor is influenced by the cell adhesion molecules, one of the most important of which are cadherins. Animal studies have shown that a down-regulation of E-cadherin expression, resulting in lower levels, correlated with metastatic behavior in vivo, suggesting that cadherins function as invasion suppressor gene products.

It is the metastatic process and tumor spreading that are mainly responsible for the lethal effects of many common human tumors. In many cases gene mutations are believed to be the driving force for tumor metastasis, with the development of tumor vasculature playing an important role in the disease progression .

Tumor angiogenesis: Tumor growth depends on the supply of growth factors and efficient removal of toxic molecules, which comes through an adequate blood supply. In solid tumors, efficient oxygen diffusion from capillaries occurs to a radius of 150-200(m, beyond which the cells become anoxic and die. Therefore, increase in tumor mass to more than 1-2 mm will depend on adequate blood supply through development of blood capillaries (angiogenesis). P. Schubik was the first to coin the term ‘tumor angiogenesis’. But it was Judah Folkman who hypothesized the importance of tumor angiongenesis in the development and metastasis of solid tumors. His theories are widely accepted today. Folkman and colleagues established that tumor growth beyond about 2mm size could proceed only if a vascular supply is established. A number of tissue factors have been identified, which stimulate endothelial cell proliferation. These include the tumor angiogenesis factor, the vascular endothelial growth factor, angioproteins - ang-1 and ang - 2, transforming growth factors (TGFs), interleukin - 1, and platelet-derived endothelial cell growth factor.

Although the blood vessels that supply the developing tumors are derived from the host vasculature, their architecture differs considerably from that in the normal tissue. Tumor vessels are often dilated, saccular and tortuous and may contain tumor cells within the endothelial lining of the vessel (Jain 1989). Therefore, the blood flow in the tumor may be sluggish compared to that in the adjacent normal tissues and the tumor microvasculature may show hyperpermeability to plasma proteins.

Cancer Genes

Somatic gene mutations are widely accepted as the basic event in the conversion of a normal cell into cancer cell. Many different genes are demonstrated to be involved in carcinogenesis. The gene mutation theory of oncogenesis maintains that carcinogens interact with DNA resulting in irreversible changes in the gene (point mutations), which predispose the cells to malignant transformation. The somatic genetic changes in cells that contribute to multistage tumor development potentially involve sequential mutation of different classes of genes, i.e. Proto-oncogenes, tumor suppressor genes, genes involved in cell cycle regulation, and genes that play roles in maintaining normal genomic stability. Biochemical interactions between tumor gene mutations may destabilize the genome, compromise control of cell signaling, proliferation, and differentiation, and interfere with the normal interaction of cells in tissues.

Two classes of regulatory genes are directly involved in carcinogenesis, the oncogenes and the antioncogenes.

Oncogenes: They are positive regulators of carcinogenesis. In non-transformed cells, they are inactive (proto-oncogenes). Gene mutations can activate proto-oncogenes, resulting in a gain of function. Several proto-oncgenes were first identified through viral transformation of cellular genome, e.g.. c-erbB, cmos, c-myc, c-myb, C-H-ras. A large number of mutations in specific oncogenes - e.g.. ras, myc, etc. - have been found to be closely associated with different types of cancers.

Anti-oncogenes or tumor suppressor genes: They are negative growth regulators. Many human tumors, e.g. retinoblastoma, Wilm's tumor, colon carcinoma, result from recessive mutation, which cause cancer when present on both homologues. These genes function as anti-oncogenes or tumor suppressor genes. In normal cells they regulate cell proliferation by checking cell cycle progression. Mutation in these genes results in a loss of gene function (the protein product will not be produced), which promotes carcinogenesis. Such gene mutations have been detected in several solid tumors, e.g.. cancers of breast, lung, rectum, etc., but only few such mutations have been seen in leukemias.

The two most widely studied tumor suppressor genes are the Rb gene and p53 gene. The proteins encoded by these genes inhibit cell cycle progression by blocking transcription of gene products necessary for transition from G1 to S phase. Mutation in the Rb gene could lead to loss of normal inhibitory control of cell cycle progression and, thereby, increase cell proliferation. This effect, coupled with genetic changes that cause loss of apoptotic signals, would enhance malignant transformation.

p53 has a major role in maintaining the genomic stability and cellular equilibrium. In normal cells, this gene promotes apoptosis, regulates cell cycle through G1 - S checkpoint control and induces cell differentiation. p53 participates in a cell cycle checkpoint signal transduction pathway that causes either a G1 arrest or apoptotic cell death after DNA damage. Mutations in p53, resulting in loss of function, will cause suppression of apoptosis, promote cell division by releasing the G1-S block and prevent differentiation of the cells, leading to neoplasm development. Mutations in the p53 gene are the most common genetic change observed in a
large number of human malignancies; at least 50% of all human cancers have been found to contain p53 abnormality. Mutations in this gene have been observed in a wide range of human cancers like cancers of

the breast, lung, colon, skin, urinary bladder, ovary and lymphoid organs. More than 500 mutations of this gene have been documented in breast cancer.

Theories of Carcinogenesis

Gene mutation theory:
This theory maintains that somatic gene mutations form the basis of neoplastic transformation and their clonal expansion leading to carcinogenesis. It is the most widely accepted and is supported by a large volume of experimental data. However, it does not explain tumor heterogeneity and aneuploidy and also the long latent periods between exposure to carcinogens and the development of tumors.

Aneuploidy theory:
Another theory that is currently gaining momentum is the aneuploidy hypothesis. According to this hypothesis, a carcinogen initiates carcinogenesis by a preneoplastic aneuploidy, which destabilizes mitosis. This initiates an autocatalytic karyotype evolution that generates new chromosomal variants, including rare neoplastic aneuploidy. The aneuploidy hypothesis provides a plausible explanation for the long latent periods from carcinogen treatment to cancer development and the clonality.

Epigenetic theory:
It has been recognized that non-mutational stable changes occur in cellular genome, which can contribute to carcinogenesis (Feinberg 1993 Cross and Bird 1995). Such events are broadly termed epigenetic and are thought to involve DNA methylation, genome imprinting and changes in DNA - nucleoprotein structure. Increased levels of methylated cytosine (one of the pyrimidine bases in DNA) results in the elevation of spontaneous mutation rates in the affected genome.

While each theory has its own merits, it may not be possible to assign an exclusive role to a single process alone in carcinogenesis. In many cases, a combination of the two or all process may work in cooperation. An initiating somatic gene mutation can destabilize the genome and lead to aneuploidy and chromosome heterogeneity, characteristic of solid tumors, while epigenetic events can contribute to the neoplastic cell transformation and also facilitate promotional changes.

Factors Influencing Cancer Development

A number of intrinsic (biological) and external factors are associated with the development of cancers. The intrinsic factors include the age and hormonal status of the individual, familial history and genetic predisposition. The extraneous factors include diet and life style, individuals habits like smoking and alcohol use, exposure to toxic chemicals and radiation, some infections, etc. Several external factors, including asbestos, many chemicals, dyes, food additives, vehicular emissions, act as promoters in carcinogenesis.

Biological factors:
Age and hormonal status: Cancer is considered to be an old age disease. Some types of cancers are almost entirely found in people above 50-55 years, e.g. prostate cancer. Similarly cervix cancer in women are more commonly detected at the peri- or post-menopausal ages. However, no age group is immune to this disease.

Hormonal factors play an important role in the development of gender-specific cancers, e.g. estrogen in cancers of ovary and uterus in female.

Family history: Some cancers are indicated to have a link with familial occurrence. For example, women whose close relatives like grandmother, mother, maternal aunt or sister has suffered from breast cancer, are found to run about 3 times higher risk of developing breast cancer than those who do not have such a family history. Similarly, cancers of the uterine cervix (females) and of prostate (males) are also thought to have a familial connection.

Genetic predisposition: Certain genetic conditions are known to predispose the individual to cancer. For example, individuals with genetic conditions like xeroderma pigmentosum, ataxia telangiectasia, Bloom's syndrome, and Fanconi's anemia are found to be highly susceptible to different types of cancer.

External factors: Diet, alcohol, and tobacco use: More than 50% of all cancers are related to the diet and individual habits like alcoholism, tobacco chewing and smoking. High fat diet and obesity are associated with breast cancer. A positive correlation has been reported between age-adjusted breast cancer mortality rates and the average per capita fat consumption in a given nation on a daily basis. Similarly, deep-fried and burnt food and preserved (high salt) food are associated with increase in gastric cancer incidence. Regular consumption of food low in fiber content and rich in animal fat increased the risk of cancers of stomach and esophagus. High intake of red meat and low fiber diet has been considered to be the cause of the high incidence of gastric cancer in the USA. The role of cigarette smoking in lung cancer is established. Tobacco smoke contains a chemical, nitrosamine, which can induce neoplastic changes in the lung cells. Non-smoking tobacco habits, like chewing, are found to greatly increase the cancers of the upper alimentary tract and buccal mucosa. India has the highest incidence of oral cancers in the world, which is correlated with the tobacco chewing habit.

Alcoholism is found to increase the risk of liver and bladder cancers. Smoking combined with alcohol consumption poses a higher risk of cancers of the breast, esophagus, liver, stomach and urinary bladder. Alcoholism along with hepatitis B virus infection is a more serious risk factor in liver cancer.

Radiation and cancer:
Ionizing radiation is an established carcinogen, having both initiating and promoting effects. The positive correlation between ionizing radiation and carcinogenesis has been established from the studies on the early radiologists, radium dial painters and atom bomb victims of Japan. A positive association has been seen in the increase in childhood cancers and obstetric X-ray exposures of the mother. Tumors induced by radiation have relatively long latencies, which vary in different species as a more or less constant function. Within a given species the latency varies also with age at the time of irradiation and with the type of neoplasm induced. The age differences in latencies appear to be related to similar age differences in the rates of corresponding spontaneous leukemias. The risk of adult type of malignancies tend to increase progressively with time after irradiation, in parallel with the age-dependent increase in the underlying base-line incidence.

Viruses and cancer:
Oncoviruses play an important role in specific human cancers, e.g. human papilloma virus in cervix cancer, and certain skin cancer; Epstein-Barr virus in Burkitt lymphoma and nasopharyngeal carcinoma ; hepatitis B virus in hepatocellular carcinoma; human T-cell leukemia virus in leukemia. The viruses are of two types: DNA viruses which incorporate into the cellular genome and the retroviruses (RNA viruses) which cause transformation of cellular genome, leading to malignant changes in the infected cell.

Role of free radicals:
Reactive oxygen species (ROS) and other free radicals are produced in the body, both during the normal metabolic process as well as by interaction with external toxic agents, for example, radiation and toxic chemicals. They include superoxide anions, hydroxyl radicals, peroxy radicals and hydroperoxides. These interact with DNA and produce gene mutations and chromosomal aberrations, leading to cell transformation. Free radicals are considered to have a major role in the induction of cancers by chemicals and radiation. Several factors of our modern life style, e.g. excess alcohol consumption, tobacco chewing and smoking habits, exposure to toxic chemicals and radiations, all add to the free radical production in the body and increase the risk of cancer.

Cellular Defense Mechanisms in Relation to Cancer Prevention and Carcinogenesis

Normal cells are naturally equipped with efficient defense mechanisms that work at different levels.

Antioxidants:
The cells synthesize their own defense molecules, which include the non-protein thiol gluthathione, and antioxidant enzymes like superoxide dismutase, catalase, glutathione peroxidase, reductase and S-transferases. These scavenge the ROS before they can reach the target molecules in the cell and thus protect against their attack on the vital molecules like DNA. Thus they serve as the biological watchdogs in safeguarding against free radical induced initiating changes, mutations and chromosomal aberrations. Many dietary ingredients like green vegetables, fruits, tea, spices and some diet supplements contain antioxidants. These include the vitamins A, C, and E, beta-carotene, alpha-tocopherol, ascorbic acid, flavonoids, lycopenes, curcumins and enzymes like caspasine. They act as chemo-preventers by scavenging free radicals and enhancing cellular defense through their adaptogenic properties.

DNA repair:
Damage to cellular DNA is the crucial early event in the neoplastic transformation of a cell. The DNA lesions may include altered bases, co-valent binding of bulky adducts, inter- and intra-strand crosslinks and generation of strand breaks. A range of alkylated products is formed in DNA by exposure to nitroso-compounds and other alkylating agents. Ionizing radiation and many genotoxic chemicals generate free radicals, which interact with DNA and produce different lesions ranging from base damage, deletions and complex and multiple lesions. Most normal cells possess a high capacity for repair of DNA damage. However, efficient repair depends on the type of damage, its severity and the time available for repair. The base damage and single strand breaks are repaired fast and without error, restoring the molecular structure. But double strand breaks and multiple breaks and local cluster lesions are not properly repaired and often contain errors (error-prone repair or misrepair), leading to cell death or cell survival with abnormal gene functions and chromosomal abnormalities which are associated with malignant cell transformation. DNA repair involves a number of genes, the products of which operate in a co-ordinated manner to form repair pathways that control restitution of DNA structure.

Apoptosis or programmed cell death is an important mechanism of cellular defense in reducing the risks of error-prone repair. Cells with DNA damage undergo apoptosis, thus preventing these cells from surviving and entering the proliferating cell pool and, thereby, preventing the possibility of tumor development. Apoptosis is a genetically controlled process involving p53, bcl2 and other genes. Mutations in p53 can block the tumor-suppressive effect by eliminating apoptosis, and, thus, allowing the damaged cells to survive and undergo proliferation. Some of the gene products that control cell cycle also influence apoptotic tendencies,

e.g. c-myc, pRb, Tp53.

Role of Diet in Cancer Control

Researchers Doll and Peto (1981) were the first to point out an association between dietary constituents and cancer. A vegetarian diet is considered to be beneficial in reducing cancer incidence. Epidemiological studies have suggested that diets rich in vegetables, and fruits reduces the risk of certain cancers. For example, diets rich in fiber, vitamins A,C, and E, beta-carotene, retinols, alpha-tocopherol, polyphenols, and flavonoids, and minerals like selenium and zinc, have cancer chemopreventive effect. Fruits and vegetables are rich sources of chemopreventive chemicals. These include inhibitors of carcinogen formation, blocking agents (block conversion of procarcinogens to carcinogens), stimulators of detoxifying system, trapping agents (trap and eliminate potential carcinogens) and suppressing agents (suppress the different steps of the metabolic pathway leading to cancer)

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A study in China showed a high incidence of esophageal and gastric cancers in a population whose diet is deficient in beta-carotene and vitamins C and E. An interventional program, where the diet was supplemented with beta-carotenes, vitamin E and selenium, produced a 20% reduction in the stomach cancer mortality over a period 5 years. WHO has recommended dietary intervention in the cancer control strategy for the new millennium.

Dietary intervention follows two approaches:

1. Intervention through supplementing with vitamins, antioxidants and other dietary factors.
2. Intervention through dietary modification in which target levels are established for consumption of meat, fat, fiber, fruits and vegetables

Conclusions

Cancer is a broad term to describe a large variety of diseases, the common feature of which is uncontrolled cell division. The process of carcinogenesis consists of three major steps: initiation, where an irreversible change is affected in the cellular genes; promotion, where the initiated cells expand by self-proliferation leading to abnormal growth and further mutations; and progression, where the cells detach from the primary tumor and invade other organs and tissues, forming metastatic growths. Angiogenesis plays an important role in the tumor metastasis.

Different types of cancer genes - oncogenes and antioncogenes (tumor suppressor genes) - are involved in cancer development. Gain of function mutations in the oncogenes, leading to abnormal cell proliferation, and loss of function mutations in the anti-oncogenes leading to suppression of cell differentiation and apoptosis, are the major events leading to cancer development. Chromosomal aneuploidy and epigenetic events are also thought to be important. Several factors like age, sex, genetic predisposition, along with extrinsic factors like diet, environmental pollutants, alcoholism and tobacco habits have a major role in determining the cancer risk. Dietary intervention as a cancer preventive measure is a primary agenda on the WHO program.

Fundamentals of Oncology

What is Cancer?

Cancer is the uncontrolled growth of malignant cells, which if left unchecked, can destroy organs or their functions. Oncology, the study of cancer and its treatment, is very complex, as more than 200 distinct forms of cancer have been identified and hundreds of chemotherapeutic agents are approved for the treatment of cancer. (By MaryAnn Foote, PhD Director, Global Regulatory Writing, Amgen Inc.)

The National Cancer Institute (NCI) has estimated that 1,334,100 people living in the US were diagnosed with some form of cancer in 2003 and that 556,500 deaths were attributed to cancer that year.1 The popular media are replete with reports of cancer prevention through diet, lifestyle modification, or early detection.
Cancer remains a frightening and mysterious disease that appears to strike indiscriminately. As biomedical communicators, we must understand the facts and avoid being swayed by sensationalism or rumors. Thus, it is important for biomedical communicators to understand the complex subject of oncology.

Definition of Cancer
The word "cancer" is derived from the Latin word for "crab." Because many tumors, or clusters of cancer cells, are capable of wildly uncontrolled cell division, malignant tumors often are thought to have the silhouette of a crab, with many appendages radiating from a central body. (Normally, cells form orderly layers or sheets of tissue.) Other names for a tumor are lesion, malignancy, mass, or neoplasm. Cancer cells are able to divide more rapidly than normal cells and can displace normal neighboring cells. Intrinsic changes in cancer cell composition allow them to multiply without the usual restraints placed on cells (i.e., most cells must "obey" territorial limits placed on them by their neighboring cells, but cancer cells do not); cancer cells appear to divide more rapidly than normal cells and fewer daughter cells undergo apoptosis.

When cells divide rapidly but keep within their normal territory and do not invade the surrounding tissues, the cell cluster is referred to as a benign tumor. Usually, benign tumors pose no threat, but if they are contained in an enclosed space, such as the cranial cavity, they can continue to increase in size and put pressure on an organ. For this reason, benign tumors are often removed.

Malignant cancers are capable of spreading through the body by 2 mechanisms: invasion and metastasis. Invasion is the direct migration and penetration by cancer cells into neighboring tissues. Metastasis refers to the ability of cancer cells to penetrate into lymphatic and blood vessels, circulate through the bloodstream, and invade normal tissues elsewhere in the body.

Almost all cells in the body are susceptible to cancer, and more than 200 distinct varieties of cancers have been described. Most varieties of cancer are rare, and deaths due to cancer are mainly attributable to only a few common ones such as lung, breast, colon, skin, and blood cancers. Cancers are classified according to the type of tissue and type of cell in which they originate. For example, if the disease is believed to have originated in the tissues of the breast, the diagnosis may be breast cancer. The cancer may spread to other organs such as the lung, and the diagnosis would be primary breast cancer with lung metastases.

All cancers can be placed into 1 of 6 broad categories: carcinoma, sarcoma, leukemia, lymphoma, melanoma, and glioma. The different types of cancers are defined by the organ of the body in which the cancer started. Carcinomas originate in epithelial issues, such as the liver, lungs, glands (e.g., prostate or thyroid), bladder, kidney, breast, ovary, uterus, testes, colon, skin, and brain. Approximately 80% of all cancer cases are carcinomas. Sarcomas originate in bone, muscle, cartilage, fat, and fibrous tissue. Sarcomas are rare, representing approximately 1% of all cancers. Leukemias originate in the bone

marrow; myeloma is a subset of leukemia and is a cancer of plasma cells. When cancers affect the blood or blood-forming organs, they are called myeloid; when the cancer involves other tissues that do not directly affect the formation of blood cells, it is referred to as nonmyeloid. Lymphomas originate in the lymphatic system, i.e., the lymph nodes.

Melanomas are cancers that originate in skin cells called melanocytes (although melanomas can be found in organs other than skin), and gliomas are cancers of the nervous tissue, i.e., the brain and spinal cord. Most organs of the body are composed of several types of tissue, which means that each organ can be the site of different types of cancers. For example, most cases of uterine cancer are carcinomas and are found in the
endometrium of the uterus. Some uterine cancers, however, are found in the muscle of the uterus, classifying them as sarcomas.

Symptoms of Cancer
Symptoms of cancer can be silent, particularly in the early stages of development. Some symptoms are specific to certain types of cancer, such as difficult urination for prostate cancer or flu-like symptoms and easy bruising for acute leukemias. Sudden weight loss, a thickening or lump, unexplained bleeding, coughing, or a wound that will not heal are some of the many symptoms that may be related to cancer . Often, symptoms are nonspecific; that is, common to many other conditions.

Diagnosis of Cancer
Cancers are diagnosed a variety of ways, again depending on the primary source of the cancer. The biopsy, which involves surgically obtaining a small tissue sample and examining it under a microscope, is often used to help identify the primary cancer. A biopsy can be done on all tissues including the bone marrow. When examined microscopically, cancer tissue has a distinctive appearance, including a large number of dividing cells, variation in the size and shape of cells and nuclei, loss of specialized cell features and normal tissue organization, and poorly defined tumor boundary. Microscopic examination of a biopsy specimen will sometimes detect a condition called hyperplasia.

The cell structure and orderly arrangement of cells within the tissue remain normal, and the process of hyperplasia is potentially reversible. Microscopic examination of a biopsy specimen can detect another type of noncancerous condition called dysplasia, an abnormal type of excessive cell proliferation characterized by loss of normal tissue arrangement and cell structure. Often such cells revert to normal behavior, but occasionally they gradually become malignant. Because of their potential for becoming malignant, areas of dysplasia should be closely monitored and sometimes require treatment. The most severe cases of dysplasia are sometimes referred to as carcinoma in situ (“cancer in place”), which refers to an uncontrolled growth of cells that remains in the original location. Carcinoma in situ may develop into an invasive, metastatic malignancy and, therefore, is usually removed surgically, if possible.

Microscopic examination also provides information regarding the likely behavior of a tumor and its responsiveness to treatment. Cancers with highly abnormal cell appearance and large numbers of dividing cells tend to grow more quickly, spread to other organs more frequently, and be less responsive to therapy than cancers whose cells have a more normal appearance.

Based on these differences in microscopic appearance, oncologists assign a numerical grade to most cancers. In this grading system, a low number grade (grade I or II) refers to cancers with fewer cell abnormalities than those with higher numbers (grade III or IV). Disease progression is determined by the size of the tumor and its invasion into surrounding tissues, and metastases to regional lymph nodes or

other regions of the body. Based on these criteria, the cancer is assigned a stage. A patient's chances for survival are better when cancer is detected at a lower stage number.

Another diagnostic tool is the endoscope, which can be used to examine major organs and the entire digestive system. Endoscopy is routinely used to screen for the presence of colon cancer. Radiographs (i.e., x-rays) ultrasonography, computed axial tomography (CAT; often called computed tomography or CT) scan, positron emission tomography (PET) scan, and magnetic resonance imaging (MRI) are other ways that tumors can be detected. Additionally, blood tests may help to diagnose cancers. Some tumors have tumor markers that include genetic markers, cellular and tissue markers, and circulating markers that can be detected in the blood.

A blood test for prostate cancer measures the amount of prostate-specific antigen (PSA), a tumor marker. Higher-than-normal concentrations of PSA may indicate cancer. Recently, a blood test for ovarian cancer, known as CA-125, has become available. It should be stressed that blood tests by themselves, however, are inconclusive because more than 300 markers have been identified but their relationships to cancer are not fully elucidated.

Presence of a tumor marker is not conclusive proof that a tumor exists.
- Change in bowel or bladder habits
- Sore that will not heal
- Unusual bleeding or discharge
- Thickening or lump in the breast or other part of the body
- Indigestion or difficulty in swallowing
- Obvious change in a wart or a mole
- Persistent cough or hoarseness

The biggest risk for the development of cancer is aging. The longer a person lives, the more likely it is that some form of cancer will develop. Some types of cancer are preventable (e.g., lung cancer from tobacco), while others types of cancer are caused by environmental factors (e.g., lung cancer in heavy smokers who use beta carotene supplements) or by genetic factors (e.g., MYC marker in lung cancer). Because cancer usually requires a number of genetic mutations, the chances of developing cancer increases as a person gets older because more time has been available for mutations to accumulate.

In addition to chemicals and radiation, bacteria and a few viruses can trigger the development of cancer. The bacterium Helicobacter pylori, which can cause stomach ulcers, has been associated with an increased risk for the development of gastric cancer. In the case of cancer viruses, some of the viral genetic information is inserted into the chromosomes of the infected cell, causing the cell to become malignant.

Very strong evidence suggests that the human papilloma viruses (HPV) are associated with most types of cervical cancer (squamous and adenocarcinomas), and results of several large studies suggest that HPV infection precedes the development of cervical cancer by 10 to 15 years. The use of tobacco products has been implicated in nearly 30% of cancer-related deaths, making it the largest single cause of death from cancer. Cigarette smoking is responsible for nearly all cases of lung cancer, and smoking has been implicated in cancer of the mouth, larynx, esophagus, stomach, pancreas, kidney, and bladder. Tobacco is the main environmental risk factor for lung cancer, **and it has been estimated that each cigarette smoked shortens the smoker's life by 14 minutes.**

Skin cancer caused by exposure to sunlight is the most frequently observed type of human cancer. Because skin cancer is often easy to cure, the danger posed by sunlight is perhaps not taken seriously enough. Mortality may be low, but morbidity can be high if the lesions must be excised from a cosmetically sensitive area (i.e., the face). Chronic exposure to radiation in sunlight and fair skin that is susceptible to sunburns appear to be the most important risk factors, with increasing frequency of exposure, age, immune status, male gender, and DNA repair disorders (such as xeroderma pigmentosum) as other risk factors.

Drinking excessive amounts of alcohol is linked to an increased risk for several kinds of cancer, especially those of the mouth, throat, and esophagus. The combination of alcohol and tobacco appears to be especially dangerous: in heavy smokers or heavy drinkers, the risk of cancer of the esophagus is approximately 6 times greater than that for nonsmokers/nondrinkers. For people who both smoke and drink, the risk of cancer is 40 times greater than that for nonsmokers/nondrinkers. Alcohol cannot cause cancer but can convert damaged cells into malignant cells.

Studies suggest that differences in diet may play a role in determining cancer risk. In contrast to the clear-cut identification of tobacco, sunlight, and alcohol, the exact identity of the dietary components that influence cancer risk has been difficult to determine. Limiting fat consumption and calorie intake appears to be one possible strategy to decrease the risk of some cancers because people who consume large amounts of meat (rich in fat) and large numbers of calories have an increased risk for cancer, especially for colon cancer.

Causes of Cancer

Cancer is a multifaceted disease, sometimes the result of the unlucky convergence of genetics and environment. The etiology of cancer is different from the risk of cancer. Avoidance of the causes (etiology) of cancer may greatly reduce a person's risk of cancer. For example, smoking is a cause of cancer; not smoking reduces one's risk of cancer, even if he or she has a genetic defect that is a predisposition to cancer.

Genes and Cancer: Is Cancer Hereditary

All cancers are caused by a defect in a gene that allows the cell to proliferate wildly. The genetic effect occurs through small mutations in the DNA, little "hits" over many years. (Dr. Alfred Knudson developed the "2-hit" theory of cancer; he was the McGovern Award recipient at the 1999 AMWA meeting in Philadelphia.) Not all cancers are hereditary—actually only 5% of cancers are due to genetic inheritance. People born with the defective gene must still be subjected to prolonged or repeated exposure to a carcinogen.

Chemicals (e.g., from smoking), radiation, viruses, and heredity all contribute to the development of cancer by triggering changes in a cell's genes. The chemicals that trigger changes are called initiators. Chemicals and radiation act by damaging genes, viruses introduce their own genes into cells, and heredity passes on alterations in genes that make a person more susceptible to cancer. Genes are altered, or "mutated," in various ways as part of the mechanism by which cancer arises.

Several groups of genes have a role in carcinogenesis. The first group of genes implicated in the development of cancer are damaged genes, called oncogenes. Oncogenes are genes whose presence in certain forms and/or overactivity can stimulate the development of cancer. Cell growth and division is normally controlled by proteins called growth factors, which bind to receptors on the cell surface. This binding activates a series of enzymes inside the cell, which in turn activate special proteins called

transcription factors inside the cell's nucleus. The activated transcription factors turn on genes required for cell growth and proliferation.

Oncogenes in normal cells can cause the cells to become malignant by instructing cells to make proteins that stimulate excessive cell growth and division. By producing abnormal versions or quantities of cellular growth-control proteins, oncogenes cause a cell's growth-signaling pathway to become hyperactive. A cancer cell may contain 1 or more oncogenes, which means that 1 or more components in this pathway will be abnormal. Oncogenes are related to proto-oncogenes, a family of normal genes that code primarily for proteins involved in a cell's normal growth. A second class of genes implicated in cancer are tumor suppressor genes.

Tumor suppressor genes are normal genes whose absence can lead to cancer. Tumor suppressor genes instruct cells to produce proteins that restrain cell growth and division. Because tumor suppressor genes code for proteins that slow down cell growth and division, the loss of such proteins allows a cell to grow and divide in an uncontrolled fashion. One particular tumor suppressor gene codes for a protein called p53 that can trigger apoptosis. In cells that have undergone DNA damage, the p53 protein halts cell growth and division. If the damage cannot be repaired, the p53 protein eventually initiates cell suicide, thereby preventing the genetically damaged cell from growing out of control. If a pair of tumor suppressor genes are either lost from a cell or inactivated by mutation, their functional absence can cause cancer.

Individuals who inherit an increased risk for the development of cancer often are born with one defective copy of a tumor suppressor gene. Because genes come in pairs (one inherited from each parent), an inherited defect in one copy will not cause cancer because the other normal copy is still functional. If the second copy undergoes mutation, cancer may then develop because there no longer is any functional copy of the gene.

A third class of genes implicated in cancer are called mismatch repair genes. Mismatch repair genes code for proteins whose normal function is to correct errors that arise when cells duplicate their DNA before cell division. Mutations in mismatch repair genes can lead to a failure in DNA repair, which in turn allows subsequent mutations in tumor suppressor genes and proto-oncogenes to accumulate.

People with a condition called xeroderma pigmentosum have an inherited defect in a mismatch repair gene. As a result, the DNA damage that normally occurs when skin cells are exposed to sunlight cannot be effectively repaired, and so the incidence of skin cancer is abnormally high for people with this condition. Certain forms of hereditary colon cancer also involve defects in DNA repair.

Cancer often arises because of the accumulation of mutations involving oncogenes, tumor suppressor genes, and mismatch repair genes. Colon cancer can begin with a defect in a tumor suppressor gene that allows excessive cell proliferation. The proliferating cells acquire subsequent mutations involving a mismatch repair gene, an oncogene, and several other tumor suppressor genes. The accumulated damage yields a highly malignant, metastatic tumor.

Another type of gene involved in the development of cancer is the telomerase gene. The ends of chromosomes are called telomeres, pieces of DNA that allow the chromosome to survive functionally intact after a lifetime of cell divisions. When cells divide, little bits of DNA are lost from each telomere, and eventually cells are unable to divide. Errant telomere genes repair the ongoing damage from cell division and allow the cell to divide indefinitely. Whatever gene is involved, the result is cancer, fed by relentless cell division that has escaped the normal constraints. The mass of cells eventually invades other tissues and organs and disrupts their function.

Treatment for Cancer

The primary and oldest treatment for cancer is surgery, and several special surgical techniques can be used. Surgery is used also in diagnosis and staging to determine the extent and amount of disease. Patients may elect to have prophylactic surgery, which is done to remove tissue that is not malignant but which may become malignant. Some women with a known mutation in the BRCA gene elect to have prophylactic mastectomies of healthy breasts to avoid breast cancer.

Curative surgery removes the tumor and is often done in conjunction with chemotherapy or radiotherapy to achieve a cure. Palliative surgery is not done to cure cancer but is used to treat complications of advanced disease. For example, palliative surgery can debulk tumors that are blocking the function of organs. Palliative surgery is also used to treat pain that is difficult to control in other ways.

Radiotherapy uses radiation to kill cells. Cells cycle through stages of division: G0, G1, S, G2, and M. Radiation is most effective on cells in the dividing stages and less effective on cells in the "resting" phase of G0. The aim of radiation therapy is to stop cancer cells from dividing, thus killing them and destroying the tumor. Unfortunately, other rapidly dividing cells, such as cells that line the mouth and hair cells, are often destroyed also, leading to mucositis and alopecia, respectively.

Other rapidly dividing cells that are often destroyed are blood cells, leading to neutropenia, anemia, or thrombocytopenia when white cells, red cells, and platelets, respectively, are damaged or destroyed.

Radiotherapy is a gradual process, with the total dose measured in grays given over an extended period of time. Very often, patients receive radiotherapy every week day (i.e., Monday through Friday) for 6 weeks.
Because normal cells repair faster, the "weekend break" allows them to recover, while the cancer cells die and are naturally removed from the body.

Radiotherapy often incorporates drugs such as radioprotectors or radiosensitizers to lessen damage to healthy tissue and improve the outcomes. Hyperfractionated radiotherapy delivers radiation in smaller doses administered every 4 to 6 hours, 2 or 3 times a day. Hyperfractionated radiotherapy works well on tumors that are known to divide extremely rapidly, particularly those of the head and neck. Another form of radiotherapy is internal radiation, in which an implanted radioactive material is used to deliver a continuous dose of radiation over several days. Unlike with other forms of radiotherapy, with internal radiation, sometimes grouped in the general category of brachytherapy, the patient is radioactive for a few days.

Children under the age of 18 years must not visit patients receiving internal radiation; others must remain at least 6 feet away and can only stay in the same room for 45 minutes.

Chemotherapy is the administration of drugs to kill cancer cells. Chemotherapeutic drugs can be administered as a pill, as an injection, or as an intravenous infusion. Hundreds of chemotherapeutic drugs are used, alone or in combination, to treat cancer.

Like radiotherapy, chemotherapy targets rapidly dividing cells, usually aiming to disrupt cell division. Most patients who have surgery to remove tumors also have chemotherapy to "clean up" stray cancer

cells in the body. Various forms of chemotherapy exist and most are categorized as antineoplastic therapy. Many types of
drugs are used as antineoplastic therapy, including alkylating agents, antimetabolites, and enzyme inhibitors.

Chemotherapy is given in cycles, with a rest period between cycles, and cycles can last from 3 months to 3 years, depending on a number of factors, including disease (i.e., what type of cancer), drugs (e.g.,
antimetabolites or monoclonal antibodies), and responses (i.e., tumor shrinkage or progression). Chemotherapy is generally given as 3 courses: induction, consolidation, and maintenance. The number of cycles in each course can vary. Chemotherapy is further classified as adjuvant or neoadjuvant, if given after or before surgery, respectively.

Some newer therapies are antiangiogenesis therapy and photodynamic therapy. Tumors, like all cells in the
body, need a rich blood supply to grow. Antiangiogenesis therapy involves the use of drugs to stop the formation of new blood vessels, effectively limiting the size of a tumor to a few millimeters in diameter. Photodynamic therapy combines light and a photosensitizing agent (i.e., a drug that is activated by light). The drug accumulates in the target of interest, the diseased organ. When the drug is exposed to laser light or another light source, chemicals are produced that destroy the cancer cells.

Photodynamic therapy is limited to areas close to the surface. A common use of photodynamic therapy is for the treatment of actinic keratosis, a precancerous skin condition caused by repeated and prolonged sun exposure. A solution is applied to the face or scalp and a special light is used to activate the drugs.

Gene therapy is a new area of cancer treatment and is highly experimental. The goal of gene therapy is to alter the genetic makeup of the tumor or of the body by inserting a desirable gene into the DNA of cells that have been removed from the patient. The removed cells are “reprogrammed” to produce different proteins and then are injected into the patient’s body or into the tumor. In some cases, the reprogrammed cells fortify the patient’s immune system; in other cases, the reprogrammed cells sensitize cancer cells to antineoplastic agents.

Bone marrow transplantation and stem cell transplantation are often the primary therapy for leukemias and
lymphomas and are being used as experimental treatments for other cancers. Transplantation allows the use of very intense chemotherapy with or without radiotherapy to better eradicate tumor cells; the greater eradication comes at the cost of the bone marrow. Both bone marrow and stem cell transplantation are complex, worthy of an entire course just on that topic.

Concluding Remarks on Oncology

Oncology is a complex area of study. Research suggests that both genetic makeup and the environment, including behaviors, interact to allow cancers to develop. It is difficult to state unequivocally “X causes cancer”; in reality, “X” probably allows other factors to engage in the development of a cancer. The future is very much open ended in regards to where “cures” will be found for cancer. In this course, now we shall look more closely at some of the issues raised in this overview, and look at some of the most frequently asked questions regarding cancer, review the various types of cancer, and this course introduces the fundamentals of cancer biology, oncogenesis, management of cancer-related symptoms, cancer treatment, palliative care, and patient and family care.

Overview-FAQs

What Is Cancer?

Cancer develops when cells in a part of the body begin to grow out of control. Although there are many kinds of cancer, they all start because of out-of-control growth of abnormal cells.

Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide more rapidly until the person becomes an adult. After that, cells in most parts of the body divide only to replace worn-out or dying cells and to repair injuries.

Because cancer cells continue to grow and divide, they are different from normal cells. Instead of dying, they outlive normal cells and continue to form new abnormal cells.

Cancer cells develop because of damage to DNA. This substance is in every cell and directs all activities. Most of the time when DNA becomes damaged the body is able to repair it. In cancer cells, the damaged DNA is not repaired. People can inherit damaged DNA, which accounts for inherited cancers. More often, though, a person's DNA becomes damaged by exposure to something in the environment, like smoking.

Cancer usually forms as a tumor. Some cancers, like leukemia, do not form tumors. Instead, these cancer cells involve the blood and blood-forming organs and circulate through other tissues where they grow.

Often, cancer cells travel to other parts of the body where they begin to grow and replace normal tissue. This process is called metastasis. Regardless of where a cancer may spread, however, it is always named for the place it began. For instance, breast cancer that spreads to the liver is still called breast cancer, not liver cancer.

Not all tumors are cancerous. Benign (noncancerous) tumors do not spread (metastasize) to other parts of the body and, with very rare exceptions, are not life threatening.

Different types of cancer can behave very differently. For example, lung cancer and breast cancer are very different diseases. They grow at different rates and respond to different treatments. That is why people with cancer need treatment that is aimed at their particular kind of cancer.

Cancer is the second leading cause of death in the United States. Half of all men and one third of all women in the United States will develop cancer during their lifetimes. Today, millions of people are living with cancer or have had cancer. The risk of developing most types of cancer can be reduced by changes in a person's lifestyle, for example, by quitting smoking and eating a better diet. The sooner a cancer is found and treatment begins, the better are the chances for living for many years.

Who Gets Cancer?

Over one million people get cancer each year. Approximately one out of every two American men and one out of every three American women will have some type of cancer at some point during their

lifetime. Anyone can get cancer at any age; however, about 77% of all cancers are diagnosed in people age of 55 and older. Although cancer occurs in Americans of all racial and ethnic groups, the rate of cancer occurrence (called the incidence rate) varies from group to group.

Today, millions of people are living with cancer or have been cured of the disease. The sooner a cancer is found and the sooner treatment begins, the better a patient's chances are of a cure. That's why early detection of cancer is such an important weapon in the fight against cancer.

What Are the Risk Factors for Cancer?

A risk factor is anything that increases a person's chance of getting a disease. Some risk factors can be changed, and others cannot. Risk factors for cancer can include a person's age, sex, and family medical history. Others are linked to cancer-causing factors in the environment. Still others are related to lifestyle choices such as tobacco and alcohol use, diet, and sun exposure.

Having a risk factor for cancer means that a person is more likely to develop the disease at some point in their lives. However, having one or more risk factors does not necessarily mean that a person will get cancer. Some people with one or more risk factors never develop the disease, while other people who do develop cancer have no apparent risk factors. Even when a person who has a risk factor is diagnosed with cancer, there is no way to prove that the risk factor actually caused the cancer.

Different kinds of cancer have different risk factors. Some of the major risk factors include the following:

- Cancers of the lung, mouth, larynx, bladder, kidney, cervix esophagus, and pancreas are related to tobacco use, including cigarettes, cigars, chewing tobacco, and snuff. Smoking alone causes one-third of all cancer deaths.
- Skin cancer is related to unprotected exposure to strong sunlight.
- Breast cancer risk factors include several factors: age; changes in hormone levels throughout life, such as age at first menstruation, number of pregnancies, and age at menopause; obesity; and physical activity. Some studies have also shown a connection between alcohol consumption and an increased risk of breast cancer. Also, women with a mother or sister who have had breast cancer are more likely to develop the disease themselves.
- While all men are at risk for prostate cancer, several factors can increase the chances of developing the disease, such as age, race, and diet. The chance of getting prostate cancer goes up with age. Prostate cancer is more common among African-American men than among white men. (We do not yet know why this is so.) A high-fat diet may play a part in causing prostate cancer. Also, men with a father or brother who have had prostate cancer are more likely to get prostate cancer themselves.

Overall, environmental factors, defined broadly to include tobacco use, diet, and infectious diseases, as well as chemicals and radiation cause an estimated 75% of all cancer cases in the United States. Among these factors, tobacco use, unhealthy diet, and physical activity are more likely to affect personal cancer risk. Research shows that about one-third of all cancer deaths are related to dietary factors and lack of physical activity in adulthood.

Certain cancers are related to viral infections and could be prevented by behavior changes or vaccines. More than 1 million skin cancers expected to be diagnosed in 2003 could have been prevented by protection from the sun's rays.

Can Cancer be prevented?

Smoking and drinking alcohol cause some people to get certain types of cancer. These cancers might be prevented by avoiding tobacco and alcohol. The best idea is to never use tobacco at all. Cigarettes, cigars, pipes and smokeless tobacco cause cancer and should not be used. People who already smoke should try to quit. Former smokers have less risk of cancer than do people who continue to smoke.

The chances of getting skin cancer can be lowered by staying in the shade as much as you can, wearing a hat and shirt when you are in the sun, and using sunscreen.

It has been shown in numerous studies that diet is linked to some types of cancer, although the exact reasons are not yet clear. The best advice is to eat a lot of fresh fruits and vegetables and whole grains like pasta and bread, and to cut down on high fat foods.

There are tests, called screening examinations, that adults should have in order to find cancer early. If cancer is found early it can often be cured.

What Causes Cancer?

Some kinds of cancer are caused by things people do. Smoking can cause cancers of the lungs, mouth, throat, bladder, kidneys and several other organs, as well as heart disease and stroke. While not everyone who smokes will get cancer, smoking increases a person's chance of getting the disease. Drinking a lot of alcohol has also been shown to increase a person's chance of getting cancer of the mouth, throat, and some other organs. This is especially true if the person drinks and smokes.

Radiation (x-rays) can cause cancer. But the x-rays used by the doctor or dentist are safe. Too much exposure to sunlight without any protection can cause skin cancer.

In many cases, the exact cause of cancer remains a mystery. We know that certain changes in our cells can cause cancer to start, but we don't yet know exactly how this happens. Many scientists are studying this problem.

What Are Symptoms and Signs?

A **symptom** is an indication of disease, illness, injury, or that something is not right in the body. Symptoms are felt or noticed by a person, but may not easily be noticed by anyone else. For example, chills, weakness, achiness, shortness of breath, and a cough are possible symptoms of pneumonia.

A **sign** is also an indication that something is not right in the body. But signs are defined as observations made by a doctor, nurse, or other health care professional. Fever, rapid breathing rate, and abnormal breathing sounds heard through a stethoscope are possible signs of pneumonia.

The presence of one symptom or sign may not give enough information to suggest a cause. For example, a rash in a child could be a symptom of a number of things including poison ivy, an infectious disease like measles, an infection limited to the skin, or a food allergy. But if the rash is seen along with other signs and symptoms like a high fever, chills, achiness, and a sore throat, then a doctor can get a better picture of the illness. In many cases, a patient's signs and symptoms do not provide enough clues by themselves to determine the cause of an illness, and medical tests such as x-rays, blood tests, or a biopsy may be needed.

How Does Cancer Produce Signs and Symptoms?

Cancer is a group of diseases that may cause almost any sign or symptom. The signs and symptoms will depend on where the cancer is, the size of the cancer, and how much it affects the surrounding organs or structures. If a cancer spreads (metastasizes), then symptoms may appear in different parts of the body.

As a cancer grows, it begins to push on nearby organs, blood vessels, and nerves. This pressure creates some of the signs and symptoms of cancer. If the cancer is in a critical area, such as certain parts of the brain, even the smallest tumor can produce early symptoms.

Sometimes, however, cancers form in places where there may be no symptoms until the cancer has grown quite large. Pancreas cancers, for example, do not usually grow large enough to be felt from the outside of the body. Some pancreatic cancers do not produce symptoms until they begin to grow around nearby nerves, causing a backache. Others grow around the bile duct, which blocks the flow of bile and leads to a yellowing of the skin known as jaundice. By the time a pancreatic cancer causes these signs or symptoms, it has usually reached an advanced stage.

A cancer may also cause symptoms such as fever, fatigue, or weight loss. This may be caused by cancer cells using up much of the body’s energy supply or releasing substances that change the body’s metabolism. Or the cancer may cause the immune system to react in ways that produce these symptoms.

Sometimes, cancer cells release substances into the bloodstream that cause symptoms not usually thought to result from cancers. For example, some cancers of the pancreas can release substances which cause blood clots to develop in veins of the legs. Some lung cancers make hormone-like substances that affect blood calcium levels, affecting nerves and muscles and causing weakness and dizziness.

How Are Signs and Symptoms Helpful?

Treatment is most successful when cancer is found as early as possible. Finding cancer early usually means it can be treated while it is still small and is less likely to have spread to other parts of the body. This often means a better chance for a cure, especially if initial treatment is to be surgery.

A good example of the importance of detecting cancer early is melanoma skin cancer. It is easily removed if it has not yet grown deeply into the skin, and the 5-year survival rate (percentage of people living at least 5 years after diagnosis) at this stage is nearly 100%. But once melanoma has spread to other parts of the body the survival rate drops dramatically.

Sometimes people ignore symptoms either because they do not recognize the symptoms as being significant or because they are frightened by what they might mean and don't want to seek medical help. General symptoms, such as fatigue, are more likely to have a cause other than cancer and can seem unimportant, especially if they have an obvious cause or are only temporary. In a similar way, a person may reason that a more specific symptom like a breast mass is probably a cyst that will go away by itself. But neither of these symptoms should be discounted or overlooked, especially if they have been present for a long period of time or are getting worse.

Most likely, any symptoms a person may have will not be caused by cancer, but it's important to have them checked out by a doctor, just in case. If cancer is not the cause, the doctor can help figure out what is and treat it, if needed.

In some cases it is possible to detect some cancers before symptoms occur. The American Cancer Society and other health groups encourage the early detection of certain cancers before symptoms occur by recommending a cancer-related checkup and specific tests for people who do not have any symptoms.

General Cancer Signs and Symptoms

It is important to know what some of the general (non-specific) signs and symptoms of cancer are. They include unexplained weight loss, fever, fatigue, pain, and changes in the skin. Of course, it's important to remember that having any of these does not necessarily mean that cancer is present -- there are many other conditions that can cause these signs and symptoms as well.

Unexplained weight loss: Most people with cancer will lose weight at some time with their disease. An unexplained (unintentional) weight loss of 10 pounds or more may be the first sign of cancer, particularly cancers of the pancreas, stomach, esophagus, or lung.

Fever: Fever is very common with cancer, but is more often seen in advanced disease. Almost all patients with cancer will have fever at some time, particularly if the cancer or its treatment affects the immune system and reduces resistance to infection. Less often, fever may be an early sign of cancer, such as with leukemia or lymphoma.

Fatigue: Fatigue may be a significant symptom as cancer progresses. It may occur early, however, in cancers such as with leukemia or if the cancer is causing a chronic loss of blood, as in some colon or stomach cancers.

Pain: Pain may be an early symptom with some cancers, such as bone cancers or testicular cancer. Most often, however, pain is a symptom of advanced disease.

Skin changes: In addition to cancers of the skin (see next section), some internal cancers can produce visible skin signs such as darkening (hyperpigmentation), yellowing (jaundice), reddening (erythema), itching, or excessive hair growth.

Specific Cancer Signs and Symptoms

In addition to the above general symptoms, you should be watchful for the following common symptoms, which could be an indication of cancer. Again, there may be other causes for each of these, but it is important to bring them to your doctor's attention as soon as possible so that they can be investigated.

Change in bowel habits or bladder function: Chronic constipation, diarrhea, or a change in the size of the stool may indicate colon cancer. Pain with urination, blood in the urine, or a change in bladder function (such as more frequent or less frequent urination) could be related to bladder or prostate cancer. Any changes in bladder or bowel function should be reported to your doctor.

Sores that do not heal: Skin cancers may bleed and resemble sores that do not heal. A persistent sore in the mouth could be an oral cancer and should be dealt with promptly, especially in patients who smoke, chew tobacco, or frequently drink alcohol. Sores on the penis or vagina may either be signs of infection or an early cancer, and should not be overlooked in either case.

Unusual bleeding or discharge: Unusual bleeding can occur in either early or advanced cancer. Blood in the sputum (phlegm) may be a sign of lung cancer. Blood in the stool (or a dark or black stool) could be a sign of colon or rectal cancer. Cancer of the cervix or the endometrium (lining of the uterus) can cause vaginal bleeding. Blood in the urine is a sign of possible bladder or kidney cancer. A bloody discharge from the nipple may be a sign of breast cancer.

Thickening or lump in breast or other parts of the body: Many cancers can be felt through the skin, particularly in the breast, testicle, lymph nodes (glands), and the soft tissues of the body. A lump or thickening may be an early or late sign of cancer. Any lump or thickening should be reported to your doctor, especially if you've just discovered it or noticed it has grown in size. You may be feeling a lump that is an early cancer that could be treated successfully.

Indigestion or trouble swallowing: While they commonly have other causes, these symptoms may indicate cancer of the esophagus, stomach, or pharynx (throat).

Recent change in a wart or mole: Any change in color or shape, loss of definite borders, or an increase in size should be reported to your doctor without delay. The skin lesion may be a melanoma which, if diagnosed early, can be treated successfully.

Nagging cough or hoarseness: A cough that does not go away may be a sign of lung cancer. Hoarseness can be a sign of cancer of the larynx (voice box) or thyroid.

While the signs and symptoms listed above are the more common ones seen with cancer, there are many others that are less common and are not listed here. If you notice any major changes in the way your body functions or the way you feel, especially if it lasts for a long time or gets worse, let your doctor know. If it has nothing to do with cancer, your doctor can investigate it and treat it, if needed. If it is cancer, you'll give yourself the best chance to have it treated early, when treatment is most likely to be effective.

What Is Remission?

Remission is a period of time when the cancer is responding to treatment or is under control. In a complete remission, all the signs and symptoms of the disease disappear. It is also possible for a patient to have a partial remission in which the cancer shrinks but does not completely disappear. Remissions can last anywhere from several weeks to many years. Complete remissions may continue for years and be considered cures. If the disease returns, another remission often can occur with further treatment. A cancer that has recurred may respond to a different type of therapy, including a different drug combination.

What Is Staging?

Staging is the process of finding out how far the cancer has spread. Staging the cancer is a vital step in determining your treatment choices, and it will also give your health care team a clearer idea of the outlook for recovery.

Staging can take time, and people are usually anxious to begin treatment soon. They should not worry that the staging process is taking up treatment time. They should keep in mind that by staging the cancer, they and their health care team will know which treatments are likely to be the most effective before beginning the treatment. There is more than one system for staging. The **TNM system** is the one used most often. It gives three key pieces of information:

- T describes the size of the tumor, and whether the cancer has spread to nearby tissues and organs.
- N describes how far the cancer has spread to nearby lymph nodes.
- M shows whether the cancer has spread (metastasized) to other organs of the body.

Letters or numbers after the T, N, and M give more details about each of these factors. For example, a tumor classified as T1, N0, M0 is a tumor that is very small, has not spread to the lymph nodes, and has not spread to distant organs of the body. Once the TNM descriptions have been established, they can be grouped together into a simpler set of stages, stages 0 through stage IV (0-4).

In general, the lower the number, the less the cancer has spread. A higher number, such as stage IV (4), means a more serious, widespread cancer.

After looking at a patient's test results, the doctor will tell the patient the stage of their cancer. Patients should be sure to ask any questions they might have about what the stage of their cancer means and how it will impact their treatment options.

How Is Cancer Treated?

The number of treatment choices depends on the type of cancer, the stage of the cancer, and other individual factors such as your age, health status, and personal preferences. The patient is a vital part of your cancer care team – and should be included in discussions regarding which treatment choices are best.

The four major types of treatment for cancer are surgery, radiation, chemotherapy, and biologic therapies. There are also hormone therapies such as tamoxifen and transplant options such as those done with bone marrow.

Biologic Therapies

There is a lot of evidence that suggests that the immune system, the body's natural defense mechanism, plays a major role in the body's response to cancer. At least some forms of cancer occur when the immune system fails to destroy cancer cells or to prevent their growth. Biologic therapy is an effective treatment for certain cancers. It is sometimes called immunotherapy, biotherapy, or biological response modifier therapy. Biologic therapies use the body's immune system to fight cancer or to lessen the side effects of some cancer treatments.

Biologic therapies can act in several ways in cancer treatment. These include interfering with cancer

cell growth, acting indirectly to help healthy immune cells control cancer, and helping to repair normal cells damaged by other forms of cancer treatment.

There are several kinds of biologic therapy now in use. More than one kind of biologic therapy may be used, or biologic therapy may be combined with chemotherapy or radiation therapy to treat cancer.

Chemotherapy

While surgery and radiation therapy are used to treat localized cancers, chemotherapy is used to treat cancer cells that have metastasized (spread) to other parts of the body. Depending on the type of cancer and its stage of development, chemotherapy can be used to cure cancer, to keep the cancer from spreading, to slow the cancer's growth, to kill cancer cells that may have spread to other parts of the body, or to relieve symptoms caused by cancer.

Chemotherapy is treatment with powerful medicines that are most often given by mouth or by injection. Unlike radiation therapy or surgery, chemotherapy drugs can treat cancers that have spread throughout the body, because they travel throughout the body in the bloodstream. Often, a combination of chemotherapy is used instead of a single drug.

Chemotherapy is given in cycles, each followed by a recovery period. The total course of chemotherapy is often about six months, usually ranging from three to nine months. After a cancer is removed by surgery, chemotherapy can significantly reduce the risk of cancer returning. The chances of cancer returning and the potential benefit of chemotherapy depend on the type of cancer and other individual factors.

Side effects of chemotherapy

Side effects of chemotherapy depend on the type of drugs, the amounts taken, and the length of treatment. The most common are nausea and vomiting, temporary hair loss, increased chance of infections, and fatigue. Many of these side effects can be uncomfortable or emotionally upsetting. However, most side effects can be controlled with medicines, supportive care measures, or by changing the treatment schedule. If a patient experience side effects, he/she should ask the doctor about ways to help ease or eliminate them. Also, the doctor should be kept informed of all side effects that experienced, as some may require immediate medical attention.

Fatigue is one of the most common side effects of radiation and chemotherapy. Like most other side effects, it will disappear once the treatment is complete. Patients can help themselves by getting enough rest, eating a well-balanced diet, drinking plenty of liquids, and by planning activities to include frequent rest periods.

Though it is not medically harmful, hair loss can be an upsetting side effect. Most people feel that their hairstyle is a part of their identity, so it is only normal that hair loss is distressing. Some people experience hair loss during chemotherapy treatments (and sometimes with radiation treatment to the head) while others do not, even with the same drugs. Not all drugs cause hair loss. When it does occur, the hair almost always grows back after the treatments are completed. If hair loss does occur, it usually begins within two weeks of the start of therapy and gets worse 1-2 months after the start of therapy. Hair regrowth often begins even before therapy is completed. Most people are able to find suitable ways of managing the hair loss until it grows back, with specially designed hats, scarves, and wigs.

People having chemotherapy sometimes become discouraged about the length of time their treatment is taking or the side effects they are having.

Clinical Trials

The purpose of clinical trials: Studies of promising new or experimental treatments in patients are known as clinical trials. A clinical trial is only done when there is some reason to believe that the treatment being studied may be valuable to the patient. Treatments used in clinical trials are often found to have real benefits. Researchers conduct studies of new treatments to answer the following questions:

- Is the treatment helpful?
- How does this new type of treatment work?
- Does it work better than other treatments already available?
- What side effects does the treatment cause?
- Are the side effects greater or less than the standard treatment?
- Do the benefits outweigh the side effects?
- In which patients is the treatment most likely to be helpful?

Types of clinical trials: There are 3 phases of clinical trials in which a treatment is studied before it is eligible for approval by the FDA (Food and Drug Administration).

Phase I clinical trials: The purpose of a phase I study is to find the best way to give a new treatment and how much of it can be given safely. The cancer care team watches patients carefully for any harmful side effects. The treatment has been well tested in lab and animal studies, but the side effects in patients are not completely known. Doctors conducting the clinical trial start by giving very low doses of the drug to the first patients and increasing the dose for later groups of patients until side effects appear. Although doctors are hoping to help patients, the main purpose of a phase I study is to test the safety of the drug.

Phase II clinical trials: These studies are designed to see if the drug works. Patients are given the highest dose that doesn't cause severe side effects (determined from the phase I study) and closely observed for an effect on the cancer. The cancer care team also looks for side effects.

Phase III clinical trials: Phase III studies involve large numbers of patient – often several hundred. One group (the control group) receives the standard (most accepted) treatment. The other group receives the new treatment. All patients in phase III studies are closely watched. The study will be stopped if the side effects of the new treatment are too severe or if one group has had much better results than the others.

Patients in a clinical trial have a team of experts taking care of them and monitoring their progress very carefully. The study is especially designed to pay close attention to the patient.

However, there are some risks. No one involved in the study knows in advance whether the treatment will work or exactly what side effects will occur. That is what the study is designed to find out. While most side effects disappear in time, some can be permanent or even life threatening. Patients should keep in mind, though, that even standard treatments have side effects. Depending on many factors, individual patients may decide to enroll in a clinical trial.

Deciding to enter a clinical trial: Enrollment in any clinical trial is completely up to the individual patient. Their doctors and nurses explain the study to in detail and provide forms to read and sign indicating the patient's desire to take part. This process is known as informed consent. Even after signing the form and after the clinical trial begins, patients are free to leave the study at any time, for any reason. Taking part in the study does not prevent them from getting other medical care they may need.

To find out more about clinical trials, patients should ask their cancer care team. Among the questions patients should ask are:

- Is there a clinical trial for which I would be eligible?
- What is the purpose of the study?
- What kinds of tests and treatments does the study involve?
- What does this treatment do? Has it been used before?
- Will I know which treatment I receive?
- What is likely to happen in my case with, or without, this new treatment?
- What are my other choices and their advantages and disadvantages?
- How could the study affect my daily life?
- What side effects can I expect from the study? Can the side effects be controlled?
- Will I have to be hospitalized? If so, how often and for how long?
- Will the study cost me anything? Will any of the treatment be free?
- If I were harmed as a result of the research, what treatment would I be entitled to?
- What type of long-term follow-up care is part of the study?
- Has the treatment been used to treat other types of cancers?

The American Cancer Society offers a clinical trials matching service for patients, their family, and friends. Patients can reach this service at 1-800-303-5691 or on their Web site at http://clinicaltrials.cancer.org.. Based on the information provided about cancer type, stage, and previous treatments, this service can compile a list of clinical trials that match the patient's medical needs. In finding a center most convenient for the individual patient, the service can also take into account where they you live and whether they are willing to travel.

A list of current clinical trials is also available from the National Cancer Institute's Cancer Information Service toll free at 1-800-4-CANCER or by visiting the NCI clinical trials Web site at http://www.cancer.gov/clinicaltrials.

Complementary and Alternative Therapies

Complementary and alternative therapies are a diverse group of health care practices, systems, and products that are not part of usual medical treatment. They may include products such as vitamins, herbs, or dietary supplements, or procedures such as acupuncture, massage, and a host of other types of treatment. There is a great deal of interest today in complementary and alternative treatments for cancer. Many are now being studied to find out if they are truly helpful to people with cancer.

Patients may hear about different treatments from family, friends, and others, which may be offered as a way to treat their cancer or to help them feel better. Some of these treatments are harmless in certain situations, while others have been shown to cause harm. Most of them are without proven benefits.

The American Cancer Society defines *complementary* medicine or methods as those that are used along with your regular medical care. If these treatments are carefully managed, they may add to the patient's comfort and well-being. *Alternative* medicines are defined as those that are used instead of your regular medical care. Some of them have been proven not to be useful or even to be harmful, but are still promoted as "cures." If a patient chooses to use these alternatives, they may reduce his/her chance of fighting their cancer by delaying, replacing, or interfering with regular cancer treatment.

Before changing treatment or adding any of these methods, patients should discuss this openly with their doctor or nurse. Some methods can be safely used along with standard medical treatment. Others, however, can interfere with standard treatment or cause serious side effects. That is why the patient should also consult his/her personal doctor or nurse.

Cancer Pain

Pain is one of the reasons people fear cancer so much. It is normal to be afraid of witnessing pain. In fact, there are some cancers, which cause no physical pain at all. When it does occur, cancer pain can happen for a variety of reasons. Some people have pain as a result of the growth of a tumor or as a result of advanced cancer, while others may experience pain as a result of treatment side effects.

Patients should know that doctors can treat and manage cancer pain with modern techniques and medicines. A great deal of progress has been made in pain control, so pain can be reduced or alleviated in almost all cases. Even patients with advanced disease can be kept comfortable.

Patients may also be concerned that someone taking pain medication for cancer will become addicted to the medication. However, all evidence shows that people who take prescribed drugs for cancer pain do not become addicted. In addition, some methods of pain reduction, such as acupuncture and guided imagery, do not involve drugs.

What About Fatigue?

Fatigue is one of the most common side effects of chemotherapy. It can range from mild lethargy to feeling completely wiped out. Fatigue tends to be the worst at the beginning and at the end of a treatment cycle. Like most other side effects, fatigue will disappear once chemotherapy is complete.

Techniques to help with fatigue include:

- Get plenty of rest and allow time during the day for periods of rest.
- Patients should talk with their doctor or nurse about a program of regular exercise.
- Eat a well-balanced diet and drink plenty of liquids.
- Limit activities: Patients should do only the things that are most important to them.
- Patients should get help when they need it. Ask family, friends, and neighbors to pitch in with activities such as childcare, shopping, housework, or driving. For example, neighbors might pick up some items at the grocery store while doing their own shopping.
- Get up slowly to help prevent dizziness when sitting or lying down.

Feeling Tired vs. Cancer-Related Fatigue

If you are fighting cancer, chances are you're also fighting fatigue. Fatigue is the most common side effect of cancer treatment, and it often hits unexpectedly. Everyday activities — talking on the telephone, shopping for groceries, even lifting a fork to eat —can become daunting tasks.

Cancer-related fatigue feels very different from everyday fatigue, said Lillian Nail, PhD, RN, a cancer survivor who has studied this side effect at the University of Utah School of Nursing."

"'Overwhelming' is the most common description," said Dr. Nail. "When compared with the fatigue experienced by healthy people, cancer-related fatigue is more severe, it lasts longer, and sleep just doesn't bring relief." The causes of cancer-related fatigue are not fully known. Problems like a low blood count, sleep disruption, stress, eating too little, and other factors may contribute to this condition.

A Common, Frustrating Problem

About 90 % of patients experience fatigue during chemotherapy or radiation therapy treatment, added Dr. Nail. For patients receiving cyclic chemotherapy, fatigue often peaks within a few days and declines until the next treatment when the pattern begins again. For patients receiving radiation, fatigue usually increases as the treatment continues. It may last from three months to one year after treatment ends. And it may last even longer for patients receiving bone marrow transplants. For these patients, their personal definition of what is normal changes; being tired becomes the new normal, said Barbara Piper, DNSc, RN, associate professor of nursing at the University of Nebraska.

Mental fatigue often results from the intensive mental effort and excessive attention that is necessary when coping with a serious illness. "For example, a woman with newly diagnosed breast cancer must absorb the impact of the diagnosis as well as make treatment decisions to go on with her life," added Piper. Physicians often don't prepare patients for this frustrating side-effect of cancer, said Russell Portenoy, MD, chairman of the Department of Pain Medicine and Palliative Care at Beth Israel Medical Center in New York City, and a member of the Fatigue Coalition, a group of medical researchers and practitioners who are making more patients and health care providers aware of this condition. Left untreated, fatigue can upset the patient's quality of life.

Fatigue or Depression?

Because some fatigue symptoms seem to mirror those of depression, health care providers often confuse the two, said Dr. Nail. Depression involves an inability to feel pleasure — people who are depressed feel sad, unworthy, despair or guilt. "It's entirely possible to be fatigued but not depressed," she explained, adding patients sometimes have trouble finding a label for what they're feeling. They simply know they can be overwhelmed with fatigue at any time, no matter what they are doing.

Some signs of cancer-related fatigue are:

- Feeling tired, weary or exhausted even after sleeping
- Lacking energy to do your regular activities
- Having trouble concentrating, thinking clearly, or remembering
- Feeling negative, irritable, impatient, or unmotivated
- Lacking interest in normal day-to-day activities
- Spending less attention on personal appearance
- Spending more time in bed or sleeping

At times, there may be physical causes of fatigue, like infection or pain that disrupts sleep.

It's important that people speak up about any unpleasant side-effects they experience, so the health care team can identify and treat those problems, both during active cancer treatment and afterward when some physical problems can linger.

When there are no obvious physical causes for a patient or survivor's excessive fatigue, doctors may want to run tests to rule out hidden medical problems. That process is described further in the NCCN Cancer-Related Fatigue Treatment Guidelines for Patients.

When medical issues are ruled out, certain practical methods have been developed to manage and minimize cancer-related fatigue, including good "sleep hygiene," appropriate and approved physical activities, and smart use of your time and energy. Dr. Nail added, "It's a matter of identifying the times of day when you have more energy than others," she explained. "It means finding alternative ways of doing things, deciding what you can give up, setting priorities, and then getting help."

Common Cancer Types

The list of common cancers includes cancers that are diagnosed with the greatest frequency in the United States. Cancer incidence statistics from the American Cancer Society[1] and other resources were used to create the list. To qualify as a common cancer, the estimated annual incidence for 2006 had to be 30,000 cases or more.

The most common type of cancer on the list is non-melanoma skin cancer, with more than 1,000,000 new cases expected in the United States in 2006. Non-melanoma skin cancers represent about half of all cancers diagnosed in this country.

The cancer on the list with the lowest incidence is thyroid cancer. The estimated number of new cases of thyroid cancer for 2006 is 30,180.

Because colon and rectal cancers are often referred to as "colorectal cancers," these two cancer types were combined for the list. For 2006, the estimated number of new cases of colon cancer is 106,680, and the estimated number of new cases of rectal cancer is 41,930. These numbers are slightly larger than those estimated for 2005.

Kidney cancers can be divided into two major groups, renal parenchyma cancers and renal pelvis cancers. Approximately 82 percent of kidney cancers develop in the renal parenchyma,[2] and nearly all of these cancers are renal cell cancers. The estimated number of new cases of renal cell cancer for 2006 is 31,890.

Leukemia as a cancer type includes acute lymphoblastic (or lymphoid) leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, chronic myelogenous (or myeloid) leukemia, and other forms of leukemia. It is estimated that more than 35,000 new cases of leukemia will be diagnosed in the United States in 2006, with acute myeloid leukemia being the most common type (approximately 12,000 new cases). The total number of new leukemia cases estimated for 2006 is slightly larger than the number estimated for 2005.

The following table gives the estimated numbers of new cases and deaths for each common cancer type:

Cancer Type	Estimated New Cases	Estimated Deaths
Bladder	**61,420**	**13,060**
Breast (Female -- Male)	**212,920 -- 1,720**	**40,970 -- 460**
Colon and Rectal (Combined)	**148,610**	**55,170**
Endometrial	**41,200**	**7,350**
Kidney (Renal Cell) Cancer	**31,890**	**10,530**
Leukemia (All)	**35,070**	**22,280**
Lung (Including Bronchus)	**174,470**	**162,460**
Melanoma	**62,190**	**7,910**
Non-Hodgkin's Lymphoma	**58,870**	**18,840**
Pancreatic	**33,730**	**32,300**

Prostate	**234,460**	**27,350**
Skin (Non-melanoma)	**>1,000,000**	**Not Available**
Thyroid	**30,180**	**1,500**

References

1. **American Cancer Society: Cancer Facts and Figures 2006. Atlanta, Ga: American Cancer Society, 2006. Also available online. Last accessed March 24, 2006.**

Bladder Cancer

Overview

The bladder is an organ located in the pelvic cavity that stores and discharges urine. Urine is produced by the kidneys, carried to the bladder by the ureters, and discharged from the bladder through the urethra. Bladder cancer accounts for approximately 90% of cancers of the urinary tract (renal pelvis, ureters, bladder, urethra).

Types

Bladder cancer usually originates in the bladder lining, which consists of a mucous layer of surface cells that expand and deflate (transitional epithelial cells), smooth muscle, and a fibrous layer. Tumors are categorized as low-stage (superficial) or high-stage (muscle invasive).

In industrialized countries (e.g., United States, Canada, France), more than 90% of cases originate in the transitional epithelial cells (called **transitional cell carcinoma**; TCC). In developing countries, 75% of cases are squamous cell carcinomas caused by *Schistosoma haematobium* (parasitic organism) infection. Rare types of bladder cancer include small cell carcinoma, carcinosarcoma, primary lymphoma, and sarcoma.

Incidence and Prevalence

According to the National Cancer Institute, the highest incidence of bladder cancer occurs in industrialized countries such as the United States, Canada, and France. Incidence is lowest in Asia and South America, where it is about 70% lower than in the United States.

Incidence of bladder cancer increases with age. People over the age of 70 develop the disease 2 to 3 times more often than those aged 55–69 and 15 to 20 times more often than those aged 30–54.

Bladder cancer is 2 to 3 times more common in men. In the United States, approximately 38,000 men and 15,000 women are diagnosed with the disease each year. Bladder cancer is the fourth most common type of cancer in men and the eighth most common type in women. The disease is more prevalent in Caucasians than in African Americans and Hispanics.

A three-year study to validate a test to detect the recurrence of bladder cancer has been initiated by the National Cancer Institute (NCI), part of the National Institutes of Health (NIH), at 13 centers* across the United States and Canada. This test was conceived and is being conducted by NCI's Early Detection Research Network (EDRN). By examining genetic changes in DNA obtained through urine

samples, the test, if successfully validated, will provide a sensitive and non-invasive method of screening for bladder cancer recurrence.

"This is the first study of its' kind," said Sudhir Srivastava, Ph.D., who heads EDRN as chief of the Cancer Biomarkers Research Group in NCI's Division of Cancer Prevention. "It's the first study testing a marker for bladder cancer, and the first Phase III study for an EDRN-created test." The leading investigator and the coordinator of this study is Dr. Mark Schoenberg, form the James Buchanan Brady Urological Institute, Johns Hopkins University, Baltimore, MD..

Bladder cancer, with over 60,000 estimated new cases this year, is both one of the more common cancers and one that has a high recurrence rate. Frequent surveillance of bladder cancer patients is critical, but current procedures have shortcomings. Urine cytology, which checks the number and appearance of cells in urine samples, often fails to detect early tumors. Cystoscopy -- examining the urethra and bladder with a thin lighted scope -- can give patients a false-positive result in addition to being invasive and unpleasant.

The new EDRN-created test looks to improve upon these weaknesses. EDRN, established by NCI in early 2000, is a broad, interdisciplinary consortium whose work is aimed at both identifying and validating cancer biomarkers for use in early cancer detection. Numerous proteins and genes have been linked with a variety of cancers, which can make them targets for therapy, as well as targets for identifying the risk of cancer onset, progression, or recurrence. The validation -- proving that the link accurately signifies the risk for or presence of cancer -- is the critical step to create a truly useful test.

The bladder cancer test uses a technology known as microsatellite DNA analysis (MSA). Microsatellites, also known as short tandem repeats, are repeating units of one to six nucleotides (e.g. CACACACA) found throughout human chromosomes. These repeating regions are frequently mutated in tumors, either through deletions or by an extension of the number of repeats. For screening for recurrent bladder cancer, DNA can be easily extracted from cells that are normally present in urine, and compared to DNA sequences of unaffected cells, such as lymphocytes, from the same patients. Early studies have shown this non-invasive analysis can have over 90 percent accuracy.

In the validation study, overseen by Jacob Kagan, Ph.D., program director of NCI's Cancer Biomarkers Research Group, 15 different biomarkers in 300 patients diagnosed with bladder cancer will be examined in an effort to predict cancer recurrence. Individuals with healthy bladders and individuals with non-cancerous bladder problems that could be misdiagnosed as cancer, such as kidney stones or urinary tract infections, will be used as controls. The participating institutions will collect samples from patients in this study, and the samples will be analyzed by Commonwealth Biotechnologies Inc., located in Richmond, Va. "The primary goal of this study is to monitor MSA for bladder cancer recurrence," said Srivastava, "but the longer goal is to also use the test for early detection of new bladder cancer occurrence."

This trial will run for three years and final results are expected in September 2007. After Phase III validation, Cangen Biotechnologies Inc., which holds the license for this MSA test, plans to seek Food and Drug Administration approval for this test to make it publicly available. Additionally, EDRN is working on two other early detection tests involving examination of protein biomarkers in blood serum to detect early tumors of the prostate and liver.

Interpreting Laboratory Test Results

A laboratory test is a medical procedure in which a sample of blood, urine, or other tissues or substances in the body is checked for certain features. Such tests are often used as part of a routine checkup to identify possible changes in a person's health before any symptoms appear. Laboratory tests also play an important role in diagnosis when a person has symptoms. In addition, tests may be used to help plan a patient's treatment, evaluate the response to treatment, or monitor the course of the disease over time.

Laboratory test samples are analyzed to determine whether the results fall within normal ranges. They also may be checked for changes from previous tests. Normal test values are usually given as a range, rather than as a specific number, because normal values vary from person to person. What is normal for one person may not be normal for another person. Many factors (including the patient's sex, age, race, medical history, and general health) can affect test results. Sometimes, test results are affected by specific foods, drugs the patient is taking, and how closely the patient follows pre-test instructions. That is why a patient may be asked not to eat or drink for several hours before a test. It is also common for normal ranges to vary somewhat from laboratory to laboratory.

Some laboratory tests are precise, reliable indicators of specific health problems. Others provide more general information that simply gives doctors clues to possible health problems. Information obtained from laboratory tests may help doctors decide whether other tests or procedures are needed to make a diagnosis. The information may also help the doctor develop or revise a patient's treatment plan. All laboratory test results must be interpreted in the context of the overall health of the patient and are generally used along with other exams or tests. The doctor who is familiar with the patient's medical history and current condition is in the best position to explain test results and their implications. Patients are encouraged to discuss questions or concerns about laboratory test results with the doctor.

Tumor Markers: Questions and Answers

Key Points

- **Tumor markers are substances that can be found in abnormal amounts in the blood, urine, or tissues of some patients with cancer (see Question 1).**
- **Different tumor markers are found in different types of cancer (see Question 1).**
- **Tumor markers may be used to help diagnose cancer, predict a patient's response to particular therapies, check a patient's response to treatment, or determine if cancer has returned (see Questions 3 and 4).**
- **In general, tumor markers cannot be used alone to diagnose cancer; they must be combined with other tests (see Question 3).**
- **Researchers continue to study tumor markers and to develop more accurate methods to detect, diagnose, and monitor cancer (see Question 7).**

1. What are tumor markers?

Tumor markers are substances produced by tumor cells or by other cells of the body in response to cancer or certain benign (noncancerous) conditions. These substances can be found in the blood, in the urine, in the tumor tissue, or in other tissues. Different tumor markers are

found in different types of cancer, and levels of the same tumor marker can be altered in more than one type of cancer. In addition, tumor marker levels are not altered in all people with cancer, especially if the cancer is early stage. Some tumor marker levels can also be altered in patients with noncancerous conditions.

To date, researchers have identified more than a dozen substances that seem to be expressed abnormally when some types of cancer are present. Some of these substances are also found in other conditions and diseases. Scientists have not found markers for every type of cancer.

2. **What are risk markers?**

Some people have a greater chance of developing certain types of cancer because of a change, known as a mutation or alteration, in specific genes. The presence of such a change is sometimes called a risk marker. Tests for risk markers can help the doctor to estimate a person's chance of developing a certain cancer. Risk markers can indicate that cancer is more likely to occur, whereas tumor markers can indicate the presence of cancer[1].

3. **How are tumor markers used in cancer care?**

Tumor markers are used in the detection, diagnosis, and management of some types of cancer. Although an abnormal tumor marker level may suggest cancer, this alone is usually not enough to diagnose cancer. Therefore, measurements of tumor markers are usually combined with other tests, such as a biopsy, to diagnose cancer.

Tumor marker levels may be measured before treatment to help doctors plan appropriate therapy. In some types of cancer, tumor marker levels reflect the stage (extent) of the disease. (More information about staging is available in the National Cancer Institute (NCI) fact sheet *Staging: Questions and Answers*, which can be found at http://www.cancer.gov/cancertopics/factsheet/Detection/staging on the Internet.)

Tumor marker levels also may be used to check how a patient is responding to treatment. A decrease or return to a normal level may indicate that the cancer is responding to therapy, whereas an increase may indicate that the cancer is not responding. After treatment has ended, tumor marker levels may be used to check for recurrence (cancer that has returned).

4. **How and when are tumor markers measured?**

The doctor takes a blood, urine, or tissue sample and sends it to the laboratory, where various methods are used to measure the level of the tumor marker.

If the tumor marker is being used to determine whether a treatment is working or if there is recurrence, the tumor marker levels are often measured over a period of time to see if the levels are increasing or decreasing. Usually these "serial measurements" are more meaningful than a single measurement. Tumor marker levels may be checked at the time of diagnosis; before, during, and after therapy; and then periodically to monitor for recurrence.

5. **Does the NCI have guidelines for the use of tumor markers?**

No, the NCI does not have such guidelines. However, some organizations do have these guidelines for some types of cancer.

The American Society of Clinical Oncology (ASCO), a nonprofit organization that represents more than 21,500 cancer professionals worldwide, has published clinical practice guidelines on a variety of topics, including tumor markers for breast and colorectal cancer. These guidelines, called Patient Guides, are available on the ASCO Web site at http://www.plwc.org/plwc/MainConstructor/1,1744,_12-001125-00_14-00Patient+Guides-00_21-008,00.asp on the Internet.

The National Comprehensive Cancer Network® (NCCN), which is also a nonprofit organization, is an alliance of cancer centers. The NCCN provides Patient Guidelines, which include tumor marker information for several types of cancer. Most of the guidelines are available in English and Spanish versions. The Patient Guidelines are on the NCCN's Web site at http://www.nccn.org/patients/patient_gls.asp on the Internet.

The National Academy of Clinical Biochemistry (NACB) is a professional organization dedicated to advancing the science and practice of clinical laboratory medicine through research, education, and professional development. The Academy publishes *Practice Guidelines and Recommendations for Use of Tumor Markers in the Clinic*, which focuses on the appropriate use of tumor markers for specific cancers. More information can be found on the NACB Web site at http://www.nacb.org on the Internet.

6. **Can tumor markers be used as a screening test for cancer?**

Screening tests are a way of detecting cancer early, before there are any symptoms. For a screening test to be helpful, it should have high sensitivity and specificity. Sensitivity refers to the test's ability to identify people who have the disease. Specificity refers to the test's ability to identify people who do not have the disease. Most tumor markers are not sensitive or specific enough to be used for cancer screening.

Even commonly used tests may not be completely sensitive or specific. For example, prostate-specific antigen (PSA) levels are often used to screen men for prostate cancer, but this is controversial. It is not yet known if early detection using PSA screening actually saves lives. Elevated PSA levels can be caused by prostate cancer or benign conditions, and most men with elevated PSA levels turn out not to have prostate cancer. Moreover, it is not clear if the benefits of PSA screening outweigh the risks of follow-up diagnostic tests and cancer treatments. (More information about PSA screening is available in the NCI fact sheet *The Prostate-Specific Antigen (PSA) Test: Questions and Answers*, which can be found at http://www.cancer.gov/cancertopics/factsheet/Detection/PSA on the Internet.)

Another tumor marker, CA 125, is sometimes used to screen women who have an increased risk for ovarian cancer. Scientists are studying whether measurement of CA 125, along with other tests and exams, is useful to find ovarian cancer before symptoms develop. So far, CA 125 measurement is not sensitive or specific enough to be used to screen all women for ovarian cancer. Mostly, CA 125 is used to monitor response to treatment and check for recurrence in women with ovarian cancer.

7. **What research is being done in this field?**

Scientists continue to study tumor markers and their possible role in the early detection and diagnosis of cancer. The NCI is currently conducting the Prostate, Lung, Colorectal, and Ovarian Cancer screening trial, or PLCO trial, to determine if certain screening tests reduce the number of deaths from these cancers. Along with other screening tools, PLCO researchers are

studying the use of PSA to screen for prostate cancer and CA 125 to screen for ovarian cancer. Final results from this study are expected in several years.

Cancer researchers are turning to proteomics (the study of protein shape, function, and patterns of expression) in hopes of developing better cancer screening and treatment options. Proteomics technology is being used to search for proteins that may serve as markers of disease in its early stages, or predict the effectiveness of treatment or the chance of the disease returning after treatment has ended. More information about proteomics can be found in *Questions and Answers: Proteomics and Cancer*, which is available at http://www.cancer.gov/newscenter/pressreleases/proteomicsQandA on the Internet.

Scientists are also evaluating patterns of gene expression (the step required to translate what is in the genes to proteins) for their ability to predict a patient's prognosis (likely outcome or course of disease) or response to therapy. NCI's Early Detection Research Network is developing a number of genomic- and proteomic-based biomarkers, some of which are being validated. More information about this program can be found at http://www3.cancer.gov/prevention/cbrg/edrn/ on the Internet.

Bladder Cancer Treatment

Note: Estimated new cases and deaths from bladder cancer in the United States in 2006:

- **New cases: 61,420.**
- **Deaths: 13,060.**

Approximately 70% to 80% of patients with newly diagnosed bladder cancer will present with superficial bladder tumors (i.e., stage Ta, Tis, or T1). Those who do present with superficial, noninvasive bladder cancer can often be cured, and those with deeply invasive disease can sometimes be cured by surgery, radiation therapy, or a combination of modalities that include chemotherapy. Studies have demonstrated that some patients with distant metastases have achieved long-term complete response following treatment with combination chemotherapy regimens. There are clinical trials suitable for patients with all stages of bladder cancer; whenever possible, patients should be included in clinical trials designed to improve on standard therapy.

The major prognostic factors in carcinoma of the bladder are the depth of invasion into the bladder wall and the degree of differentiation of the tumor. Most superficial tumors are well differentiated. Patients in whom superficial tumors are less differentiated, large, multiple, or associated with carcinoma in situ (Tis) in other areas of the bladder mucosa are at greatest risk for recurrence and the development of invasive cancer. Such patients may be considered to have the entire urothelial surface at risk for the development of cancer. Tis may exist for variable durations. Adverse prognostic features associated with a greater risk of disease progression include the presence of multiple aneuploid cell lines, nuclear p53 overexpression, and expression of the Lewis-x blood group antigen. Patients with Tis who have a complete response to bacillus Calmette-Guérin have approximately a 20% risk of disease progression at 5 years; patients with incomplete response have approximately a 95% risk of disease progression. Several treatment methods (i.e., transurethral surgery, intravesical medications, and cystectomy) have been used in the management of patients with superficial tumors, and each method can be associated with 5-year survival in 55% to 80% of patients treated.

Invasive tumors that are confined to the bladder muscle on pathologic staging after radical cystectomy are associated with approximately a 75% 5-year progression-free survival rate. Patients with more deeply invasive tumors, which are also usually less well differentiated, and those with lymphovascular invasion experience 5-year survival rates of 30% to 50% following radical cystectomy. When the patient presents with locally extensive tumor that invades pelvic viscera or with metastases to lymph nodes or distant sites, 5-year survival is uncommon, but considerable symptomatic palliation can still be achieved.

Expression of the tumor suppressor gene p53 also has been associated with an adverse prognosis for patients with invasive bladder cancer. A retrospective study of 243 patients treated by radical cystectomy found that the presence of nuclear p53 was an independent predictor for recurrence among patients with stage T1, T2, or T3 tumors. Another retrospective study showed p53 expression to be of prognostic value when considered with stage or labeling index.

Treatment

Treatment for bladder cancer depends on the stage of the disease, the type of cancer, and the patient's age and overall health. Options include surgery, chemotherapy, radiation, and immunotherapy. In some cases, treatments are combined (e.g., surgery or radiation and chemotherapy, preoperative radiation).

Surgery

The type of surgery depends on the stage of the disease. In early bladder cancer, the tumor may be removed (resected) using instruments inserted through the urethra (**transurethral resection**).

Bladder cancer that has spread to surrounding tissue (e.g., Stage T2 tumors, Stage T3a tumors) usually requires **partial** or **radical** removal of the bladder (cystectomy). Radical cystectomy also involves the removal of nearby lymph nodes and may require a urostomy (opening in the abdomen created for the discharge of urine). **Complications** include infection, urinary stones, and urine blockages. Newer surgical methods may eliminate the need for an external urinary appliance.

In men, the standard surgical procedure is a cystoprostatectomy (removal of the bladder and prostate) with pelvic lymphadenectomy (removal of the lymph nodes within the hip cavity). The seminal vesicles (semen-conducting tubes) also may be removed. In some cases, this can be performed in a manner that preserves sexual function.

In women with T2 to T3a tumors, the standard surgical procedure is radical cystectomy (removal of the bladder and surrounding organs) with pelvic lymphadenectomy. Radical cystectomy in women also involves removal of the uterus (womb), ovaries, fallopian tubes, anterior vaginal wall (front of the birth canal), and urethra (tube that carries urine from the bladder out of the body).

Segmental cystectomy (partial removal of the bladder), which is a bladder-preserving procedure, may be used in some cases (e.g., patients with squamous cell carcinomas or adenocarcinomas that arise high in the bladder dome). When segmental cystectomy is performed, it may be preceded by radiation therapy.

Urinary Tract Diversion

Until recently, most bladder cancer patients who underwent cystectomy (bladder removal) required an ostomy (surgical creation of an artificial opening) and an external bag to collect urine. Newer reconstructive surgical methods include the continent urinary reservoir, the neobladder, and the ileal conduit.

The **continent urinary reservoir** is a urinary diversion technique that involves using a piece of the colon (large intestine) to form an internal pouch to store urine. The pouch is specially refashioned to prevent back-up of urine into the ureters (tubes that carry urine out of the kidneys and into the bladder) and kidneys. The patient drains the pouch with a catheter several times a day, and the stoma site is easily concealed by a band aid.

The **neobladder** procedure involves suturing a similar intestinal pouch to the urethra so the patient is able to urinate as before, without the need for a stoma. In many cases, there is no sensation to void, but some patients experience abdominal cramping as the neobladder fills.

Complications of the continent urinary reservoir and neobladder include bowel (intestine) obstruction, blood clots, pneumonia (lung inflammation), ureteral reflux (back-flow), and ureteral blockage.

The **ileal conduit** is a urinary channel that is surgically created from a small piece of the patient's bowel. During this procedure, the ureters are attached to one end of the bowel segment and the other end is brought out of the surface of the body to make a stoma. An external, urine-collecting bag is attached to the stoma and is worn at all times.

Complications of the ileal conduit procedure include bowel obstruction, urinary tract infection (UTI), blood clots, pneumonia, upper urinary tract damage, and skin breakdown around the stoma.

Chemotherapy
Chemotherapy is a systemic treatment (i.e., affects the entiry body) that uses drugs to destroy cancer cells. It is administered orally or intravenously (through a vein) and in early bladder cancer, may be infused into the bladder through the urethra (called **intravesical** chemotherapy). Chemotherapy also may be administered before surgery (neoadjuvant therapy) or after surgery (adjuvant therapy).

Drugs commonly used to treat bladder cancer include valrubicin (Valstar®), thiotepa (Thioplex®), mitomycin, and doxorubicin (Rubex®). **Side effects** can be severe and include the following:

- Abdominal pain
- Anemia
- Bladder irritation
- Blurred vision
- Excessive bleeding or bruising
- Fatigue
- Headache
- Infection
- Loss of appetite
- Nausea and vomiting
- Weakness

Radiation
Radiation uses high-energy x-rays to destroy cancer cells. External beam radiation is emitted from a machine outside the body and internal radiation is emitted from radioactive "seeds" implanted into the tumor. Either type of radiation therapy may be used after surgery to destroy cancer cells that may remain. Radiation therapy is also used to relieve symptoms (called palliative treatment) of advanced bladder.

Side effects include inflammation of the rectum (proctitis), incontinence, skin irritation, hematuria, fibrosis (buildup of fibrous tissue), and impotence (erectile dysfunction).

Immunotherapy
Immunotherapy, also called biological therapy, may be used in some cases of superficial bladder cancer. This treatment is used to enhance the immune system's ability to fight disease. A vaccine derived from the bacteria that causes tuberculosis (BCG) is infused through the urethra into the bladder, once a week for 6 weeks to stimulate the immune system to destroy cancer cells. Sometimes BCG is used with interferon.

Side effects include inflammation of the bladder (cystitis), inflammation of the prostate (prostatitis), and flu-like symptoms. High fever (over 101.5°F) may indicate that the bacteria have entered the bloodstream (called bacteremia). This condition is life threatening and requires antibiotic treatment. Immunotherapy is not used in patients with gross hematuria.

Photodynamic therapy is a new treatment for early bladder cancer. It involves administering drugs to make cancer cells more sensitive to light and then shining a special light onto the bladder. This treatment is being studied in clinical trials.

Follow-Up
Bladder cancer has a high rate of recurrence. Urine cytology and cystoscopy are performed every 3 months for 2 years, every 6 months for the next 2 years, and then yearly.

Breast Cancer

Evaluation of Breast Symptoms

Breast symptoms may suggest a diagnosis of breast cancer. During a 10-year period, 16% of 2,400 women aged 40 to 69 years sought medical attention for breast symptoms at their health maintenance organization. Women younger than 50 years were twice as likely to seek evaluation. Additional examinations were performed in 66% of patients, with 27% undergoing invasive procedures. Cancer was diagnosed in 6.2% of patients with breast symptoms, most being stage II or III. Of the breast symptoms prompting medical attention, a mass was most likely to lead to a cancer diagnosis (10.7%) and pain was least likely (1.8%).

Pathologic Diagnosis of Breast Cancer

Breast cancer is diagnosed by pathologic review of a fixed specimen of breast tissue. The breast tissue can be obtained from a symptomatic area or from an area identified by a screening test, usually mammography. A palpable lesion can be excised surgically or biopsied with fine-needle aspirate or

core needle biopsy (CNBx). Nonpalpable lesions can be excised by surgical needle localization under x-ray guidance (SNLBx). Alternatively, a CNBx of a mammographically suspicious area can be obtained with use of stereotactic x-ray or ultrasound. In a retrospective study of 939 patients with 1,042 mammographically detected lesions who underwent CNBx or SNLBx, sensitivity for malignancy was greater than 95% and the specificity was greater than 90%. Compared with SNLBx, CNBx resulted in fewer surgical procedures for definitive treatment, with a higher likelihood of clear surgical margins at the initial excision.

Fine-needle aspiration, nipple aspiration, and ductal lavage are 3 methods of obtaining cells from breast tissue or ductal epithelium for cytological examination (Tissue Sampling [Fine-Needle Aspiration, Nipple Aspirate, Ductal Lavage]).

None of these technologies has been tested in controlled trials of screening or compared with other breast cancer screening modalities.

Ductal Carcinoma In Situ

Ductal carcinoma in situ (DCIS) is a noninvasive condition that can progress to invasive cancer, with variable frequency and time course. While some authors include DCIS with invasive breast cancer statistics, it has been suggested that the term DCIS be replaced by a classification system of ductal intraepithelial neoplasia (DIN), similar to those used to grade cervical and prostate precursor lesions. DCIS is usually diagnosed by mammography, so it is rare in unscreened women. In the United States in 1983, the pre-screening era, 4,900 women were diagnosed with DCIS, compared with 61,980 that will be diagnosed in 2006.

The natural history of untreated DCIS is poorly understood because women diagnosed with DCIS undergo surgery, with or without radiation and hormone therapy. According to data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute on women with newly diagnosed DCIS treated between 1984 and 1989, 1.9% died of breast cancer within 10 years of diagnosis. Development of breast cancer after treatment of DCIS varies according to treatment. One large randomized trial found that 13.4% of women treated by lumpectomy alone developed ipsilateral invasive breast cancer by 90 months, compared with 3.9% of those treated by lumpectomy and radiation. Another series of 706 DCIS patients, however, allowed definition of the University of Southern California/Van Nuys Prognostic Scoring Index, which defines the risk of recurrence based on age, margin width, tumor size, and grade. The low-risk group, comprising a third of the cases, experienced few DCIS recurrences (1%) and no invasive cancers, regardless of whether radiation was given. The moderate- and high-risk groups had higher recurrences rates, with a beneficial preventive effect of radiation. Nonetheless, only approximately 1% had death from breast cancer. The addition of tamoxifen also reduces the incidence of invasive breast cancer after excision of DCIS. Because all these studies include excision of mammographically detected DCIS, the natural history of this condition remains unknown.

Some information about the natural history of untreated, palpable DCIS is available. A retrospective review of 11,760 biopsies performed between 1952 and 1968 identified 28 cases of untreated DCIS (noncomedo type). All were found by clinical examination, underwent biopsy only, and were followed for 30 years. Nine women (32%) developed invasive breast cancer in the area of previous DCIS. Of these, 7 cancers were diagnosed within 10 years of DCIS biopsy, and 2 were diagnosed between 10 and 30 years after biopsy. Many of the cancers were diagnosed at advanced stages, possibly because of the false reassurance of the previous “negative” biopsy. None of the women with invasive cancer

received adjuvant systemic therapy. Four eventually died of the disease. These findings have been used as an argument both for and against aggressive diagnosis and treatment of DCIS.

Many DCIS cases will not progress to invasive cancer, and those that do are likely to be managed successfully at the time of progression. Thus, treatment of all screen-detected DCIS with surgery, radiation, and/or hormone therapy represents overdiagnosis and overtreatment for many. The Canadian National Breast Screening Study-2 of women aged 50 to 59 years found a 4-fold increase in DCIS cases in women screened by clinical breast examination plus mammography compared with those screened by clinical breast examination alone, with no difference in breast cancer mortality.

Screening by Mammography

Statement of Benefit

Based on fair evidence, screening mammography in women aged 40 to 70 years decreases breast cancer mortality. The benefit is higher for older women, in part because their breast cancer risk is higher.

Description of the Evidence

- Study Design**: Meta-analysis of individual data from 4 randomized controlled trials (RCTs) and 3 additional RCTs.**
- Internal Validity**: Validity of RCTs varies from poor to good. Internal validity of meta-analysis is good.**
- Consistency**: Fair.**
- Magnitude of Effects on Health Outcomes**: Relative breast cancer–specific mortality is decreased by 15% for follow-up analysis and 20% for evaluation analysis. Absolute benefit is approximately 1% overall but depends on inherent breast cancer risk, which rises with age.**
- External Validity: **Good.**

Statement of Harms

Based on solid evidence, screening mammography may lead to the following harms:

Harms of Screening Mammography Harm	Study Design	Internal Validity	Consistency	Magnitude of Effects	External Validity
Treatment of insignificant cancers (overdiagnosis, true positives) can result in breast deformity, lymphedema, thromboembolic events, new cancers, or chemotherapy-induced toxicities.	**Descriptive population-based, autopsy series, and series of mammary reduction specimens**	**Good**	**Good**	**Approximately 20% to 50% of breast cancers detected by screening mammograms represent overdiagnosis.**	**Good**

Harms of Screening Mammography Harm	Study Design	Internal Validity	Consistency	Magnitude of Effects	External Validity
Additional testing (false positives)	**Descriptive population-based**	**Good**	**Good**	**Estimated to occur in 50% of women screened annually for 10 years, 25% of whom will have biopsies.**	**Good**
False sense of security, delay in cancer diagnosis (false negatives)	**Descriptive population-based**	**Good**	**Good**	**6% to 46% of women with invasive cancer will have negative mammograms, especially if young, with dense breasts, or with mucinous, lobular, or fast-growing cancers.**	**Good**
Radiation-induced mutations can cause breast cancer, especially if exposed before age 30 years. Latency is more than 10 years, and the increased risk persists lifelong.	**Descriptive population-based**	**Good**	**Good**	**Between 9.9 and 32 breast cancers per 10,000 women exposed to a cumulative dose of 1 Sv. Risk is higher for younger women.**	**Good**

Screening by Clinical Breast Examination

Statement of Benefits

Based on fair evidence, screening by clinical breast examination reduces breast cancer mortality.

Description of the Evidence

- Study Design**: RCT, with inference.**
- Internal Validity**: Good.**
- Consistency**: Poor.**
- Magnitude of Effects on Health Outcomes**: Breast cancer mortality was the same for women aged 50 to 59 years undergoing screening clinical breast examinations with or without mammograms.**
- External Validity**: Poor.**

Statement of Harms

Based on solid evidence, screening by clinical breast examination may lead to the following harms:

Harms of Screening Clinical Breast Examination **Enlarge** Harms	Study Design	Internal Validity	Consistency	Magnitude of Effects	External Validity
Additional testing (false positives)	**Descriptive population-based**	**Good**	**Good**	**Specificity in women aged 50 to 59 years ranged between 88% and 96%.**	**Good**
False reassurance, delay in cancer diagnosis (false negatives)	**Descriptive population-based**	**Good**	**Fair**	**Of women with cancer, 17% to 43% had a negative clinical breast examination.**	**Poor**

Screening by Breast Self-Examination

Statement of Benefit

Based on fair evidence, teaching breast self-examination does not reduce breast cancer mortality.

Description of the Evidence

- Study Design**: One RCT, case-control trials, and cohort evidence.**
- Internal Validity**: Good.**
- Consistency**: Fair.**
- Magnitude of Effects on Health Outcomes**: No difference in breast cancer mortality was seen after 10 years in Shanghai factory workers randomized to receive breast self-examination instruction and reinforcement, compared with the control group. Forty percent of the women enrolled, however, were younger than 40 years.**
- External Validity**: Poor.**

Statement of Harms

Based on solid evidence, formal instruction and encouragement to perform breast self-examination leads to more breast biopsies and to the diagnosis of more benign breast lesions.

Description of the Evidence

- Study Design**: One RCT.**
- Internal Validity**: Good.**
- Consistency**: Fair.**

- Magnitude of Effects on Health Outcomes**: Biopsy rate is 1.8% among study population, compared with 1.0% among the control group.**
- External Validity**: Poor.**

Colon Cancer

Estimated new cases and deaths from colon cancer in the United States in 2006:

- New cases: 106,680.
- Deaths (colon and rectal cancers combined): 55,170.

Cancer of the colon is a highly treatable and often curable disease when localized to the bowel. Surgery is the primary form of treatment and results in cure in approximately 50% of patients. Recurrence following surgery is a major problem and is often the ultimate cause of death.

Prognostic factors

The prognosis of patients with colon cancer is clearly related to the degree of penetration of the tumor through the bowel wall, the presence or absence of nodal involvement, and the presence or absence of distant metastases. These 3 characteristics form the basis for all staging systems developed for this disease. Bowel obstruction and bowel perforation are indicators of poor prognosis. Elevated pretreatment serum levels of carcinoembryonic antigen (CEA) have a negative prognostic significance. The American Joint Committee on Cancer and a National Cancer Institute-sponsored panel recommended that at least 12 lymph nodes be examined in patients with colon and rectal cancer to confirm the absence of nodal involvement by tumor. This recommendation takes into consideration that the number of lymph nodes examined is a reflection of the aggressiveness of lymphovascular mesenteric dissection at the time of surgical resection and the pathologic identification of nodes in the specimen. Retrospective studies demonstrated that the number of lymph nodes examined in colon and rectal surgery may be associated with patient outcome.

Many other prognostic markers have been evaluated retrospectively for patients with colon cancer, though most, including allelic loss of chromosome 18q or thymidylate synthase expression, have not been prospectively validated. Microsatellite instability, also associated with hereditary nonpolyposis colon cancer (HNPCC), has been associated with improved survival independent of tumor stage in a population-based series of 607 patients younger than 50 years with colorectal cancer. Treatment decisions depend on factors such as physician and patient preferences and the stage of the disease rather than the age of the patient. Racial differences in overall survival after adjuvant therapy have been observed, without differences in disease-free survival, suggesting that comorbid conditions play a role in survival outcome in different patient populations.

Risk factors

Because of the frequency of the disease, ability to identify high-risk groups, demonstrated slow growth of primary lesions, better survival of patients with early-stage lesions, and relative simplicity and

accuracy of screening tests, screening for colon cancer should be a part of routine care for all adults starting at age 50 years, especially for those with first-degree relatives with colorectal cancer. Groups that have a high incidence of colorectal cancer include those with hereditary conditions, such as familial polyposis, HNPCC or Lynch syndrome variants I and II, and those with a personal history of ulcerative colitis or Crohn's colitis. Together, they account for 10% to 15% of colorectal cancers.

Patients with HNPCC reportedly have better prognoses in stage-stratified survival analysis than patients with sporadic colorectal cancer, but the retrospective nature of the studies and possibility of selection factors make this observation difficult to interpret. More common conditions with an increased risk include a personal history of colorectal cancer or adenomas; first-degree family history of colorectal cancer or adenomas; and a personal history of ovarian, endometrial, or breast cancer. These high-risk groups account for only 23% of all colorectal cancers. Limiting screening or early cancer detection to only these high-risk groups would miss the majority of colorectal cancers.

Follow-up

Following treatment of colon cancer, periodic evaluations may lead to the earlier identification and management of recurrent disease. The impact of such monitoring on overall mortality of patients with recurrent colon cancer, however, is limited by the relatively small proportion of patients in whom localized, potentially curable metastases are found. To date, no large-scale randomized trials have documented the efficacy of a standard, postoperative monitoring program. CEA is a serum glycoprotein frequently used in the management of patients with colon cancer. A review of the use of this tumor marker suggests the following:

- A CEA level is not a valuable screening test for colorectal cancer because of the large numbers of false-positive and false-negative reports.
- Postoperative CEA testing should be restricted to patients who would be candidates for resection of liver or lung metastases.
- Routine use of CEA levels alone for monitoring response to treatment should not be recommended.

The optimal regimen and frequency of follow-up examinations are not well defined, however, because the impact on patient survival is not clear and the quality of data is poor. New surveillance methods, including CEA immunoscintigraphy and positron emission tomography are under clinical evaluation.

Treatment

Cancer of the rectum is a highly treatable and often curable disease when localized. Surgery is the primary treatment and results in cure in approximately 45% of all patients. The prognosis of rectal cancer is clearly related to the degree of penetration of the tumor through the bowel wall and the presence or absence of nodal involvement. These 2 characteristics form the basis for all staging systems developed for this disease. Preoperative staging procedures include digital rectal examination, computed tomographic scan or magnetic resonance imaging scan of the abdomen and pelvis, endoscopic evaluation with biopsy, and endoscopic ultrasound (EUS). EUS is an accurate method of evaluating tumor stage (up to 95% accuracy) and the status of the perirectal nodes (up to 74% accuracy). Accurate staging can influence therapy by helping to determine which patients may be

candidates for local excision rather than more extensive surgery and which patients may be candidates for preoperative chemotherapy and radiation therapy to maximize the likelihood of resection with clear margins.

The American Joint Committee on Cancer and a National Cancer Institute-sponsored panel recommended that at least 12 lymph nodes be examined in patients with colon and rectal cancer to confirm the absence of nodal involvement by tumor. This recommendation takes into consideration that the number of lymph nodes examined is a reflection of both the aggressiveness of lymphovascular mesenteric dissection at the time of surgical resection and the pathologic identification of nodes in the specimen. Retrospective studies demonstrated that the number of lymph nodes examined in colon and rectal surgery may be associated with patient outcome. Many other prognostic markers have been evaluated retrospectively in the prognosis of patients with rectal cancer, though most, including allelic loss of chromosome 18q or thymidylate synthase expression, have not been prospectively validated.

Microsatellite instability, also associated with hereditary nonpolyposis rectal cancer, has been shown to be associated with improved survival independent of tumor stage in a population-based series of 607 patients less than 50 years of age with colorectal cancer. Racial differences in overall survival after adjuvant therapy have been observed, without differences in disease-free survival, suggesting that comorbid conditions play a role in survival outcome in different patient populations. A major limitation of surgery is the inability to obtain wide radial margins because of the presence of the bony pelvis. In those patients with disease penetration through the bowel wall and/or spread into lymph nodes at the time of diagnosis, local recurrence following surgery is a major problem and often ultimately results in death. The radial margin of resection of rectal primaries may also predict for local recurrence.

Because of the frequency of the disease, the demonstrated slow growth of primary lesions, the better survival of patients with early-stage lesions, and the relative simplicity and accuracy of screening tests, screening for rectal cancer should be a part of routine care for all adults over the age of 50 years, especially those with first-degree relatives with colorectal cancer. There are groups that have a high incidence of colorectal cancer. These groups include those with hereditary conditions, such as familial polyposis, hereditary nonpolyposis colon cancer (HNPCC) or Lynch Syndrome Variants I and II, and those with a personal history of ulcerative colitis or Crohn's colitis. Together they account for 10% to 15% of colorectal cancers.

As mentioned above “Patients with HNPCC reportedly have better prognoses in stage-stratified survival analysis than patients with sporadic colorectal cancer, but the retrospective nature of the studies and the possibility of selection factors make this observation difficult to interpret. More common conditions with an increased risk include: a personal history of colorectal cancer or adenomas, first degree family history of colorectal cancer or adenomas, and a personal history of ovarian, endometrial, or breast cancer. These high-risk groups account for only 23% of all colorectal cancers. Limiting screening or early cancer detection to only these high-risk groups would miss the majority of colorectal cancers. Following treatment of rectal cancer, periodic evaluations may lead to the earlier identification and management of recurrent disease.”

However, the impact of such monitoring on overall mortality of patients with recurrent rectal cancer is limited by the relatively small proportion of patients in whom localized, potentially curable metastases are found. To date, there have been no large-scale randomized trials documenting the efficacy of a standard, postoperative monitoring program. Carcinoembryonic antigen (CEA) is a serum glycoprotein frequently used in the management of patients with rectal cancer. A review of the use of this tumor marker suggests: that CEA is not useful as a screening test; that postoperative CEA testing be restricted

to patients who would be candidates for resection of liver or lung metastases; and that routine use of CEA alone for monitoring response to treatment not be recommended. However, the optimal regimen and frequency of follow-up examinations are not well defined, since the impact on patient survival is not clear and the quality of data is poor. New surveillance methods including CEA immunoscintigraphy and positron tomography are under clinical evaluation.

Although a large number of studies have evaluated various clinical, pathological, and molecular parameters with prognosis, as yet, none have had a major impact on prognosis or therapy. Clinical stage remains the most important prognostic indicator. Gastrointestinal stromal tumors can occur in the rectum.

Adjuvant therapy

Patients with stage II or stage III rectal cancer are at high risk for local and systemic relapse. Adjuvant therapy should address both problems. Most trials of preoperative or postoperative radiation therapy alone have shown a decrease in the local recurrence rate but no definite effect on survival; although a Swedish trial has shown a survival advantage from preoperative radiation therapy compared to surgery alone. Two trials have confirmed that fluorouracil (5-FU) plus radiation therapy is effective and may be considered standard treatment.

In these trials, combined modality adjuvant treatment with radiation therapy and chemotherapy following surgery also resulted in local failure rates lower than with either radiation therapy or chemotherapy alone. An analysis of patients treated with postoperative chemotherapy and radiation therapy suggests that these patients may have more chronic bowel dysfunction compared to those who undergo surgical resection alone. Improved radiation planning and techniques can be used to minimize treatment-related complications. These techniques include the use of multiple pelvic fields, prone positioning, customized bowel immobilization molds (belly boards), bladder distention, visualization of the small bowel with oral contrast, and the incorporation of three-dimensional or comparative treatment planning. Ongoing clinical trials comparing preoperative and postoperative adjuvant chemoradiotherapy should further clarify the impact of either approach on bowel function and other important quality-of-life issues (e.g., sphincter preservation) in addition to the more conventional endpoints of disease-free and overall survival.

Advanced disease

Radiation therapy in rectal cancer is palliative in most situations but may have greater impact when used perioperatively. Palliation may be achieved in approximately 10% to 20% of patients with 5-FU. Several studies suggest an advantage when leucovorin is added to 5-FU in terms of response rate and palliation of symptoms but not always in terms of survival. Irinotecan (CPT-11) has been approved by the US Food and Drug Administration for the treatment of patients whose tumors are refractory to 5-FU. Participation in clinical trials is appropriate. A number of other drugs are undergoing evaluation for the treatment of colon cancer. Oxaliplatin, alone or combined with 5-FU and leucovorin, has also shown activity in 5-FU refractory patients.

Colorectal Cancer: Prevention

Use of Nonsteroidal Anti-Inflammatory Drugs

Based on solid evidence, use of nonsteroidal anti-inflammatory drugs, including piroxicam, sulindac, and aspirin, may prevent adenoma formation or cause adenomatous polyps to regress in individuals with prior colorectal cancer or adenomatous polyps and in the setting of familial adenomatous polyposis.

Description of the Evidence

- Study Design**: Evidence obtained from randomized controlled trials.**
- Internal Validity**: Good.**
- Consistency**: Good.**
- Magnitude of Effects of Health Outcomes**: Small positive.**
- External Validity**: Good.**

Based on solid evidence, harms of nonsteroidal anti-inflammatory drug use include upper gastrointestinal bleeding and serious cardiovascular events such as myocardial infarction, heart failure, and hemorrhagic stroke.

Description of the Evidence

- Study Design**: Evidence obtained from randomized controlled trials.**
- Internal Validity**: Good.**
- Consistency**: Good.**
- Magnitude of Effects on Health Outcomes**: Increased risk, small magnitude.**
- External Validity**: Good.**

Postmenopausal Hormone Use

There is inadequate evidence to determine whether postmenopausal hormone use would decrease the incidence of colorectal cancer.

Description of the Evidence

- Study Design**: Evidence obtained from a randomized controlled trial.**
- Internal Validity**: Fair.**
- Consistency**: One study.**
- Magnitude of Effects on Health Outcomes**: Fair.**
- External Validity**: Fair.**

Based on fair evidence, harms of postmenopausal hormone use include increased risk of endometrial cancer, breast cancer, thromboembolic events, and coronary heart disease.

Description of the Evidence

- Study Design**: Evidence from randomized controlled trials.**
- Internal Validity**: Fair.**
- Consistency**: Fair.**
- Magnitude of Effects on Health Outcomes**: Negative, small.**
- External Validity**: Fair.**

Diet Modification

A Diet Low in Fat and High in Fiber, Fruits, and Vegetables

There is inadequate evidence to suggest that a diet low in fat and high in fiber, fruits, and vegetables decreases the risk of colorectal cancer.

Description of the Evidence

- Study Design**: Evidence obtained from randomized controlled trials.**
- Internal Validity**: N/A.**
- Consistency**: N/A.**
- Magnitude of Effects on Health Outcomes**: N/A.**
- External Validity**: N/A.**

There are no known harms from dietary modification, including reduction of fatty acids and increase in the intake of fiber, fruits, and vegetables.

Description of the Evidence

- Study Design**: Multiple types.**
- Internal Validity**: Good.**
- Consistency**: Good.**
- Magnitude of Effects on Health Outcomes**: None known.**
- External Validity**: Good.**

Polyp Removal

Based on solid evidence, removal of adenomatous polyps reduces the risk of colorectal cancer.

Description of the Evidence

- Study Design**: Evidence obtained from cohort studies.**
- Internal Validity**: Good.**
- Consistency**: N/A.**
- Magnitude of Effects on Health Outcomes**: Good.**

- External Validity**: Good.**

Based on solid evidence, harms of polyp removal include infrequent perforation of the colon during the procedure as well as bleeding and infection following the procedure.

Description of the Evidence

- Study Design**: Evidence obtained from randomized controlled trials and cohort studies.**
- Internal Validity**: Good.**
- Consistency**: Good.**
- Magnitude of Effects on Health Outcomes**: Negative, small.**
- External Validity**: Good.**

Endometrial Cancer

Estimated new cases and deaths from endometrial (uterine corpus) cancer in the United States in 2006:

- **New cases: 41,200.**
- **Deaths: 7,350.**

Cancer of the endometrium is the most common gynecologic malignancy and accounts for 6% of all cancers in women. It is a highly curable tumor. To detect endometrial cancer, a technique that directly samples the endometrial tissue is mandatory. The Pap smear is not reliable as a screening procedure in endometrial cancer, though a retrospective study found a strong correlation between positive cervical cytology and high-risk disease (i.e., high-grade tumor and deep myometrial invasion) as well as an increased risk of nodal disease.

The degree of tumor differentiation has an important impact on the natural history of this disease and on treatment selection. An increased incidence of endometrial cancer has been found in association with prolonged, unopposed estrogen exposure. In contrast, combined estrogen and progesterone therapy prevents the increase in risk of endometrial cancer associated with unopposed estrogen use. In some patients, an antecedent history of complex hyperplasia with atypia can be demonstrated. An increased incidence of endometrial cancer has also been found in association with tamoxifen treatment of breast cancer, perhaps related to the estrogenic effect of tamoxifen on the endometrium. Because of this increase, patients on tamoxifen should have follow-up pelvic examinations and should be examined if there is any abnormal uterine bleeding.

The pattern of spread is partially dependent on the degree of cellular differentiation. Well-differentiated tumors tend to limit their spread to the surface of the endometrium; myometrial extension is less common. In patients with poorly differentiated tumors, myometrial invasion occurs much more frequently. Myometrial invasion is frequently a harbinger of lymph node involvement and distant metastases and is often independent of the degree of differentiation. Metastatic spread occurs in a characteristic pattern. Spread to the pelvic and para-aortic nodes is common. Distant metastases can occur and most commonly involve the lungs, inguinal and supraclavicular nodes, liver, bones, brain, and vagina.

Another factor found to correlate with extrauterine and nodal spread of tumor is involvement of the capillary-lymphatic space on histopathologic examination. Three prognostic groupings of clinical stage I disease become possible by careful operative staging. Patients with grade 1 tumors involving only endometrium and no evidence of intraperitoneal disease (i.e., adnexal spread or positive washings) have a low risk (<5%) of nodal involvement. Patients with grade 2 or 3 tumors and invasion of less than 50% of the myometrium and no intraperitoneal disease have a 5% to 9% incidence of pelvic node involvement and a 4% incidence of positive para-aortic nodes. Patients with deep muscle invasion and high-grade tumors and/or intraperitoneal disease have a significant risk of nodal spread, 20% to 60% to pelvic nodes and 10% to 30% to para-aortic nodes. One study was directed specifically at stage I, grade 1 carcinomas of favorable histologic type. The authors identified 4 statistically significant adverse prognostic factors: myometrial invasion, vascular invasion, 8 or more mitoses per 10 high-power fields, and an absence of progesterone receptors.

Another group identified aneuploidy and a high S-phase fraction as predictive of poor prognosis. A Gynecologic Oncology Group study related surgical-pathologic parameters and postoperative treatment to recurrence-free interval and recurrence site. For patients without extrauterine spread, the greatest determinants of recurrence were grade 3 histology and deep myometrial invasion. In this study, the frequency of recurrence was greatly increased with positive pelvic nodes, adnexal metastasis, positive peritoneal cytology, capillary space involvement, involvement of the isthmus or cervix, and, particularly, positive para-aortic nodes (includes all grades and depth of invasion). Of the cases with aortic node metastases, 98% were in patients with positive pelvic nodes, intra-abdominal metastases, or tumor invasion of the outer 33% of the myometrium.

When the only evidence of extrauterine spread is positive peritoneal cytology, the influence on outcome is unclear. The value of therapy directed at this cytologic finding is not well founded. The preponderance of evidence, however, would suggest that other extrauterine disease must be present before additional postoperative therapy is considered.

One report found progesterone receptor levels to be the single most important prognostic indicator of 3-year survival in clinical stage I and II disease. Patients with progesterone receptor levels >100 had a 3-year disease-free survival of 93% compared with 36% for a level <100. Only cervical involvement and peritoneal cytology were significant prognostic variables after adjusting for progesterone receptor levels. Other reports confirm the importance of hormone receptor status as an independent prognostic factor. Additionally, immunohistochemical staining of paraffin-embedded tissue for both estrogen and progesterone receptors has been shown to correlate with International Federation of Gynecology and Obstetrics grade as well as survival. On the basis of these data, progesterone and estrogen receptors, assessed either by biochemical or immunohistochemical methods, should be included, when possible, in the evaluation of stage I and II patients. Oncogene expression, DNA ploidy, and the fraction of cells in S-phase have also been found to be prognostic indicators of clinical outcome. For example, overexpression of the *Her-2/neu* oncogene has been associated with a poor overall prognosis. A general review of prognostic factors has been published.

Prevention of Endometrial Cancer

Hormone Therapy

Based on solid evidence, giving progestin in combination with estrogen therapy eliminates the excess risk of endometrial cancer associated with unopposed estrogen among postmenopausal women who have a uterus and are taking hormone therapy.

Description of the Evidence

- Study Design**: Evidence obtained from randomized controlled trials, cohort, and case-control studies.**
- Internal Validity**: Good.**
- Consistency**: Good.**
- Magnitude of Effects on Health Outcomes**: For women with a uterus, the risk of endometrial cancer associated with unopposed estrogen use for 5 or more years is more than 10-fold higher compared with women not taking estrogen replacement therapy. The addition of progestin therapy to estrogen eliminates the risk of endometrial cancer. Based on data from the Women's Health Initiative, the hazard ratio for endometrial cancer associated with combined hormone therapy, after an average follow-up of 5.6 years was 0.81 (95% confidence interval, 0.48-1.36) compared with women randomized to placebo.**
- External Validity**: Good.**

Oral Contraceptives

Based on solid evidence, the use of combination oral contraceptives (estrogen plus a progestin) is associated with a decreased risk of developing endometrial cancer.

Description of the Evidence

- Study Design**: Evidence obtained from case-control and prospective studies.**
- Internal Validity**: Good.**
- Consistency**: Good.**
- Magnitude of Effects on Health Outcomes**: Oral contraceptive use is associated with a reduced risk of endometrial cancer ranging from 50% reduction associated with 4 years of use up to 72% reduction in risk with 12 or more years of use.**
- External Validity**: Fair.**

Obesity, Body Mass Index and Endometrial Cancer

There is inadequate evidence to determine if weight reduction alters the incidence of endometrial cancer.

Description of the Evidence

- Study Design**: Evidence obtained from one cohort study.**
- Internal Validity**: Good.**
- Consistency**: N/A**
- Magnitude of Effects on Health Outcomes**: Intentional weight loss of 20 pounds or more was not associated with a statistically significant reduction in the incidence of endometrial cancer.**
- External Validity**: Fair.**

Kidney (Renal Cell) Cancer

General Information

Note: Estimated new cases and deaths from kidney (renal cell and renal pelvis) cancer in the United States in 2006:

- **New cases: 38,890.**
- **Deaths: 12,840.**

Renal cell cancer, also called renal adenocarcinoma, or hypernephroma, can often be cured if it is diagnosed and treated when still localized to the kidney and to immediately surrounding tissue. The probability of cure is directly related to the stage or degree of tumor dissemination. Even when regional lymphatics or blood vessels are involved with tumor, a significant number of patients can achieve prolonged survival and probable cure. When distant metastases are present, disease-free survival is poor; however, occasional selected patients will survive after surgical resection of all known tumor. Because a majority of patients are diagnosed when the tumor is still relatively localized and amenable to surgical removal, approximately 40% of all patients with renal cancer survive 5 years. Occasional patients with locally advanced or metastatic disease may exhibit indolent courses lasting several years. Late tumor recurrence many years after initial treatment occasionally occurs.

Renal cell cancer is one of the few tumors in which well-documented cases of spontaneous tumor regression in the absence of therapy exist, but this occurs very rarely and may not lead to long-term survival. Surgical resection is the mainstay of treatment of this disease.

Even in patients with disseminated tumor, locoregional forms of therapy may play an important role in palliating symptoms of the primary tumor or of ectopic hormone production. Systemic therapy has demonstrated only limited effectiveness.

There is much speculation that renal cancer has its roots in genetics. Here is some information regarding cancer and genetics:

Cancer Genetics—Overview

Knowledge about cancer genetics is rapidly expanding, with implications for all aspects of cancer management, including prevention, screening, and treatment. PDQ cancer genetics summaries provide information on the genetics of specific cancers, inherited cancer syndromes, and the ethical, legal, social, and psychological implications of cancer genetics knowledge. Sections on the genetics of specific cancers include information on the prevalence and characteristics of cancer-predisposing mutations, the risk implications of a family history of cancer, known modifiers of genetic risk, opportunities for genetic testing, outcomes of genetic counseling and testing, and interventions available for people with increased cancer risk resulting from an inherited predisposition.

Significance of the Terms Mutation and Carrier

A mutation is a change in the usual deoxyribonucleic acid (DNA) sequence of a particular gene. Mutations can have harmful, beneficial or neutral effects on health, and may be inherited as autosomal dominant, autosomal recessive, or X-linked traits. Mutations that cause serious disability early in life are usually rare in the population, because of their adverse effect on life expectancy and reproduction. If the mutation is autosomal recessive, that is, if the health effect of the mutation is caused only when 2 copies of the mutation are inherited, carriers (healthy people carrying one copy of the mutation) may be relatively common. The term common, in this context generally refers to a prevalence of 1% or

more. Mutations that cause health effects in middle and old age, including several mutations known to cause a predisposition to cancer, may also be relatively common. Many cancer-predisposing mutations are autosomal dominant, that is, the cancer susceptibility occurs when only one copy of the mutation is inherited. For autosomal dominant conditions, the term carrier is often used in a different way, to denote people who have inherited the genetic predisposition conferred by the mutation. Detailed information on known cancer-predisposing mutations is reviewed in relevant PDQ summaries on genetics of specific cancers.

Assumptions Concerning the Identification of People With an Increased Susceptibility to Cancer

Genetic information, including information from family history and from DNA-based testing, provides a means to identify people who have an increased risk of cancer. Family history often identifies people with a moderately increased risk of cancer, and in some cases may be an indicator of the presence of polymorphisms that influence cancer susceptibility, through such mechanisms as changes in the rate of metabolism of agents that predispose to cancer or catabolism of carcinogens, or effects on DNA repair or regulation of cell division. Less often, family history indicates the presence of an inherited cancer predisposition conferring a relatively high lifetime risk of cancer. In some cases, DNA-based testing can be used to confirm a specific mutation as the cause of the inherited risk, and to determine whether family members have inherited the mutation.

Identifying a person with an increased risk of cancer can reduce the occurrence of cancer through clinical management strategies (e.g., tamoxifen for breast cancer, colonoscopy for colon cancer) or improve that person's health outcome or quality of life through intrinsic benefits of the information itself (e.g., no genetic predisposition).

Intrinsic benefits may include better ability to plan for the future (having children, career, retirement or other decisions) with improved knowledge about cancer risk. Methods of genetic risk assessment include assessment of personal and family history of disease and genetic testing; the latter is generally undertaken only when family history of disease or other clinical characteristics, such as early onset of cancer, indicate a substantial likelihood of an inherited predisposition to cancer.

Genetic testing may also be sought by people affected with cancer, both newly diagnosed individuals and survivors of earlier cancers. Testing may be desired to define personal cancer etiology, to clarify risk to offspring, to define the appropriateness of particular surveillance approaches, or to aid in decision-making about risk-reducing prophylactic surgery. While there are effective interventions specific for some cancer genetic syndromes (e.g., multiple endocrine neoplasia type 2A [MEN 2A], familial adenomatous polyposis [FAP], retinoblastoma [RB]), genetic testing is still being integrated into the management of patients with hereditary forms of common cancers (e.g., breast cancer). Some patients and physicians may wish to include genetic risk status as a factor in consideration of treatment options.

A genetic assessment is likely to aid clinical decision-making only when management is based on genetic information (e.g., when the clinical interventions being considered would be offered to genetically susceptible people but not to those of average risk, or when interventions that are effective in people of average risk are ineffective in those with genetic susceptibility). Intrinsic benefits of genetic information, for example, improvement in quality of life as a result of knowledge about genetic susceptibility, may be accompanied by potential personal and social risks as well (e.g., reduced self-worth; guilt; family disruption; stigmatization; or loss of health, disability, or life insurance). PDQ summaries on cancer genetics include available evidence addressing these points. Genetic information may sometimes provide a direct health benefit by demonstrating the lack of a known inherited cancer susceptibility. For example, if a family is known to carry a cancer-predisposing mutation, a family

member may experience reduced worry and lower health care costs if his/her genetic test indicates that he/she does not carry the mutation. The family member may be able to forego certain medical tests, such as early use of colonoscopy for persons at high risk of a hereditary nonpolyposis colon cancer (*HNPCC*) mutation.

Evaluation of Evidence

Creating evidence-based summaries in cancer genetics is challenging because the rapid evolution of new information often results in evidence that is incomplete or of limited quality. In addition, established methods for evaluating the quality of the evidence are available for some but not all aspects of cancer genetics. Varying levels of evidence are available for different topics, and PDQ summaries are subject to modification as new evidence becomes available. As in other aspects of medicine, testing and treatment decisions must be based on information that sometimes falls short of the optimal level of evidence, i.e., data from randomized trials.

Evidence Related to the Clinical Value of Genetic Tests and Family History Information

In assessing a genetic test (or other method of genetic assessment, including family history), the analytic validity, clinical validity, and clinical utility of the test need to be considered.

Analytic validity

Analytic validity refers to how well the genetic assessment performs in measuring the property or characteristic it is intended to measure. In the case of family history, analytic validity refers to the accuracy of the family history information.

In the case of a test for a specific mutation, analytic validity refers to the accuracy of a genetic test in identifying the presence or absence of the mutation. Analytic validity of a genetic test is affected by the technical accuracy and reliability of the testing procedure, and also by the quality of the laboratory processes (including specimen handling).

The evaluation of analytic validity is complex for some genetic tests. A panel test, for example, tests for the presence of a particular set of mutations (e.g., the known deleterious mutations in the *BRCA1* gene), and the analytic validity of the different components of the test may vary. Some genetic tests involve the evaluation of the DNA sequence of portions of a gene, to determine whether any mutations are present. The sensitivity and specificity of these sequencing tests may vary with the laboratory techniques employed, the proportion of the gene tested, and the structural nature of the mutations present in the gene.

Clinical validity

Clinical validity refers to the predictive value of a test for a given clinical outcome (e.g., the likelihood that cancer will develop in someone with a positive test), and is in large measure determined by the sensitivity and specificity with which a test identifies people with a defined clinical condition. Sensitivity of a test refers to the proportion of persons who test positive from among those with a clinical condition; specificity refers to the proportion of persons who test negative from among those without the clinical condition. In the case of genetic susceptibility to cancer, clinical validity can be thought of at 2 levels: (1) Does a positive test identify a person as having an increased risk of cancer? (2) If so, how high is the cancer risk associated with a positive test? Thus, the clinical validity of a genetic test is the likelihood that cancer will develop in someone with a positive test result. This likelihood is affected not only by the presence of the gene itself, but also by any modifying factors that affect the penetrance of the mutation, for example, the carrier's environment or behaviors (or perhaps by the presence or absence of mutations in other genes). For this reason, the clinical validity of a genetic test for a specific mutation may vary in different populations. If the cancer risk associated with

a given mutation is unknown or variable, a test for the mutation will have uncertain clinical validity. A summary of definitions of concepts relevant to understanding clinical validity and other aspects of cancer genetics testing has been published.

The test should be evaluated in the population in which the test will be used. Evidence that mutations in a particular gene result in a cancer predisposition often derives initially from linkage studies that use samples of families meeting stringent criteria for autosomal dominant inheritance of cancer risk. The demonstration of strong linkage of cancer to a pattern of autosomal dominant inheritance supports a causal molecular mechanism for the inherited cancer predisposition. Once linkage is established, a strong case for an association between the genetic trait and a disease can be made, even though the families used in the study are not representative of the general population. The genetic trait measured in linkage studies is not always the causal function itself, but may instead be a genetic trait closely linked to it. Additional molecular studies are required to identify the specific gene associated with inherited risk, after linkage studies have determined its chromosomal location.

Linkage studies, however, provide only limited evidence concerning either the range of cancer types associated with a mutation or the magnitude of risk and lifetime probability of cancer conferred by a mutation in less selected populations. In addressing these questions, the best information for clinical decisions comes from naturally occurring populations in which people with all degrees of risk are represented, similar to those in which clinical or public health decisions must be made.

Thus, observations about cancer risk in families having multiple members with early breast cancer are applicable only to other families meeting those same clinical criteria. Ideally, the families tested should also have similar exposures to factors that can modify the expression of the gene(s) being studied. The mutation-associated risk in other populations, such as families with less dramatic cancer aggregation, or the general population, can best be assessed by direct study of those populations.

Clinical utility

The clinical utility of the test refers to the likelihood that the test will, by prompting an intervention, result in an improved health outcome. The clinical utility of a genetic test is based on the health benefits of the interventions offered to persons with positive test results. Three strategies are available to improve the health outcome of people with a genetic susceptibility to cancer:

1. screening to detect early cancer or precancerous lesions,
2. interventions to reduce the risk of developing cancer,
3. and interventions to improve quality of life.

Evaluation of interventions should consider their efficacy (capacity to produce an improved health outcome) and effectiveness (likelihood that the improved outcome will occur, taking into account actual use of the intervention and recommended follow-up). Sometimes genetic information may lead to consideration of changes in the approach to clinical management, based on expert opinion, in the absence of proof of clinical utility.

Genetic Counseling

Genetic counseling has been defined by the American Society of Human Genetics as “a communication process which deals with the human problems associated with the occurrence or risk of occurrence of a genetic disorder in a family. The process involves an attempt by one or more appropriately trained persons to help the individual or family to:

1. comprehend the medical facts, including the diagnosis, probable course of the disorder, and the available management;
2. appreciate the way that heredity contributes to the disorder and to the risk of recurrence in specific relatives;
3. understand the alternatives for dealing with the risk of recurrence;
4. choose a course of action which seems to them appropriate in view of their risk, their family goals, and their ethical and religious standards and act in accordance with that decision; and
5. make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder."

Central to genetic counseling philosophy and practice are the principles of voluntary utilization of services, informed decision-making, nondirective and noncoercive counseling when the medical benefits of one course of action are not demonstrably superior to another, attention to psychosocial and affective dimensions of coping with genetic risk, and protection of client confidentiality and privacy.

Genetic counseling generally involves some combination of rapport building and information gathering; establishing or verifying diagnoses; risk assessment and calculation of quantitative occurrence/recurrence risks; education and informed consent processes; and psychosocial assessment, support, and counseling appropriate to a family's culture and ethnicity. Readers interested in the nature and history of genetic counseling are referred to a number of comprehensive reviews.

In the 1990s, genetic counseling expanded to include discussion of genetic testing for cancer risk as more genes associated with inherited cancer risk were discovered. Cancer genetic counseling often involves a multidisciplinary team of health professionals who have expertise in this area. The team may include a genetic counselor, genetic advanced practice nurse, medical geneticist, mental health professional, and medical expert such as oncologist, surgeon, or internist. The process of counseling may require a number of visits in order to address the medical, genetic testing, and psychosocial issues. Even when cancer risk counseling is initiated by an individual, inherited cancer risk has implications for the entire family. Because genetic risk affects biological relatives, contact with these relatives is often essential to collect an accurate family and medical history. Cancer genetic counseling may involve several family members, some of whom may have had cancer and others who have not.

Quality of Evidence

The quality of evidence depends on the appropriateness of the type of study to the question being evaluated and on how well the study is designed and implemented. In evaluating interventions, the strongest evidence is obtained from a well-designed and well-conducted randomized clinical trial. Other questions, particularly those related to the prevalence and clinical validity of genetic information, and emotional and familial outcomes, require well-designed descriptive studies. For some studies, particular elements of study design, such as the nature of the population studied or the duration of observation, may be crucial in assessing the quality of the study.

During early phases of research in a new area, information relevant to the needs of patients and clinicians may come from work at all levels of evidence. These include well-designed quasi-experimental (nonrandomized, controlled single-group, pre/post, cohort, time, or matched case-control series) or nonexperimental studies (case reports, clinical examples, qualitative or narrative studies, or

theoretical work). Such research may yield information important to patients and clinicians who must make decisions before full data are available on the risks and benefits of cancer genetic testing. In addition, such work helps to focus future research using rigorous designs with adequate statistical power.

Evidence cited in PDQ cancer genetics summaries is evaluated in terms of its quality. Where relevant, the level of evidence is cited, as described below, or particular strengths or limitations of the evidence are described.

Study Populations

Studies assessing the clinical validity of genetic information from population-based data are not biased by common selection factors. The level of evidence required for informed decision-making about genetic testing, however, depends on the circumstances of testing. Evidence from a sample of high-risk families may be sufficient to provide useful information for testing decisions among people with similar family histories, but it may be insufficient to inform early recommendations for or decisions about testing in the general public. Even among people with similar family histories, however, other contributing genes or different exposures could modify the effect of the mutation for which testing is done.

In evaluating evidence, the most important consideration is the relevance of the available data to the patient for whom a genetic assessment is being considered. In summaries addressing the cancer risk associated with mutations and polymorphisms, the study populations used for each risk assessment will be noted, according to the following categories.

1. Population-based.
2. Proxy for population-based. (The study population selected is assumed to be generally representative of the population from which it is drawn. Example: Persons participating in a community-based Tay-Sachs screening program, as a proxy for persons of Jewish descent.)
3. Public recruitment of volunteers, e.g., using a newspaper advertisement.
4. Sequential case series.
5. Convenience sample.
6. An affected family or several families.

Evidence Related to Screening

Evidence related to screening is evaluated using the same criteria developed for other PDQ summaries. Refer to the PDQ screening and prevention summaries for more information.

The PDQ Cancer Genetics Editorial Board has adopted the following definitions related to screening:

- Screening is a means of accomplishing early detection of disease in people without symptoms of the disease being sought.

- Detection examinations, tests, or procedures used in screening are usually not diagnostic, but sort out persons suspicious for the presence of cancer from those who are not.

- Diagnosis of disease is made following a work-up, biopsy, or other tests in pursuing symptoms or positive detection procedures.

Five requirements should be met before it is considered appropriate to screen for a medical condition:

1. The medical condition being sought causes a substantial burden of suffering, measured both as mortality and the frequency and severity of morbidity and loss of function.
2. A screening test or procedure exists that will detect cancers earlier in their natural history than diagnosis prompted by symptoms, and is acceptable to patients and society in terms of convenience, comfort, risk, and cost.
3. Strong evidence exists that early detection and treatment improve disease outcomes.
4. The harms of screening are known and acceptable.
5. Screening is judged to do more good than harm, considering all benefits and harms it induces as well as the cost, and cost-effectiveness of the screening program.

In order of strength of evidence, the levels are as follows:

1. Evidence obtained from at least one well-designed and conducted randomized controlled trial.
2. Evidence obtained from well-designed and conducted nonrandomized controlled trials.
3. Evidence obtained from well-designed and conducted cohort or case-control analytic studies, preferably from more than one center or research group.
4. Evidence obtained from multiple-time series with or without intervention.
5. Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Evidence Related to Cancer Prevention

Evidence related to cancer prevention is evaluated using the same criteria developed for other PDQ summaries. Refer to the PDQ screening and prevention summaries for more information.

Prevention is defined as a reduction in the incidence of cancer and, therefore, cancer-related morbidity and mortality. Examples of prevention strategies are a diet high in fiber, fruits and vegetables; regular exercise; smoking cessation; and drugs such as aspirin and folic acid. The strongest evidence is obtained from a well-designed and well-conducted randomized clinical trial with cancer-specific mortality as the endpoint. It is, however, not always practical to conduct such a trial to address every question in the field of cancer prevention. For each summary of evidence statement, the associated levels of evidence are listed. In order of strength of evidence, the levels are as follows:

1. Evidence obtained from at least one well-designed and conducted randomized controlled trial that has:
    1. A cancer mortality endpoint.
    2. A cancer incidence endpoint.

3. A generally accepted intermediate endpoint (e.g., large adenomatous polyps for studies of colorectal cancer prevention; high-grade squamous intraepithelial lesions of the cervix for studies of cervical cancer prevention).

2. Evidence obtained from well-designed and conducted nonrandomized controlled trials that have:

    1. A cancer mortality endpoint.

    2. A cancer incidence endpoint.

    3. A generally accepted intermediate endpoint (e.g., large adenomatous polyps for studies of colorectal cancer prevention; high-grade squamous intraepithelial lesions of the cervix for studies of cervical cancer prevention).

3. Evidence obtained from well-designed and conducted cohort or case-control studies, preferably from more than one center or research group, that have:

    1. A cancer mortality endpoint.

    2. A cancer incidence endpoint.

    3. A generally accepted intermediate endpoint (e.g., large adenomatous polyps for studies of colorectal cancer prevention; high-grade squamous intraepithelial lesions of the cervix for studies of cervical cancer prevention).

4. Ecologic (descriptive) studies (e.g., international patterns studies, migration studies) that have:

    1. A cancer mortality endpoint.

    2. A cancer incidence endpoint.

    3. A generally accepted intermediate endpoint (e.g., large adenomatous polyps for studies of colorectal cancer prevention; high-grade squamous intraepithelial lesions of the cervix for studies of cervical cancer prevention).

5. Opinions of respected authorities based on clinical experience or reports of expert committees (e.g., any of the above study designs using nonvalidated surrogate endpoints).

Kidney Cancer Trial Results

1. Sunitinib and Temsirolimus: Two New Targeted Drugs for Advanced Kidney Cancer (Posted: 06/05/2006) - In separate clinical trials, two new targeted drugs - sunitinib (Sutent®) and temsirolimus - have shown positive results in patients with advanced kidney cancer, offering new standards of care, according to findings presented at the 2006 meeting of the American Society of Clinical Oncology.

2. Regression of Advanced Kidney Cancer Seen with Allogeneic Stem Cell Transplantation (Posted: 09/13/2000, Reviewed: 02/01/2005) - Researchers at the National Institutes of Health (NIH) report that advanced kidney cancer can be completely or partially reversed in some patients with the use of blood stem cell transplants from a healthy sibling donor.

3. Less Chemotherapy Needed for Wilms' Tumor Patients

(Posted: 05/01/1999, Reviewed: 02/01/2005) - People with Wilms' tumor (a cancer of the kidney that most commonly occurs in children) can now receive fewer chemotherapy treatments with fewer side effects, according to a report in the January 1998 issue of the Journal of Clinical Oncology.

Clinical trials are research studies in which people help doctors find ways to improve health and cancer care. Each study tries to answer scientific questions and to find better ways to prevent, diagnose, or treat cancer.

Why are there clinical trials?

A clinical trial is one of the final stages of a long and careful cancer research process. Studies are done with cancer patients to find out whether promising approaches to cancer prevention, diagnosis, and treatment are safe and effective.

What are the different types of clinical trials?

- Treatment trials test new treatments (like a new cancer drug, new approaches to surgery or radiation therapy, new combinations of treatments, or new methods such as gene therapy. Prevention trials test new approaches, such as medicines, vitamins, minerals, or other supplements that doctors believe may lower the risk of a certain type of cancer. These trials look for the best way to prevent cancer in people who have never had cancer or to prevent cancer from coming back or a new cancer occurring in people who have already had cancer.

- Screening trials test the best way to find cancer, especially in its early stages

- Quality of Life trials (also called Supportive Care trials) explore ways to improve comfort and quality of life for cancer patients.

What are the phases of clinical trials?

Most clinical research that involves the testing of a new drug progresses in an orderly series of steps, called phases. This allows researchers to ask and answer questions in a way that results in reliable information about the drug and protects the patients. Clinical trials are usually classified into one of three phases:

- Phase I trials: These first studies in people evaluate how a new drug should be given (by mouth, injected into the blood, or injected into the muscle), how often, and what dose is safe. A phase I trial usually enrolls only a small number of patients, sometimes as few as a dozen.

- Phase II trials: A phase II trial continues to test the safety of the drug, and begins to evaluate how well the new drug works. Phase II studies usually focus on a particular type of cancer.

- Phase III trials: These studies test a new drug, a new combination of drugs, or a new surgical procedure in comparison to the current standard. A participant will usually be assigned to the standard group or the new group at random (called randomization). Phase III trials often enroll large numbers of people and may be conducted at many doctors' offices, clinics, and cancer centers nationwide.

Introduction to NCI\s Clinical Trials

The National Cancer Institute (NCI) spent approximately 800 million dollars in fiscal year 2004 (the latest period for which actual expenditures are available) to fund a vast array of clinical trials designed to test new ways to treat, prevent, detect, or diagnose cancer as well as new methods to improve cancer patients' quality of life. NCI-supported clinical trials take place either intramurally at the National Institutes of Health (NIH) Clinical Center in Bethesda, Maryland, or extramurally at any of the hundreds of academic or private hospitals, cancer centers, or community-based medical practices located in the United States, Puerto Rico, Canada, and Europe that receive NCI funding.

The NCI clinical trials enterprise has grown incrementally over the past several decades. Today, the Institute funnels the majority of its funding dedicated to clinical trials to its extramural partners, which operate at the regional, state, and local levels in order to give the public the widest possible access to clinical studies. The major components of the Institute's extramural clinical research program include

- NCI-designated Cancer Centers and Comprehensive Cancer Centers, which are major academic and research institutions characterized by scientific excellence that sustain broad-based, interdisciplinary programs in cancer research;
- Specialized Programs of Research Excellence (SPOREs), which bring together basic scientists and clinical researchers to design and implement research programs that can improve cancer prevention, detection, diagnosis, and treatment of specific cancer types, including cancers of the breast, prostate, lung, gastrointestinal system, brain, and skin, as well as lymphoma, genitourinary cancer, head and neck cancer, and ovarian cancer;
- Clinical Trials Cooperative Groups, which are networks of research institutions organized according to region or medical specialty that collaborate to conduct large-scale, multisite clinical trials often involving thousands of patients; and
- Community Clinical Oncology Programs, which provide smaller-scale community-based medical facilities and individual physicians with opportunities to participate in clinical trials.

Each of these programs is discussed in greater detail below. Various offices throughout the Institute's major divisions provide administrative support for these programs, which are funded through a variety of mechanisms, including grants that support investigator-initiated basic, translational, or clinical research.

Because NCI's clinical research program is highly decentralized, it can be difficult to capture information that provides a comprehensive overview of the full spectrum of its activities. One of the best publicly accessible sources of up-to-date information about NCI-supported cancer clinical trials is the Physician Data Query (PDQ®) database. The first section of this report is largely based upon information drawn from PDQ and demonstrates how this resource may be used to answer specific questions about NCI-supported trials.

How many NCI-supported trials are now in progress?

There is no simple answer to this question. NCI supports clinical trials through a variety of funding programs, including grants, contracts, and cooperative agreements, and there is no single listing or database containing all NCI-sponsored trials.

One of the most comprehensive databases of cancer clinical trials is NCI's PDQ database, which is accessible through the NCI Web site, www.cancer.gov. PDQ includes most clinical trials sponsored by

NCI. It also includes many cancer trials sponsored by pharmaceutical companies, medical centers, and other groups. PDQ lists both active clinical trials (those currently enrolling patients) and those closed to enrollment but still treating patients and/or collecting data. As of January 2006, PDQ contained approximately 2,932 active cancer clinical trials, of which **1,353 - almost half of the total - were sponsored by NCI**.

Which NCI trials does PDQ include?

PDQ includes all *intramural* trials - those being conducted by NCI researchers at the NIH campus in Bethesda, Maryland. It also contains many *extramural* trials - those sponsored by NCI and taking place at cancer centers, hospitals, and community-based medical practices around the country and other parts of the world.

Of NCI's extramural trials, PDQ includes all that are conducted through the Clinical Trials Cooperative Groups (networks of researchers and institutions with funding from NCI). PDQ also includes many of the trials funded through other kinds of mechanisms, such as grants and contracts, and trials taking place at NCI-designated Cancer Centers. However, because registration of NCI-supported trials is not required, it is not possible to obtain a complete list of extramural trials through PDQ.

The January 2006 listings in PDQ included **183 active intramural clinical trials**. A single figure for the sum total of active extramural trials taking place at any given time cannot be obtained from PDQ. Instead, the database lists categories of clinical trials that have been classified according to their specific scientific review process or funding mechanism(s). In January 2006, categories of extramural trials receiving NCI support included

- 415 Cooperative Group trials,
- 382 NCI-grant-supported trials,
- 29 Specialized Programs of Research Excellence (SPORE) trials, and
- 633 trials initiated by NCI-designated Cancer Centers.

Some clinical trials are funded through more than one administrative mechanism and are therefore included under more than one of the categories listed above. As a result, the sum total of the numbers above for intramural and extramural trials (1,642) exceeds the total number of NCI-sponsored clinical trials in the answer to question 1 (1,353).

How many NCI treatment, prevention, and other kinds of trials are listed in PDQ?

As of January 2006, there were

- 1,160 treatment trials,
- 55 prevention trials,
- 58 diagnostic trials,
- 17 screening trials,
- 20 genetics trials, and
- 116 supportive-care trials.

Some clinical trials can be classified as more than one type. For example, a screening trial might also be classified as a genetics trial if it is evaluating a screening method in patients who are genetically predisposed toward developing a particular type of cancer. As a result, the sum total of the numbers above (1,426) exceeds the total number of NCI-sponsored trials in PDQ (1,353) because some trials may be classified as more than one type.

How many NCI trials are listed in PDQ for the four major types of cancer?

As of January 2006, PDQ listed the following numbers of active NCI-sponsored clinical trials for the four types of cancer with the highest numbers of new cases (incidence) and deaths (mortality) annually:

- 133 for lung cancer (including 95 for non-small cell lung cancer, 33 for small cell lung cancer, and 3 for pulmonary carcinoid tumors),
- 192 for breast cancer (including 152 for female breast cancer and 40 for male breast cancer),
- 90 for prostate cancer, and
- 57 for colon cancer.

Which criteria can be used to search PDQ?

PDQ can be searched on the Internet using either the Basic Search Form or the Advanced Search Form.

The **Basic Search Form** allows people to search for trials using the criteria of cancer type or stage as well as the trial location (ZIP code proximity or NIH campus, Bethesda, Maryland). With the Advanced Search Form, in addition to cancer type and trial location, people can search on the basis of the phase of the trial (phase I, II, III, or IV), the type of treatment or intervention (for example, chemotherapy or vaccine therapy), the drugs being tested, the sponsoring institution, and other criteria. People may also request a customized search of PDQ from NCI's Cancer Information Service by calling 1-800-4-CANCER.

Which NCI trials does PDQ *not* include?

Some NCI-sponsored trials may not appear in PDQ because it is not mandatory for investigators to submit their trials to the database. Trials missing from PDQ include some funded through NCI grants or contracts and some taking place at NCI-designated Cancer Centers.

Are there other databases that include NCI trials?

Yes. The NIH, of which NCI is a part, maintains both a registry and a database that include clinical trials:

- ClinicalTrials.gov includes all cancer trials listed in PDQ. As of January 2006, the database contained more than 11,450 actively recruiting clinical trials for all disease types - including more than 4,400 for cancer and other neoplasms - sponsored by the NIH, other federal agencies, and the pharmaceutical industry.
- The CRISP (Computer Retrieval of Information on Scientific Projects) database lists and describes biomedical research grants and contracts funded by the Department of Health and Human Services, NIH's parent agency. At the end of 2004, this database included about 275

listings for current investigator-initiated (R01) grants for research projects involving the conduct of at least 1 cancer clinical trial.* At that time, CRISP also contained information describing contracts active during the period from 2001 through 2004. These contracts were designed either to support large-scale, multiyear prevention or screening trials or to provide centralized services, such as investigational drug production, for NCI clinical trials. Some, but not all, of the clinical trials in CRISP are also listed in PDQ.

*Note: Many of the clinical trials contained in CRISP are not yet active and, therefore, not yet listed in PDQ.

There are other Web sites that make lists of cancer clinical trials available to the public, including some sites maintained by professional or voluntary groups. Some NCI-designated Cancer Centers maintain lists of their own clinical trials on their Web sites.

Most large cancer clinical trial databases, whether private or publicly accessible, derive information from PDQ. Before moving on to the next type of cancer, we are going to present you with some FAQs on biological therapies:

Biological Therapies for Cancer: Questions and Answers

Key Points

- Biological therapies use the body's immune system to fight cancer or to lessen the side effects that may be caused by some cancer treatments (see Question 1).
- Biological response modifiers (BRMs) occur naturally in the body and can be produced in the laboratory. BRMs alter the interaction between the body's immune defenses and cancer cells to boost, direct, or restore the body's ability to fight the disease (see Question 3).
- Biological therapies include interferons, interleukins, colony-stimulating factors, monoclonal antibodies, vaccines, gene therapy, and nonspecific immunomodulating agents (see Questions 4 to 10).
- Biological therapies can cause a number of side effects, which can vary widely from agent to agent and patient to patient (see Question 11).

1. **What is biological therapy?**

   Biological therapy (sometimes called immunotherapy, biotherapy, or biological response modifier therapy) is a relatively new addition to the family of cancer treatments that also includes surgery, chemotherapy, and radiation therapy. Biological therapies use the body's immune system, either directly or indirectly, to fight cancer or to lessen the side effects that may be caused by some cancer treatments.

2. **What is the immune system and what are its components?**

   The immune system is a complex network of cells and organs that work together to defend the body against attacks by "foreign" or "non-self" invaders. This network is one of the body's main defenses against infection and disease. The immune system works against diseases,

including cancer, in a variety of ways. For example, the immune system may recognize the difference between healthy cells and cancer cells in the body and works to eliminate cancerous cells. However, the immune system does not always recognize cancer cells as "foreign." Also, cancer may develop when the immune system breaks down or does not function adequately. Biological therapies are designed to repair, stimulate, or enhance the immune system's responses.

Immune system cells include the following:

- **Lymphocytes** are a type of white blood cell found in the blood and many other parts of the body. Types of lymphocytes include B cells, T cells, and Natural Killer cells.

  B cells (B lymphocytes) mature into plasma cells that secrete proteins called antibodies (immunoglobulins). Antibodies recognize and attach to foreign substances known as antigens, fitting together much the way a key fits a lock. Each type of B cell makes one specific antibody, which recognizes one specific antigen.

  T cells (T lymphocytes) work primarily by producing proteins called cytokines. Cytokines allow immune system cells to communicate with each other and include lymphokines, interferons, interleukins, and colony-stimulating factors. Some T cells, called cytotoxic T cells, release pore-forming proteins that directly attack infected, foreign, or cancerous cells. Other T cells, called helper T cells, regulate the immune response by releasing cytokines to signal other immune system defenders.

  Natural Killer cells (NK cells) produce powerful cytokines and pore-forming proteins that bind to and kill many foreign invaders, infected cells, and tumor cells. Unlike cytotoxic T cells, they are poised to attack quickly, upon their first encounter with their targets.

- **Phagocytes** are white blood cells that can swallow and digest microscopic organisms and particles in a process known as phagocytosis. There are several types of phagocytes, including **monocytes**, which circulate in the blood, and **macrophages**, which are located in tissues throughout the body.

3. **What are biological response modifiers, and how can they be used to treat cancer?**

Some antibodies, cytokines, and other immune system substances can be produced in the laboratory for use in cancer treatment. These substances are often called biological response modifiers (BRMs). They alter the interaction between the body's immune defenses and cancer cells to boost, direct, or restore the body's ability to fight the disease. BRMs include interferons, interleukins, colony-stimulating factors, monoclonal antibodies, vaccines, gene therapy, and nonspecific immunomodulating agents. Each of these BRMs is described in Questions 4 to 10.

Researchers continue to discover new BRMs, to learn more about how they function, and to develop ways to use them in cancer therapy. Biological therapies may be used to:

- Stop, control, or suppress processes that permit cancer growth.

- Make cancer cells more recognizable and, therefore, more susceptible to destruction by the immune system.
- Boost the killing power of immune system cells, such as T cells, NK cells, and macrophages.
- Alter the growth patterns of cancer cells to promote behavior like that of healthy cells.
- Block or reverse the process that changes a normal cell or a precancerous cell into a cancerous cell.
- Enhance the body's ability to repair or replace normal cells damaged or destroyed by other forms of cancer treatment, such as chemotherapy or radiation.
- Prevent cancer cells from spreading to other parts of the body.

Some BRMs are a standard part of treatment for certain types of cancer, while others are being studied in clinical trials (research studies). BRMs are being used alone or in combination with each other. They are also being used with other treatments, such as radiation therapy and chemotherapy.

4. **What are interferons?**

Interferons (IFNs) are types of cytokines that occur naturally in the body. They were the first cytokines produced in the laboratory for use as BRMs. There are three major types of interferons—interferon alpha, interferon beta, and interferon gamma; interferon alpha is the type most widely used in cancer treatment.

Researchers have found that interferons can improve the way a cancer patient's immune system acts against cancer cells. In addition, interferons may act directly on cancer cells by slowing their growth or promoting their development into cells with more normal behavior. Researchers believe that some interferons may also stimulate NK cells, T cells, and macrophages, boosting the immune system's anticancer function.

The U.S. Food and Drug Administration (FDA) has approved the use of interferon alpha for the treatment of certain types of cancer, including hairy cell leukemia, melanoma, chronic myeloid leukemia, and AIDS-related Kaposi's sarcoma. Studies have shown that interferon alpha may also be effective in treating other cancers such as kidney cancer and non-Hodgkin's lymphoma. Researchers are exploring combinations of interferon alpha and other BRMs or chemotherapy in clinical trials to treat a number of cancers.

5. **What are interleukins?**

Like interferons, interleukins (ILs) are cytokines that occur naturally in the body and can be made in the laboratory. Many interleukins have been identified; **interleukin-2** (**IL–2** or **aldesleukin**) has been the most widely studied in cancer treatment. IL–2 stimulates the growth and activity of many immune cells, such as lymphocytes, that can destroy cancer cells. The FDA has approved IL–2 for the treatment of metastatic kidney cancer and metastatic melanoma.

Researchers continue to study the benefits of interleukins to treat a number of other cancers, including leukemia, lymphoma, and brain, colorectal, ovarian, breast, and prostate cancers.

6. **What are colony-stimulating factors?**

Colony-stimulating factors (CSFs) (sometimes called hematopoietic growth factors) usually do not directly affect tumor cells; rather, they encourage bone marrow stem cells to divide and develop into white blood cells, platelets, and red blood cells. Bone marrow is critical to the body's immune system because it is the source of all blood cells.

Stimulation of the immune system by CSFs may benefit patients undergoing cancer treatment. Because anticancer drugs can damage the body's ability to make white blood cells, red blood cells, and platelets, patients receiving anticancer drugs have an increased risk of developing infections, becoming anemic, and bleeding more easily. By using CSFs to stimulate blood cell production, doctors can increase the doses of anticancer drugs without increasing the risk of infection or the need for transfusion with blood products. As a result, researchers have found CSFs particularly useful when combined with high-dose chemotherapy.

Some examples of CSFs and their use in cancer therapy are as follows:

- **G–CSF (filgrastim)** and **GM–CSF (sargramostim)** can increase the number of white blood cells, thereby reducing the risk of infection in patients receiving chemotherapy. G–CSF and GM–CSF can also stimulate the production of stem cells in preparation for stem cell or bone marrow transplants.

- Erythropoietin **(epoetin)** can increase the number of red blood cells and reduce the need for red blood cell transfusions in patients receiving chemotherapy.

- Interleukin-11 **(oprelvekin)** helps the body make platelets and can reduce the need for platelet transfusions in patients receiving chemotherapy.

Researchers are studying CSFs in clinical trials to treat a large variety of cancers, including lymphoma, leukemia, multiple myeloma, melanoma, and cancers of the brain, lung, esophagus, breast, uterus, ovary, prostate, kidney, colon, and rectum.

7. **What are monoclonal antibodies?**

Researchers are evaluating the effectiveness of certain antibodies made in the laboratory called monoclonal antibodies (MOABs or MoABs). These antibodies are produced by a single type of cell and are specific for a particular antigen. Researchers are examining ways to create MOABs specific to the antigens found on the surface of various cancer cells.

To create MOABs , scientists first inject human cancer cells into mice. In response, the mouse immune system makes antibodies against these cancer cells. The scientists then remove the mouse plasma cells that produce antibodies, and fuse them with laboratory-grown cells to create "hybrid" cells called hybridomas. Hybridomas can indefinitely produce large quantities of these pure antibodies, or MOABs.

MOABs may be used in cancer treatment in a number of ways:

- MOABs that react with specific types of cancer may enhance a patient's immune response to the cancer.

- MOABs can be programmed to act against cell growth factors, thus interfering with the growth of cancer cells.
- MOABs may be linked to anticancer drugs, radioisotopes (radioactive substances), other BRMs, or other toxins. When the antibodies latch onto cancer cells, they deliver these poisons directly to the tumor, helping to destroy it.

MOABs carrying radioisotopes may also prove useful in diagnosing certain cancers, such as colorectal, ovarian, and prostate.

Rituxan® (rituximab) and **Herceptin® (trastuzumab)** are examples of MOABs that have been approved by the FDA. Rituxan is used for the treatment of non-Hodgkin's lymphoma. Herceptin is used to treat metastatic breast cancer in patients with tumors that produce excess amounts of a protein called HER–2. (More information about Herceptin is available in the National Cancer Institute (NCI) fact sheet *Herceptin® (Trastuzumab): Questions and Answers*, which can be found at http://www.cancer.gov/cancertopics/factsheet/Therapy/herceptin on the Internet.) In clinical trials, researchers are testing MOABs to treat lymphoma, leukemia, melanoma, and cancers of the brain, breast, lung, kidney, colon, rectum, ovary, prostate, and other areas.

8. **What are cancer vaccines?**

Cancer vaccines are another form of biological therapy currently under study. Vaccines for infectious diseases, such as measles, mumps, and tetanus, are injected into a person before the disease develops. These vaccines are effective because they expose the body's immune cells to weakened forms of antigens that are present on the surface of the infectious agent. This exposure causes the immune system to increase production of plasma cells that make antibodies specific to the infectious agent. The immune system also increases production of T cells that recognize the infectious agent. These activated immune cells remember the exposure, so that the next time the agent enters the body, the immune system is already prepared to respond and stop the infection.

Researchers are developing vaccines that may encourage the patient's immune system to recognize cancer cells. Cancer vaccines are designed to treat existing cancers (therapeutic vaccines) or to prevent the development of cancer (prophylactic vaccines). Therapeutic vaccines are injected in a person after cancer is diagnosed. These vaccines may stop the growth of existing tumors, prevent cancer from recurring, or eliminate cancer cells not killed by prior treatments. Cancer vaccines given when the tumor is small may be able to eradicate the cancer. On the other hand, prophylactic vaccines are given to healthy individuals before cancer develops. These vaccines are designed to stimulate the immune system to attack viruses that can cause cancer. By targeting these cancer-causing viruses, doctors hope to prevent the development of certain cancers.

Early cancer vaccine clinical trials involved mainly patients with melanoma. Therapeutic vaccines are also being studied in the treatment of many other types of cancer, including lymphoma, leukemia, and cancers of the brain, breast, lung, kidney, ovary, prostate, pancreas, colon, and rectum. Researchers are also studying prophylactic vaccines to prevent cancers of the cervix and liver. Moreover, scientists are investigating ways that cancer vaccines can be used in combination with other BRMs.

9. **What is gene therapy?**

Gene therapy is an experimental treatment that involves introducing genetic material into a person's cells to fight disease. Researchers are studying gene therapy methods that can improve a patient's immune response to cancer. For example, a gene may be inserted into an immune cell to enhance its ability to recognize and attack cancer cells. In another approach, scientists inject cancer cells with genes that cause the cancer cells to produce cytokines and stimulate the immune system. A number of clinical trials are currently studying gene therapy and its potential application to the biological treatment of cancer. What are nonspecific immunomodulating agents?

Nonspecific immunomodulating agents are substances that stimulate or indirectly augment the immune system. Often, these agents target key immune system cells and cause secondary responses such as increased production of cytokines and immunoglobulins. Two nonspecific immunomodulating agents used in cancer treatment are **bacillus Calmette-Guerin (BCG)** and **levamisole** .

BCG, which has been widely used as a tuberculosis vaccine, is used in the treatment of superficial bladder cancer following surgery. BCG may work by stimulating an inflammatory, and possibly an immune, response. A solution of BCG is instilled in the bladder and stays there for about 2 hours before the patient is allowed to empty the bladder by urinating. This treatment is usually performed once a week for 6 weeks.

Levamisole is sometimes used along with fluorouracil (5–FU) chemotherapy in the treatment of stage III (Dukes' C) colon cancer following surgery. Levamisole may act to restore depressed immune function.

10. **Do biological therapies have any side effects?**

    Like other forms of cancer treatment, biological therapies can cause a number of side effects, which can vary widely from agent to agent and patient to patient. Rashes or swelling may develop at the site where the BRMs are injected. Several BRMs, including interferons and interleukins, may cause flu-like symptoms including fever, chills, nausea, vomiting, and appetite loss. Fatigue is another common side effect of some BRMs. Blood pressure may also be affected. The side effects of IL–2 can often be severe, depending on the dosage given. Patients need to be closely monitored during treatment with high doses of IL–2. Side effects of CSFs may include bone pain, fatigue, fever, and appetite loss. The side effects of MOABs vary, and serious allergic reactions may occur. Cancer vaccines can cause muscle aches and fever.

11. **Where can a person get more information about clinical trials?**

    Information about ongoing clinical trials involving these and other biological therapies is available from the Cancer Information Service (see below) or the clinical trials page of the NCI's Web site at http://www.cancer.gov/clinicaltrials/ on the Internet.

Now we will continue the journey through the list of various types of cancers:

General Information

Note: Estimated new cases and deaths from acute lymphocytic leukemia in the United States in 2006:

- **New cases: 3,930.**
- **Deaths: 1,490.**

Sixty percent to 80% of adults with acute lymphoblastic leukemia (ALL) can be expected to attain complete remission status following appropriate induction therapy. Approximately 35% to 40% of adults with ALL can be expected to survive 2 years with aggressive induction combination chemotherapy and effective supportive care during induction therapy (appropriate early treatment of infection, hyperuricemia, and bleeding). A few studies that use intensive multiagent approaches suggest that a 50% 3-year survival is achievable in selected patients, but these results must be verified by other investigators.

As in childhood ALL, adult patients with ALL are at risk of developing central nervous system (CNS) involvement during the course of their disease. This is particularly true for patients with L3 histology. Both treatment and prognosis are influenced by this complication. The examination of bone marrow aspirates and/or biopsy specimens should be done by an experienced oncologist, hematologist, hematopathologist, or general pathologist who is capable of interpreting conventional and specially stained specimens. Diagnostic confusion with acute myelocytic leukemia (AML), hairy-cell leukemia, and malignant lymphoma is not uncommon. Proper diagnosis is crucial because of the difference in prognosis and treatment of ALL and AML. Immunophenotypic analysis is essential because leukemias that do not express myeloperoxidase include M0 and M7 AML as well as ALL.

Appropriate initial treatment, usually consisting of a regimen that includes the combination of vincristine, prednisone, and anthracycline, with or without asparaginase, results in a complete remission rate of up to 80%. Median remission duration for the complete responders is approximately 15 months. Entry into a clinical trial is highly desirable to assure adequate patient treatment and also maximal information retrieval from the treatment of this highly responsive, but usually fatal, disease. Patients who experience a relapse after remission can be expected to succumb within 1 year, even if a second complete remission is achieved. If there are appropriate available donors and if the patient is younger than 55 years of age, bone marrow transplantation may be a consideration in the management of this disease. Transplant centers performing 5 or fewer transplants annually usually have poorer results than larger centers. If allogeneic transplant is considered, transfusions with blood products from a potential donor should be avoided if possible.

Patients with L3 morphology have improved outcomes when treated according to specific treatment algorithms. Age, which is a significant factor in childhood ALL and in AML, may also be an important prognostic factor in adult ALL. In one study, overall the prognosis was better in patients younger than 25 years; another study found a better prognosis in those younger than 35 years. These findings may, in part, be related to the increased incidence of the Philadelphia chromosome (Ph1) in older ALL patients, a subgroup associated with poor prognosis. Elevated B2-microglobulin is associated with a poor prognosis in adults as evidenced by lower response rate, increased incidence of CNS involvement, and significantly worse survival. Patients with Ph1-positive ALL are rarely cured with chemotherapy. Many patients who have molecular evidence of the bcr-abl fusion gene, which characterizes the Ph1 , have no evidence of the abnormal chromosome by cytogenetics. Because many patients have a different fusion protein from the one found in chronic myelogenous leukemia (p190 versus p210), the bcr-abl fusion gene may be detectable only by pulsed-field gel electrophoresis or

reverse-transcriptase polymerase chain reaction (RT-PCR). These tests should be performed whenever possible in patients with ALL, especially those with B-cell lineage disease. Two other chromosomal abnormalities with poor prognoses are t(4;11), which is characterized by rearrangements of the MLL gene and may be rearranged despite normal cytogenetics, and t(9;22). In addition to t(9;22) and t(4;11), patients with deletion of chromosome 7 or trisomy 8 have been reported to have a lower probability of survival at 5 years compared to patients with a normal karyotype. L3 ALL is associated with a variety of translocations which involve translocation of the c-myc proto-oncogene to the immunoglobulin gene locus: t(2;8), t(8;12), and t(8;22).

Long-term follow-up of 30 patients with ALL in remission for at least 10 years has demonstrated 10 cases of secondary malignancies. Of 31 long-term female survivors of ALL or acute myeloid leukemia under 40 years of age, 26 resumed normal menstruation following completion of therapy. Among 36 live offspring of survivors, 2 congenital problems occurred.

Cellular Classification

Leukemic cell characteristics including morphological features, cytochemistry, immunologic cell surface and biochemical markers, and cytogenetic characteristics are important. In adults, FAB L1 morphology (more mature appearing lymphoblasts) is present in fewer than 50% of patients and L2 histology (more immature and pleomorphic) predominates. Chromosomal abnormalities including aneuploidy and translocations have been described and may correlate with prognosis. In particular, patients with Philadelphia chromosome (Ph1)-positive t(9;22) acute lymphoblastic leukemia (ALL) have a poor prognosis and represent more than 30% of adult cases. The bcr-abl fusion gene resulting from the breakpoint in the Ph1 may, on occasion, be detectable only by pulse-field gel electrophoresis or reverse-transcriptase polymerase chain reaction. Bcr-abl rearranged leukemias that do not demonstrate the classical Ph1 carry a poor prognosis that is similar to those that are Ph1-positive.

Using heteroantisera and monoclonal antibodies, ALL cells can be divided into early B-cell lineage (80% approximate frequency), T cells (10%-15% approximate frequency), B cells (with surface immunoglobulins), (<5% approximate frequency), and CALLA+ (common ALL antigen), 50% approximate frequency.

About 95% of all types of ALL except B cell (which usually has an L3 morphology by the FAB classification) have elevated terminal deoxynucleotidyl transferase (TdT) expression. This elevation is extremely useful in diagnosis; if concentrations of the enzyme are not elevated, the diagnosis of ALL is suspect. However, 20% of cases of acute myeloid leukemia (AML) may express TdT; therefore, its usefulness as a lineage marker is limited. Because B-cell leukemias are treated according to different algorithms, it is important to specifically identify these cases prospectively by their L3 morphology, absence of TdT, and expression of surface immunoglobulin. These patients will typically have 1 of 3 chromosomal translocations: t(8;14), t(2;8), or t(8;22).

Childhood Acute Lymphoblastic Leukemia: Treatment

General Information

This cancer treatment information summary provides an overview of the prognosis, diagnosis, classification, and treatment of childhood acute lymphoblastic leukemia (ALL).

The National Cancer Institute provides the PDQ pediatric cancer treatment information summaries as a public service to increase the availability of evidence-based cancer information to health professionals, patients, and the public. These summaries are updated regularly according to the latest published research findings by an Editorial Board of pediatric oncology specialists.

Cancer in children and adolescents is rare. Children and adolescents with cancer should be referred to medical centers that have a multidisciplinary team of cancer specialists with experience treating the cancers that occur during childhood and adolescence. This multidisciplinary team approach incorporates the skills of the primary care physician, pediatric surgical subspecialists, radiation oncologists, pediatric medical oncologists/hematologists, rehabilitation specialists, pediatric nurse specialists, social workers, and others to ensure that children receive treatment, supportive care, and rehabilitation that will achieve optimal survival and quality of life. Guidelines for pediatric cancer centers and their role in the treatment of pediatric patients with cancer have been outlined by the American Academy of Pediatrics.

Since treatment of children with ALL entails many potential complications and requires intensive supportive care (e.g., transfusions; management of infectious complications; and emotional, financial, and developmental support), this treatment is best coordinated by pediatric oncologists and performed in cancer centers or hospitals with all of the necessary pediatric supportive care facilities. Specialized care is essential for all children with ALL, including those for whom specific clinical and laboratory features might confer a favorable prognosis. It is equally important that the clinical centers and the specialists directing the patient's care maintain contact with the referring physician in the community. Strong lines of communication optimize any urgent or interim care required when the child is at home.

In recent decades, dramatic improvements in survival have been achieved for children and adolescents with cancer. Childhood and adolescent cancer survivors require close follow-up because cancer therapy side effects may persist or develop months or years after treatment.

ALL is the most common cancer diagnosed in children and represents 23% of cancer diagnoses among children younger than 15 years. ALL occurs at an annual rate of approximately 30 to 40 per million. There are approximately 2,400 children and adolescents younger than 20 years diagnosed with ALL each year in the United States, and there has been a gradual increase in the incidence of ALL in the past 25 years. A sharp peak in ALL incidence is observed among children aged 2 to 3 years (>80 per million per year), with rates decreasing to 20 per million for ages 8 to 10 years. The incidence of ALL among children aged 2 to 3 years is approximately 4-fold greater than that for infants and is nearly 10-fold greater than that for children who are 19 years old. For unexplained reasons, the incidence of ALL is substantially higher for white children than for black children, with a nearly 3-fold higher incidence at 2 to 3 years for white children compared to black children. The incidence of ALL appears to be highest in Hispanic children (43 per million).

There are few identified factors associated with an increased risk of ALL. The primary accepted nongenetic risk factors for ALL are prenatal exposure to x-rays and postnatal exposure to high doses of radiation (e.g., therapeutic radiation as previously used for conditions such as tinea capitis and thymus enlargement). Children with Down syndrome have increased risk for developing both ALL and acute myeloid leukemia (AML), with a cumulative risk for developing leukemia of approximately 2.1% by age 5 years and 2.7% by age 30 years. Approximately one half to two thirds of the cases of acute leukemia in children with Down syndrome are ALL. Patients with ALL and Down syndrome have a lower incidence of both favorable and unfavorable cytogenetic findings and a lower incidence of T-cell phenotype. While the vast majority of cases of AML in children with Down syndrome occur before the age of 4 years (median age, 1 year), ALL in children with Down syndrome has an age distribution

similar to that of ALL in non–Down syndrome children, with a median age of 3 to 4 years. Outcome for Down syndrome children with ALL has generally been reported as poorer than that of non–Down syndrome children. The lower event-free survival and overall survival for children with Down syndrome appear to be related to higher rates of treatment-related mortality, especially during induction therapy, and to the absence of favorable biological features. Increased occurrence of ALL is also associated with certain genetic conditions, including neurofibromatosis, Shwachman syndrome, Bloom's syndrome, and ataxia telangiectasia.

Many cases of ALL that develop in children have a prenatal origin. Evidence in support of this comes from the observation that the immunoglobulin or T-cell receptor antigen rearrangements that are unique to each patient's leukemia cells can be detected in blood samples obtained at birth. Similarly, there are data to support that patients with ALL characterized by specific chromosomal abnormalities had blood cells carrying the abnormalities at the time of birth. Genetic studies of identical twins with concordant leukemia further support the prenatal origin of some leukemias.

Among children with ALL, more than 95% attain remission and 75% to 85% survive free of leukemia recurrence at least 5 years from diagnosis with current treatments that incorporate systemic therapy (e.g., combination chemotherapy) and specific central nervous system preventive therapy (i.e., intrathecal chemotherapy with or without cranial radiation).

Despite the treatment advances noted in childhood ALL, numerous important biologic and therapeutic questions remain to be answered to achieve the goal of curing every child with ALL. The systematic investigation of these issues requires large clinical trials, and the opportunity to participate in these trials is offered to most patients/families. Clinical trials for children and adolescents with ALL are generally designed to compare potentially better therapy with therapy that is currently accepted as standard. Much of the progress made in identifying curative therapies for childhood ALL and other childhood cancers has been achieved through investigator-driven discovery tested in carefully randomized, controlled clinical trials. Information about ongoing clinical trials is available from the NCI Web site.

Leukemia Trial Results

1. Nilotinib and Dasatinib Are Safe, Potentially Effective Treatment for Ph-Positive Leukemias
(Posted: 07/12/2006) - Two new targeted drugs - nilotinib and dasatinib - are safe and potentially effective for patients with chronic myelogenous leukemia and Ph-positive acute lymphocytic leukemia, according to the June 15, 2006, issue of the New England Journal of Medicine.

2. Palifermin Reduces Mouth Sores Caused by Cancer Treatment
(Posted: 12/21/2004) - An experimental drug called palifermin (Kepivance®) reduced both the severity and the duration of sores and ulcers in the mouth in patients who received intensive chemotherapy and radiation to treat lymphoma and other cancers of the blood, according to a report in the Dec. 16, 2004, issue of the New England Journal of Medicine.

3. Azacitidine May Improve Survival, Quality of Life for Patients with Pre-Leukemia
(Posted: 07/03/2002, Reviewed: 03/15/2006) - Myelodysplastic syndrome (MDS), sometimes referred to as pre-leukemia or smoldering leukemia, is a group of diseases characterized by failure of the bone marrow to produce enough normal blood cells. Now two papers published in

the May 15, 2002, issue of the Journal of Clinical Oncology suggest that the drug azacitidine may improve survival and quality of life for patients with MDS, compared to supportive care.

4. Gleevec Confirmed as More Effective Than Conventional Therapy for CML
(Posted: 05/20/2002, Reviewed: 12/20/2005) - Gleevec delayed progression of disease for longer, produced milder side effects, and resulted in a significantly better response than conventional therapy in patients with previously untreated chronic myelogenous leukemia (CML), according to a report in the March 13, 2003, issue of the New England Journal of Medicine. Preliminary findings from the study had been presented at a scientific meeting in May 2002.

5. Alternate Drug Less Toxic, Less Effective Than Standard Treatment for ALL
(Posted: 05/20/2002, Reviewed: 03/15/2006) - Acute lymphoblastic leukemia (ALL) is the most common cancer in children. Now two new studies suggest that, given at the same dose, the standard E. coli form of the drug asparaginase -- a mainstay for more than 30 years in the treatment of ALL -- appears to be more effective, though more toxic, than another form known as Erwinia asparaginase.

Lung Cancer

General Information

Note: Estimated new cases and deaths from lung cancer **(non-small cell and small cell combined)** in the United States in 2006:

- New cases: 174,470.
- Deaths: 162,460.

Non-small cell lung cancer (NSCLC) is a heterogeneous aggregate of histologies. The most common histologies are epidermoid or squamous carcinoma, adenocarcinoma, and large cell carcinoma. These histologies are often classified together because approaches to diagnosis, staging, prognosis, and treatment are similar. Patients with resectable disease may be cured by surgery or surgery with adjuvant chemotherapy. Local control can be achieved with radiation therapy in a large number of patients with unresectable disease, but cure is seen only in a small number of patients. Patients with locally advanced, unresectable disease may have long-term survival with radiation therapy combined with chemotherapy. Patients with advanced metastatic disease may achieve improved survival and palliation of symptoms with chemotherapy.

At diagnosis, patients with NSCLC can be divided into 3 groups that reflect both the extent of the disease and the treatment approach. The first group of patients has tumors that are surgically resectable (generally stage I, stage II, and selected stage III patients). This group has the best prognosis, which depends on a variety of tumor and host factors. Patients with resectable disease who have medical contraindications to surgery are candidates for curative radiation therapy. Adjuvant cisplatin-based combination chemotherapy may provide a survival advantage to patients with resected stage IB, stage II, or stage IIIA NSCLC.

The second group includes patients with either locally (T3-T4) and/or regionally (N2-N3) advanced lung cancer. This group has a diverse natural history. Selected patients with locally advanced tumors

may benefit from combined modality treatments. Patients with unresectable or N2-N3 disease are treated with radiation therapy in combination with chemotherapy. Selected patients with T3 or N2 disease can be treated effectively with surgical resection and either preoperative or postoperative chemotherapy or chemoradiation therapy.

The final group includes patients with distant metastases (M1) that were found at the time of diagnosis. This group can be treated with radiation therapy or chemotherapy for palliation of symptoms from the primary tumor. Patients with good performance status (PS), women, and patients with distant metastases confined to a single site live longer than others. Platinum-based chemotherapy has been associated with short-term palliation of symptoms and with a survival advantage. Currently, no single chemotherapy regimen can be recommended for routine use. Patients previously treated with platinum combination chemotherapy may derive symptom control and survival benefit from docetaxel, pemetrexed, or epidermal growth factor receptor inhibitor.

Multiple studies have attempted to identify prognostic determinants after surgery and have yielded conflicting evidence as to the prognostic importance of a variety of clinicopathologic factors. Factors that have correlated with adverse prognosis include the following:

- Presence of pulmonary symptoms.
- Large tumor size (>3 cm).
- Nonsquamous histology.
- Metastases to multiple lymph nodes within a TNM-defined nodal station.
- Vascular invasion.
- Increased numbers of tumor blood vessels in the tumor specimen.

Similarly, conflicting results regarding the prognostic importance of aberrant expression of a number of proteins within lung cancers have been reported. For patients with inoperable disease, prognosis is adversely affected by poor PS and weight loss of >10%. These patients have been excluded from clinical trials evaluating aggressive multimodality interventions. In multiple retrospective analyses of clinical trial data, advanced age alone has not been shown to influence response or survival with therapy.

Because treatment is not satisfactory for almost all patients with NSCLC, eligible patients should be considered for clinical trials.

Small Cell Lung Cancer: Treatment

Without treatment, small cell carcinoma of the lung has the most aggressive clinical course of any type of pulmonary tumor, with median survival from diagnosis of only 2 to 4 months. Compared with other cell types of lung cancer, small cell carcinoma has a greater tendency to be widely disseminated by the time of diagnosis but is much more responsive to chemotherapy and irradiation.

Because patients with small cell lung cancer tend to develop distant metastases, localized forms of treatment, such as surgical resection or radiation therapy, rarely produce long-term survival. With incorporation of current chemotherapy regimens into the treatment program, however, survival is

unequivocally prolonged, with at least a 4- to 5-fold improvement in median survival compared with patients who are given no therapy. Furthermore, about 10% of the total population of patients remains free of disease over 2 years from the start of therapy, the time period during which most relapses occur. Even these patients, however, are at risk of dying from lung cancer (both small and non-small cell types). The overall survival at 5 years is 5% to 10%.

Limited-stage disease

At the time of diagnosis, approximately 30% of patients with small cell carcinoma will have tumor confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes. These patients are designated as having limited-stage disease, and most 2-year disease-free survivors come from this group. In limited-stage disease, median survival of 16 to 24 months with current forms of treatment can reasonably be expected. A small proportion of patients with limited-stage disease may benefit from surgery with or without adjuvant chemotherapy; these patients have an even better prognosis.

Extensive-stage disease

Patients with tumors that have spread beyond the supraclavicular areas are said to have extensive-stage disease and have a worse prognosis than patients with limited-stage disease. Median survival of 6 to 12 months is reported with currently available therapy, but long-term disease-free survival is rare.

Prognostic factors

The pretreatment prognostic factors that consistently predict for prolonged survival include good performance status, female gender, and limited-stage disease. Patients with involvement of the central nervous system or liver at the time of diagnosis have a significantly worse outcome. In general, patients who are confined to bed tolerate aggressive forms of treatment poorly, have increased morbidity, and rarely attain 2-year disease-free survival; however, patients with poor performance status can often derive significant palliative benefit and prolongation of survival from treatment.

Regardless of stage, the current prognosis for patients with small cell lung cancer is unsatisfactory even though considerable improvements in diagnosis and therapy have been made over the past 10 to 15 years. All patients with this type of cancer may appropriately be considered for inclusion in clinical trials at the time of diagnosis.

Lung Cancer Prevention

Smoking Avoidance

Based on solid evidence, cigarette smoking causes lung cancer and therefore, smoking avoidance would result in decreased mortality from primary lung cancers.

Description of the Evidence

- Study Design**: Strong link established from epidemiological data, case-control, and cohort studies.**
- Internal Validity**: Good.**
- Consistency**: Good.**
- Magnitude of Effects on Health Outcomes**: Decreased risk, large magnitude.**

- External Validity**: Good.**

Smoking Cessation

Based on solid evidence, long-term sustained smoking cessation results in decreased incidence of lung cancer and of second primary lung tumors.

Description of the Evidence

- Study Design**: Evidence obtained from case-control and cohort studies.**
- Internal Validity**: Good.**
- Consistency**: Good.**
- Magnitude of Effects on Health Outcomes**: Decreased risk, moderate magnitude.**
- External Validity**: Good.**

Beta Carotene

Based on solid evidence, high-intensity smokers who take pharmacological doses of beta carotene have an increased lung cancer incidence and mortality that is associated with taking the supplement.

Description of the Evidence

- Study Design**: Evidence obtained from randomized controlled trials.**
- Internal Validity**: Good.**
- Consistency**: Good.**
- Magnitude of Effects on Health Outcomes**: Increased risk, small magnitude.**
- External Validity**: Good.**

Radon Exposure

Based on solid evidence, exposure to radon increases lung cancer incidence and mortality.

Description of the Evidence

- Study Design**: Evidence obtained from case-control and cohort studies.**
- Internal Validity**: Fair.**
- Consistency**: Good.**
- Magnitude of Effects on Health Outcomes**: Increased risk that follows a dose-response gradient, with small increases in risk for levels experienced in most at-risk homes.**
- External Validity**: Fair.**

Vitamin E/Tocopherol

Based on solid evidence, taking vitamin E supplements does not affect the risk of lung cancer.

Description of the Evidence

- Study Design**: Evidence obtained from 4 randomized controlled trials.**
- Internal Validity**: Good.**
- Consistency**: Fair.**
- Magnitude of Effects on Health Outcomes**: Stong evidence of no association.**
- External Validity**: Good.**

Exposure to Radon Causes Lung Cancer In Non-smokers and Smokers Alike

Lung cancer kills thousands of Americans every year. The untimely deaths of Peter Jennings and Dana Reeve have raised public awareness about lung cancer, especially among people who have never smoked. Smoking, radon, and secondhand smoke are the leading causes of lung cancer. Although lung cancer can be treated, the survival rate is one of the lowest for those with cancer. From the time of diagnosis, between 11 and 15 percent of those afflicted will live beyond five years, depending upon demographic factors. In many cases lung cancer can be prevented; this is especially true for radon.

Smoking is the leading cause of lung cancer. Smoking causes an estimated 160,000* deaths in the U.S. every year (American Cancer Society, 2004). And the rate among women is rising. On January 11, 1964, Dr. Luther L. Terry, then U.S. Surgeon General, issued the first warning on the link between smoking and lung cancer. Lung cancer now surpasses breast cancer as the number one cause of death among women. A smoker who is also exposed to radon has a much higher risk of lung cancer.

Radon is the number one cause of lung cancer among non-smokers, according to EPA estimates. Overall, radon is the second leading cause of lung cancer. Radon is responsible for about 21,000 lung cancer deaths every year. About 2,900 of these deaths occur among people who have never smoked. On January 13, 2005, Dr. Richard H. Carmona, the U.S. Surgeon General, issued a national health advisory on radon. Visit www.cheec.uiowa.edu/misc/radon.html more on a study by Dr. William Field on radon-related lung cancer in women.

Secondhand smoke is the third leading cause of lung cancer and responsible for an estimated 3,000 lung cancer deaths every year. About 1,000 of these are people that never smoked, and about 2,000 are former smokers. Smoking affects non-smokers by exposing them to secondhand smoke. Exposure to secondhand smoke can have serious consequences for children's health, including asthma attacks, affecting the respiratory tract (bronchitis, pneumonia), and may cause ear infections.

Bevacizumab Combined With Chemotherapy Prolongs Survival for Some Patients with Advanced Lung Cancer

Preliminary results from a large, randomized clinical trial for patients with previously untreated advanced non-squamous, non-small cell lung cancer show that those patients who received

bevacizumab (Avastin™) in combination with standard chemotherapy lived longer than patients who received the same chemotherapy without bevacizumab.

The clinical trial was sponsored by the National Cancer Institute (NCI), part of the National Institutes of Health, and conducted by a network of researchers led by the Eastern Cooperative Oncology Group. Genentech, Inc., South San Francisco, Calif., which manufactures bevacizumab, provided bevacizumab for the trial under the Cooperative Research and Development Agreement (CRADA) with NCI for the clinical development of bevacizumab.

The Data Monitoring Committee overseeing the trial (known as E4599)* recommended that the results of a recent interim analysis be made public because the study had met its primary endpoint of improving overall survival. Researchers found that patients in the study who received bevacizumab in combination with standard chemotherapy (a treatment regimen of paclitaxel and carboplatin) had a median overall survival of 12.5 months compared to patients treated with the standard chemotherapy alone, who had a median survival of 10.2 months. This difference is statistically significant. Detailed results from this trial were presented at a press briefing at the American Society of Clinical Oncology Annual Meeting (ASCO) in Orlando, Fla., on May 13, 2005. Specifically, it was noted that patients on bevacizumab in combination with standard chemotherapy demonstrated a higher response rate (27 percent vs. 10 percent) and a longer time until the cancer progressed (6.4 months vs. 4.5 months) than those on standard chemotherapy alone.

"The exciting results of this randomized study reveal, for the first time, an improvement in survival with the addition of a molecularly targeted agent to standard chemotherapy in this patient population," said Study Chair Alan B. Sandler, M.D., of the Vanderbilt University Medical Center in Nashville, Tenn.

"This study demonstrates that mechanistic-based interventions such as angiogenesis inhibitors are making important contributions in improving cancer outcomes," said NCI Director Andrew C. von Eschenbach, M.D. "In combination with standard therapies, they can be used for a variety of cancers, leading to increased patient survival."

A total of 878 patients with advanced non-squamous, non-small cell lung cancer (NSCLC) who had not previously received systemic chemotherapy were enrolled in this study between July 2001 and April 2004. Patients were randomized to one of the two treatment arms. One patient group received standard treatment -- six cycles of paclitaxel and carboplatin. The second group received the same six-cycle chemotherapy regimen with the addition of bevacizumab, followed by bevacizumab alone until disease progression.

Patients with squamous cell carcinoma of the lung were not included in the study because previous clinical experience suggested that patients with this particular type of NSCLC had a higher risk of serious bleeding from the lung after bevacizumab therapy. Patients with a prior history of frank hemoptysis (coughing up blood) were also not enrolled on the trial.

The most significant adverse event observed in this study was life-threatening or fatal bleeding, primarily from the lungs. This occurred infrequently, but was more common in the patient group that received bevacizumab in combination with chemotherapy than in the patient group that received only chemotherapy. A fuller description of side effects observed in this trial were presented at the ASCO press briefing as well. These included information that both treatment regimens were well-tolerated, with the most common side-effects being low white blood cell counts (24 percent on bevacizumab vs. 16 percent on standard chemotherapy), blood clots (3.8 percent vs. 3.0 percent), and bleeding (4.1

percent vs. 1.0 percent). Patients on bevacizumab had a 1.2 percent chance of life-threatening or fatal bleeding, primarily from the lungs, compared to a zero percent chance on standard chemotherapy.

Bevacizumab, a humanized monoclonal antibody**, is designed to bind to and inhibit vascular endothelial growth factor (VEGF). VEGF is a protein that plays a critical role in tumor angiogenesis, the formation of new blood vessels to the tumor.

"This trial represents another step in a series of recent important advances in treatment for patients with advanced lung cancer," said James H. Doroshow, M.D., director of NCI's Division of Cancer Treatment and Diagnosis and leader of NCI's Clinical Trials Working Group. "Important progress continues to be made by targeting molecular pathways critical to the growth and survival of cancer cells. It is through better understanding of these molecular processes that significant advances will be made in the treatment of this disease."

An estimated 172,570 people will be diagnosed with lung cancer in the United States in 2005. Lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer-related death in both men and women in this country. An estimated 163,510 deaths from lung cancer will occur in 2005 in the United States, accounting for about 29 percent of all cancer-related deaths in the nation.

Melanoma

General Information

Note: Estimated new cases and deaths from melanoma in the United States in 2006:

- **New cases: 62,190.**
- **Deaths: 7,910.**

Melanoma is a malignant tumor of melanocytes, which are the cells that make the pigment melanin and are derived from the neural crest. Although most melanomas arise in the skin, they may also arise from mucosal surfaces or at other sites to which neural crest cells migrate. Melanoma occurs predominantly in adults, and more than 50% of the cases arise in apparently normal areas of the skin. Early signs in a nevus that would suggest malignant change include darker or variable discoloration, itching, an increase in size, or the development of satellites. Ulceration or bleeding are later signs. Melanoma in women occurs more commonly on the extremities and in men on the trunk or head and neck, but it can arise from any site on the skin surface. A biopsy, preferably by local excision, should be performed for any suspicious lesions, and the specimens should be examined by an experienced pathologist to allow for microstaging. Suspicious lesions should never be shaved off or cauterized. Studies show that distinguishing between benign pigmented lesions and early melanomas can be difficult, and even experienced dermatopathologists can have differing opinions. To reduce the possibility of misdiagnosis for an individual patient, a second review by an independent qualified pathologist should be considered.

Prognosis is affected by clinical and histological factors and by anatomic location of the lesion. Thickness and/or level of invasion of the melanoma, mitotic index, presence of tumor infiltrating lymphocytes, number of regional lymph nodes involved, and ulceration or bleeding at the primary site affect the prognosis. Microscopic satellites in stage I melanoma may be a poor prognostic histologic

factor, but this is controversial. Patients who are younger, female, and who have melanomas on the extremities generally have a better prognosis.

Clinical staging is based on whether the tumor has spread to regional lymph nodes or distant sites. For disease clinically confined to the primary site, the greater the thickness and depth of local invasion of the melanoma, the higher the chance of lymph node or systemic metastases and the worse the prognosis. Melanoma can spread by local extension (through lymphatics) and/or by hematogenous routes to distant sites. Any organ may be involved by metastases, but lungs and liver are common sites. The risk of relapse decreases substantially over time, though late relapses are not uncommon.

Intraocular (Eye) Melanoma: Treatment

General Information

Melanoma of the uveal tract (iris, ciliary body, and choroid), though rare, is the most common primary intraocular malignancy in adults. The mean age-adjusted incidence of uveal melanoma in the United States is approximately 4.3 new cases/million population. The age-adjusted incidence of this cancer has remained stable for the past 25 years.

The median age at diagnosis ranges from 55 to 62 years. Several factors likely play a role in the development of uveal melanoma. Host characteristics, such as light pigmentation (skin, hair, and eye color) and genetic factors, as well as environmental exposures (sunlight and chemical), have been associated with increased risk in some studies.

Melanomas can arise in the anterior uveal tract (iris) or the posterior uveal tract (ciliary body or choroid). Iris melanomas have the best prognosis, whereas melanomas of the ciliary body have the worst. Most uveal tract melanomas originate in the choroid. The ciliary body is less commonly a site of origin, and the iris is the least common. The comparatively low incidence of this tumor in the iris has been attributed to the characteristic features of iris melanomas, i.e., they tend to be small, slow growing, and relatively dormant in comparison with their posterior counterparts. Iris melanomas rarely metastasize. Melanomas of the posterior uveal tract are cytologically more malignant, detected later, and metastasize more frequently than iris melanomas. The typical choroidal melanoma is a brown, elevated, dome-shaped subretinal mass. The degree of pigmentation ranges from dark brown to totally amelanotic.

Most melanomas of the iris, ciliary body, or choroid are initially completely asymptomatic. As the tumor enlarges, it may cause distortion of the pupil (iris melanoma), blurred vision (ciliary body melanoma), or markedly decreased visual acuity caused by secondary retinal detachment (choroidal melanoma). Serous detachment of the retina frequently complicates tumor growth. If extensive retinal detachment occurs, secondary angle-closure glaucoma occasionally develops. Clinically, several lesions simulate uveal melanoma, including metastatic carcinoma, posterior scleritis, and benign tumors such as nevi and hemangiomas.

Careful examination by an experienced clinician remains the most important test to establish the presence of intraocular melanoma. Ancillary diagnostic testing, including fluorescein angiography and ultrasonography, can be extremely valuable in establishing and/or confirming the diagnosis.

A number of factors influence prognosis. The most important are cell type, tumor size, location of the anterior margin of the tumor, the degree of ciliary body involvement, and extraocular extension. Cell type, however, remains the most often used predictor of outcome. The selection of treatment depends on the site of origin (choroid, ciliary body, or iris), the size and location of the lesion, the age of the patient, and whether extraocular invasion, recurrence, or metastasis has occurred. Extraocular

extension, recurrence, and metastasis are associated with an extremely poor prognosis, and long-term survival cannot be expected. The 5-year mortality rate caused by metastasis from ciliary body or choroidal melanoma is approximately 30%, compared with a rate of 2% to 3% for iris melanomas. In a group of patients with large tumors of the choroid or choroid and ciliary body, the concurrent presence of abnormalities in chromosomes 3 and 8 was also associated with a poor outcome.

In the past, enucleation (eye removal) was the accepted standard treatment for primary choroidal melanoma, and it remains the most commonly used treatment for large tumors. Because of the effect of enucleation on the appearance of the patient, the diagnostic uncertainty encountered by the ophthalmologist (particularly in the case of smaller tumors), and the potential for tumor spread, alternative treatments, such as radiation therapy (i.e., brachytherapy or external-beam radiation therapy, and charged-particle radiotherapy), transpupillary thermotherapy, photocoagulation, and cryotherapy have been developed in an attempt to spare the affected eye and possibly retain useful vision. Initial results from the randomized Collaborative Ocular Melanoma Study have demonstrated comparable 5-year survival rates for patients with medium-sized tumors treated primarily with brachytherapy (Iodine-125 [I^{125}] plaque radiation therapy) or enucleation. Among the patients treated with I^{125} brachytherapy, 85% retained their eye for 5 years or more, and 37% had visual acuity better than 20/200 in the irradiated eye 5 years after treatment.

Response to Immunotherapy for Melanoma Tied to Autoimmunity

Reprinted from the NCI Cancer Bulletin, vol. 3/no. 8, Feb. 21, 2006.

Patients treated for melanoma skin cancer with adjuvant interferon alfa-2b who developed clinical signs of autoimmunity were significantly more likely to respond to the treatment than patients who did not, a clinical trial has found. Autoimmunity occurs when the immune system begins to attack the body's own tissues.

Dr. Helen Gogas of the University of Athens Medical School, and colleagues enrolled 200 patients in a substudy of an ongoing trial. They prospectively evaluated the presence of autoantibodies and clinical manifestations of autoimmune disorders in melanoma patients who received adjuvant therapy with high-dose interferon alfa-2b.

The development of autoimmunity was associated with an approximate reduction by a factor of 50 in the risk of recurrence of melanoma. The benefit of interferon alfa-2b was primarily restricted to patients who showed signs of autoimmunity, the researchers report in the February 16, 2006, New England Journal of Medicine.

Efforts to identify biological markers for predicting which patients might respond have generally not been successful.

Although the new findings do not provide biological markers for patients who may have "immune-sensitive tumors," the results suggest a mechanistic connection between autoimmunity and the benefit from interferon alfa-2b in melanoma patients, says an accompanying editorial.

The study provides "the strongest data to date connecting the development of autoimmunity with a favorable antitumor effect of immunotherapy," write Drs. Henry Koon and Michael Atkins of Beth Israel Deaconess Medical Center.

Melanoma Trial Results

1. Response to Immunotherapy for Melanoma Tied to Autoimmunity
(Posted: 02/22/2006) - Patients treated for melanoma skin cancer with adjuvant interferon alfa-2b who developed clinical signs of autoimmunity were significantly more likely than those who did not to respond to the treatment, according to a report in the Feb. 16, 2006, issue of the New England Journal of Medicine.

2. Sentinel Node Biopsy Helps Some Melanoma Patients Live Longer
(Posted: 05/14/2005) - A technique called lymphatic mapping and sentinel-node biopsy - which looks for cancer in a few lymph nodes first - was better than a "watch and wait" approach in helping melanoma patients whose cancer had spread to the lymph nodes to live longer, according to findings presented at the 2005 meeting of the American Society of Clinical Oncology.

3. NCI Researchers Confirm the Effectiveness of Immunotherapy Approach to Treating Melanoma
(Posted: 03/31/2005) - A team of researchers, led by Steven A. Rosenberg, M.D., at the National Cancer Institute, part of the National Institutes of Health, have found that patients with advanced melanoma who had not responded to previous therapies experienced a significant reduction in the size of their cancers as a result of receiving a new immunotherapy.

4. Researchers Shut Off Immune Cell Inhibition, Causing Tumor Shrinkage and Autoimmunity in Patients With Metastatic Melanoma
(Posted: 06/23/2003) - Scientists at the National Cancer Institute (NCI) have found a new method for modifying the immune system of cancer patients to induce cancer regression. Inhibiting a molecule known as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), which has a critical role in regulating the immune response, can enable the immune system to attack some patients' tumors, the scientists report in the Proceedings of the National Academy of Sciences*.

5. Similar Survival Rates Found for Eye Cancer Therapies
(Posted: 07/12/2001) - Researchers with the Collaborative Ocular Melanoma Study (COMS) have found that the survival rates for two alternative treatments for primary eye cancer -- radiation therapy and removal of the eye -- are about the same.

Non-Hodgkin's Lymphoma

General Information

Note: Estimated new cases and deaths from non-Hodgkin's lymphoma (NHL) in the United States in 2006:

- **New cases: 58,870.**
- **Deaths: 18,840.**

The NHLs are a heterogeneous group of lymphoproliferative malignancies with differing patterns of behavior and responses to treatment.

Like Hodgkin's lymphoma, NHL usually originates in lymphoid tissues and can spread to other organs. NHL, however, is much less predictable than Hodgkin's lymphoma and has a far greater predilection to disseminate to extranodal sites. The prognosis depends on the histologic type, stage, and treatment.

The NHLs can be divided into 2 prognostic groups: the indolent lymphomas and the aggressive lymphomas. Indolent NHL types have a relatively good prognosis, with median survival as long as 10 years, but they usually are not curable in advanced clinical stages. Early stage (stage I and stage II) indolent NHL can be effectively treated with radiation therapy alone. Most of the indolent types are nodular (or follicular) in morphology. The aggressive type of NHL has a shorter natural history, but a significant number of these patients can be cured with intensive combination chemotherapy regimens. In general, with modern treatment of patients with NHL, overall survival at 5 years is approximately 50% to 60%. Of patients with aggressive NHL, 30% to 60% can be cured. The vast majority of relapses occur in the first 2 years after therapy. The risk of late relapse is higher in patients with a divergent histology of both indolent and aggressive disease.

While indolent NHL is responsive to radiation therapy and chemotherapy, a continuous rate of relapse is usually seen in advanced stages. Patients, however, can often be re-treated with considerable success as long as the disease histology remains low grade. Patients who present with or convert to aggressive forms of NHL may have sustained complete remissions with combination chemotherapy regimens or aggressive consolidation with marrow or stem cell support.

Radiation techniques differ somewhat from those used in the treatment of Hodgkin's lymphoma. The dose of radiation therapy usually varies from 2,500 cGy to 5,000 cGy and is dependent on factors that include the histologic type of lymphoma, the patient's stage and overall condition, the goal of treatment (curative or palliative), the proximity of sensitive surrounding organs, and whether the patient is being treated with radiation therapy alone or in combination with chemotherapy. Given the patterns of disease presentations and relapse, treatment may need to include unusual sites such as Waldeyer's ring, epitrochlear, or mesenteric nodes. The associated morbidity of the treatment, however, must be considered carefully. The majority of patients who receive radiation are usually treated on only one side of the diaphragm. Localized presentations of extranodal NHL may be treated with involved-field techniques with significant (>50%) success.

In asymptomatic patients with indolent forms of advanced NHL, treatment may be deferred until the patient becomes symptomatic as the disease progresses. When treatment is deferred, the clinical course of patients with indolent NHL varies; frequent and careful observation is required so that effective treatment can be initiated when the clinical course of the disease accelerates. Some patients have a prolonged indolent course, but others have disease that rapidly evolves into more aggressive types of NHL that require immediate treatment.

Aggressive lymphomas are increasingly seen in HIV-positive patients; treatment of these patients requires special consideration

Childhood Non-Hodgkin's Lymphoma: Treatment

General Information

This cancer treatment information summary provides an overview of the prognosis, diagnosis, classification, staging, and treatment of childhood non-Hodgkin's lymphoma (NHL).

The National Cancer Institute provides the PDQ pediatric cancer treatment information summaries as a public service to increase the availability of evidence-based cancer information to health professionals, patients, and the public. These summaries are updated regularly according to the latest published research findings by an Editorial Board of pediatric oncology specialists.

Cancer in children and adolescents is rare. Children and adolescents with cancer should be referred to medical centers that have a multidisciplinary team of cancer specialists with experience treating the cancers that occur during childhood and adolescence. This multidisciplinary team approach incorporates the skills of the primary care physician, pediatric surgical subspecialists, radiation oncologists, pediatric medical oncologists/hematologists, rehabilitation specialists, pediatric nurse specialists, social workers, and others to ensure that children receive treatment, supportive care, and rehabilitation that will achieve optimal survival and quality of life.

Guidelines for pediatric cancer centers and their role in the treatment of children with cancer have been outlined by the American Academy of Pediatrics. At these pediatric cancer centers, clinical trials are available for most of the types of cancer that occur in children and adolescents, and the opportunity to participate in these trials is offered to most patients/families. Clinical trials for children and adolescents with cancer are generally designed to compare potentially better therapy with therapy that is currently accepted as standard. Most of the progress made in identifying curative therapies for childhood cancers have been achieved through clinical trials. In recent decades, dramatic improvements in survival have been achieved for children and adolescents with cancer. Childhood and adolescent cancer survivors require close follow-up because cancer therapy side effects may persist or develop months or years after treatment. Lymphoma (Hodgkin's and non-Hodgkin's) is the third most common childhood malignancy, and non-Hodgkin's lymphoma (NHL) accounts for approximately 7% of cancers in children younger than 20 years. In the United States, about 800 new cases of NHL are diagnosed each year. Incidence is approximately 10 per 1,000,000. Although there is no sharp age peak, NHL occurs most commonly in the second decade of life, and occurs less frequently in children younger than 3 years. NHL is the most frequent malignancy in children with acquired immunodeficiency syndrome (AIDS), and it often occurs before the age of 4 years in those who have vertical transmission of the virus. Screening for human immunodeficiency virus should be considered for all children with NHL.

More than 70% of children and adolescents with NHL will survive at least 5 years with chemotherapy, though outcome is variable depending on a number of factors. The most important prognostic determinant, given optimal therapy, is the extent of disease at diagnosis as determined by pretreatment staging. Patients with a single extra-abdominal/extrathoracic tumor and those with totally resected intra-abdominal tumor have an excellent prognosis (a 5-year survival rate of approximately 90%), regardless of histology. Patients with NHL arising in bone also have an excellent prognosis regardless of histology. Patients with extensive intrathoracic or intraabdominal disease and patients with bone marrow or central nervous system involvement at diagnosis require intensified therapy. These therapies have improved the outcome for patients with advanced stage disease.

Non-Hodgkin's Lymphoma Trial Results

1. Initial Treatment with Rituximab is a New Standard for Elderly Patients with B-Cell Lymphoma (Posted: 07/10/2006) - Elderly patients with B-cell lymphoma stayed disease-free for significantly longer when they were treated with the drug rituximab, a finding that establishes a new standard of care, according to the July 1, 2006, issue of the Journal of Clinical Oncology.

2. Rituximab Benefits Younger Patients with Good-Prognosis Diffuse Large-B-Cell Lymphoma
(Posted: 05/03/2006) - Addition of the drug rituximab (Rituxan®) to a standard chemotherapy regimen for diffuse large-B-cell lymphoma significantly increased survival for patients with good-prognosis disease who were younger than 60, according to the May 2006 issue of the Lancet Oncology.

3. Rituximab Improves Outcomes in Patients with Recurrent Lymphomas
(Posted: 10/26/2005) - Two studies from Germany showed the targeted therapy rituximab (Rituxan®) to be effective in treating recurrent follicular and mantle cell lymphomas, according to findings presented at the 2005 meeting of the American Society of Clinical Oncology.

4. Follicular Lymphoma Treatment Better With Rituximab (Rituxan®)
(Posted: 05/15/2005) - Rituximab (Rituxan®), when added to a standard chemotherapy regimen for treatment of newly diagnosed follicular lymphoma, dramatically delayed the progression of disease and produced higher response rates that lasted longer, according to findings presented at the 2005 meeting of the American Society of Clinical Oncology.

5. Palifermin Reduces Mouth Sores Caused by Cancer Treatment
(Posted: 12/21/2004) - An experimental drug called palifermin (Kepivance®) reduced both the severity and the duration of sores and ulcers in the mouth in patients who received intensive chemotherapy and radiation to treat lymphoma and other cancers of the blood, according to a report in the Dec. 16, 2004, issue of the New England Journal of Medicine.

Pancreatic Cancer

General Information

Note: Estimated new cases and deaths from pancreatic cancer in the United States in 2006:

- **New cases: 33,730.**
- **Deaths: 32,300.**

Note: Some citations in the text of this section are followed by a level of evidence. The PDQ editorial boards use a formal ranking system to help the reader judge the strength of evidence linked to the reported results of a therapeutic strategy.

A variety of endpoints may be measured and reported from clinical studies in oncology. These may include total mortality (or survival from the initiation of therapy), cause-specific mortality, quality of life, or indirect surrogates of the 3 outcomes, such as disease-free survival, progression-free survival, or tumor response rate. Endpoints may also be determined within study designs of varying strength, ranging from the gold standard—the randomized, double-blinded controlled clinical trial—to case series experiences from nonconsecutive patients. The PDQ editorial boards use a formal ranking system of levels of evidence to help the reader judge the strength of evidence linked to the reported results of a therapeutic strategy. For any given therapy, results can be ranked on each of the following two scales: (1) strength of the study design and (2) strength of the endpoints. Together, the two rankings give an idea of the overall level of evidence. Depending on perspective, different expert panels, professional organizations, or individual physicians may use different cut points of overall strength of evidence in formulating therapeutic guidelines or in taking action; however, a formal description of the level of evidence provides a uniform framework for the data, leading to specific recommendations.

The PDQ Adult Treatment Editorial Board adds information on levels of evidence, described below, to the PDQ adult treatment cancer information summaries when appropriate.

Carcinoma of the pancreas has a markedly increased incidence over the past several decades and ranks as the fourth leading cause of cancer death in the United States. Despite the high mortality rate associated with pancreatic cancer, its etiology is poorly understood. Cancer of the exocrine pancreas is rarely curable and has an overall survival rate of <4%. The highest cure rate occurs if the tumor is truly localized to the pancreas; however, this stage of the disease accounts for <20% of cases. For those patients with localized disease and small cancers (<2 cm) with no lymph node metastases and no extension beyond the capsule of the pancreas, complete surgical resection can yield actuarial 5-year survival rates of 18% to 24%. [Level of evidence: 3iA] Improvements in imaging technology, including spiral computed tomographic scans, magnetic resonance imaging scans, positron emission tomographic scans, endoscopic ultrasound examination, and laparoscopic staging can aid in the diagnosis and the identification of patients with disease that is not amenable to resection. In a case series of 228 patients, positive peritoneal cytology had a positive predictive value of 94%, specificity of 98%, and sensitivity of 25% for determining unresectability. For patients with advanced cancers, the overall survival rate of all stages is <1% at 5 years with most patients dying within 1 year.

No tumor-specific markers exist for pancreatic cancer; markers such as serum CA 19-9 have low specificity. Most patients with pancreatic cancer will have an elevated CA 19-9 at diagnosis. Following or during definitive therapy, the increase of CA 19-9 levels may identify patients with progressive tumor growth. [Level of evidence: 3iDii] The presence of a normal CA 19-9, however, does not preclude recurrence.

Patients with any stage of pancreatic cancer can appropriately be considered candidates for clinical trials because of the poor response to chemotherapy, radiation therapy, and surgery as conventionally used. Palliation of symptoms, however, may be achieved with conventional treatment. Symptoms caused by pancreatic cancer may depend on the site of the tumor within the pancreas and the degree of involvement. Palliative surgical or radiologic biliary decompression, relief of gastric outlet obstruction, and pain control may improve the quality of life while not affecting overall survival. Palliative efforts may also be directed to the potentially disabling psychological events associated with the diagnosis and treatment of pancreatic cancer.

Pancreatic Cancer Trial Results

1. Gemcitabine Plus Standard Chemoradiation Improves Survival in Patients with Pancreatic Head Tumors
(Posted: 06/05/2006) - Adding gemcitabine to a standard chemoradiation regimen improved overall survival in patients with the most common kind of pancreatic tumors: those located in the head of the pancreas, according to findings presented at the 2006 meeting of the American Society of Clinical Oncology.

2. Post-Surgery Gemcitabine Delays Recurrence of Pancreatic Cancer
(Posted: 05/14/2005) - Patients with operable pancreatic cancer who got additional therapy with the drug gemcitabine lived nearly twice as long before their disease recurred as patients who were treated with surgery alone, according to findings presented at the 2005 meeting of the American Society of Clinical Oncology.

3. Erlotinib Plus Gemcitabine Boosts One-Year Survival in Pancreatic Cancer
(Posted: 05/14/2005) - Patients with advanced pancreatic cancer who were treated with the drug erlotinib (Tarceva®) in addition to gemcitabine had modest improvement in one-year survival rates

compared to patients treated with gemcitabine alone, according to findings presented at the 2005 meeting of the American Society of Clinical Oncology.

Prostate Cancer

General Information

Note: Estimated new cases and deaths from prostate cancer in the United States in 2006:

- New cases: 234,460.
- Deaths: 27,350.

Note: Some citations in the text of this section are followed by a level of evidence. The PDQ editorial boards use a formal ranking system to help the reader judge the strength of evidence linked to the reported results of a therapeutic strategy.

Carcinoma of the prostate is predominantly a tumor of older men, which frequently responds to treatment when widespread and may be cured when localized. The rate of tumor growth varies from very slow to moderately rapid, and some patients may have prolonged survival even after the cancer has metastasized to distant sites such as bone. Because the median age at diagnosis is 72 years, many patients—especially those with localized tumors—may die of other illnesses without ever having suffered significant disability from their cancer. The approach to treatment is influenced by age and coexisting medical problems. Side effects of various forms of treatment should be considered in selecting appropriate management. Controversy exists in regard to the value of screening, the most appropriate staging evaluation, and the optimal treatment of each stage of the disease.

A complicating feature of any analysis of survival after treatment of prostate cancer and comparison of the various treatment strategies is the evidence of increasing diagnosis of nonlethal tumors as diagnostic methods have changed over time. Nonrandomized comparisons of treatments may therefore be confounded not only by patient-selection factors but also by time trends. For example, a population-based study in Sweden showed that from 1960 to the late 1980s, before the use of prostate-specific antigen (PSA) for screening purposes, long-term relative survival rates after the diagnosis of prostate cancer improved substantially as more sensitive methods of diagnosis were introduced. This occurred despite the use of watchful waiting or palliative hormonal treatment as the most common treatment strategies for localized prostate cancer during the entire era (<150 radical prostatectomies per year were performed in Sweden during the late 1980s). The investigators estimated that if all cancers diagnosed between 1960 and 1964 were of the lethal variety, then at least 33% of cancers diagnosed between 1980 and 1984 were of the nonlethal variety. [Level of evidence: 3iB] With the advent of PSA screening, the ability to diagnose nonlethal prostate cancers may increase further.

Another issue complicating comparisons of outcomes among nonconcurrent series of patients is the possibility of changes in criteria for histologic diagnosis of prostate cancer. This phenomenon creates a statistical artifact that can produce a false sense of therapeutic accomplishment and may also lead to more aggressive therapy. For example, prostate biopsies from a population-based cohort of 1,858 men diagnosed with prostate cancer from 1990 through 1992 were re-read in 2002 to 2004. The contemporary Gleason score readings were an average of 0.85 points higher (95% confidence interval [CI], 0.79-0.91; $P < .001$) than the same slides read in 1990 to 1992. As a result, Gleason score-standardized prostate cancer mortality for these men was artifactually improved from 2.08 to 1.50 deaths per 100 person years–a 28% decrease even though overall outcomes were unchanged.

The issue of screening asymptomatic men for prostate cancer with digital rectal examination (DRE), PSA, and/or ultrasound is controversial. Serum PSA and transrectal ultrasound are more sensitive and will increase the diagnostic yield of prostate cancer when used in combination with rectal examination however, these screening methods are also associated with high false-positive rates and may identify some tumors that will not threaten the patient's health. The issue is further complicated by the morbidity associated with work-up and treatment of such tumors and the considerable cost beyond a routine DRE. Furthermore, because a high percentage of tumors identified by PSA screening alone have spread outside the prostate, PSA screening may not improve life expectancy. In any case, the clinician who uses PSA for the detection of prostate cancer should be aware that no uniform standard exists, so that if a laboratory changes to a different assay kit, serial assays may yield nonequivalent PSA values. In addition, the upper limit of the normal range of PSA, and therefore the threshold at which to biopsy, is not well-defined. A multicenter trial sponsored by the National Cancer Institute is under way to test the value of early detection in reducing mortality.

Survival of the patient with prostatic carcinoma is related to the extent of the tumor. When the cancer is confined to the prostate gland, median survival in excess of 5 years can be anticipated. Patients with locally advanced cancer are not usually curable, and a substantial fraction will eventually die of their tumor, though median survival may be as long as 5 years. If prostate cancer has spread to distant organs, current therapy will not cure it. Median survival is usually 1 to 3 years, and most such patients will die of prostate cancer. Even in this group of patients, however, indolent clinical courses lasting for many years may be observed.

Other factors affecting the prognosis of patients with prostate cancer that may be useful in making therapeutic decisions include histologic grade of the tumor, patient's age, other medical illnesses, and level of PSA. Poorly differentiated tumors are more likely to have already metastasized by the time of diagnosis and are associated with a poorer prognosis. For patients treated with radiation therapy, the combination of clinical tumor stage, Gleason score, and pretreatment PSA level can be used to more accurately estimate the risk of relapse. [Level of evidence: 3iDi] In most studies, flow cytometry has shown that nuclear DNA ploidy is an independent prognostic indicator for progression and for cause-specific survival in patients with pathologic stages III and IV prostate cancer without metastases (Jewett stages C and D1). Diploid tumors have a more favorable outcome than either tetraploid or aneuploid tumors. The use of flow cytometry techniques and histogram analysis to determine prognosis will require standardization.

Several nomograms have been developed to predict outcomes either prior to or after radical prostatectomy with intent to cure. Preoperative nomograms are based on clinical stage, PSA, and Gleason score. Postoperative nomograms add pathologic findings, such as capsular invasion, surgical margins, seminal vesicle invasion, and lymph node involvement. The nomograms, however, were developed at academic centers and may not be as accurate when generalized to nonacademic hospitals, where the majority of patients are treated. In addition, the nomograms use nonhealth (intermediate) outcomes such as PSA rise or pathologic surgical findings, and subjective endpoints such as the physician's perceived need for additional therapy. In addition, the nomograms may be affected by changing methods of diagnosis or neoadjuvant therapy over time.

Definitive treatment is usually considered for younger men with prostate cancer and no major comorbid medical illnesses because younger men are more likely to die of prostate cancer than older men or men with major comorbid medical illness. Elevations of serum acid phosphatase are associated with poor prognosis in both localized and disseminated disease. PSA, an organ-specific marker with greater sensitivity and high specificity for prostate tissue, is often used as a tumor marker. After radical prostatectomy, detectable PSA levels identify patients at elevated risk of local treatment failure or

metastatic disease; however, a substantial proportion of patients with elevated or rising PSA levels after surgery may remain clinically free of symptoms for extended periods of time. Biochemical evidence of failure on the basis of elevated or slowly rising PSA alone therefore may not be sufficient to alter treatment. For example, in a retrospective analysis of nearly 2,000 men who had undergone radical prostatectomy with curative intent and who were followed for a mean of 5.3 years, 315 men (15%) demonstrated an abnormal PSA ≥0.2 ng/mL, felt to be evidence of biochemical recurrence. Of these 315 men, 103 men (34%) developed clinical evidence of recurrence. The median time to development of clinical metastasis after biochemical recurrence was 8 years. After the men developed metastatic disease, the median time to death was an additional 5 years.

After radiation therapy with curative intent, persistently elevated or rising PSA may be a prognostic factor for clinical disease recurrence; however, reported case series have used a variety of definitions of PSA failure. Criteria have been developed by the American Society for Therapeutic Radiology and Oncology Consensus Panel. It is difficult to base decisions about instituting additional therapy on biochemical failure. The implication of the various definitions of PSA failure for overall survival is not known, and as in the surgical series, many biochemical relapses (rising PSA alone) may not be clinically manifested in patients treated with radiation therapy.

Preliminary data from a retrospective cohort of 8,669 patients with clinically localized prostate cancer treated with either radical prostatectomy or radiation therapy suggested that short posttreatment PSA doubling time (<3 months in this study) is a useful surrogate endpoint for all-cause mortality and prostate cancer mortality after surgery or radiation therapy. Another retrospective cohort study of 379 men with biochemical recurrence after radical prostatectomy found that PSA doubling time, pathologic Gleason score, and time to biochemical recurrence were all significant risk factors for prostate cancer-specific mortality. These observations should be independently confirmed in prospective study designs and may not apply to patients treated with hormonal therapy.

After hormonal therapy, reduction of PSA to undetectable levels provides information regarding the duration of progression-free status; however, decreases in PSA of <80% may not be very predictive.Yet, because PSA expression itself is under hormonal control, androgen deprivation therapy can decrease the serum level of PSA independent of tumor response. Clinicians, therefore, cannot rely solely on the serum PSA level to monitor a patient's response to hormone therapy; they must also follow clinical criteria.

Early Prostate Cancer: Questions and Answers

Key Points

- The prostate is a gland in the male reproductive system (see Question 1).
- The most common risk factor for prostate cancer is age (see Question 3).
- Prostate cancer often does not cause symptoms for many years. By the time symptoms occur, the disease may have spread beyond the prostate (see Question 4).
- The symptoms of prostate cancer can also be caused by noncancerous conditions (see Questions 4 and 5).
- Two tests can be used to detect prostate cancer in the absence of any symptoms: a digital rectal

exam and a blood test to detect a substance made by the prostate called prostate specific antigen (PSA) (see Questions 6 and 7).

- The diagnosis of prostate cancer can be confirmed only by a biopsy (see Question 8).
- Prostate cancer is described by both grade and stage (see Question 8).
- Three treatment options are generally accepted for men with localized prostate cancer: radical prostatectomy, radiation therapy, and surveillance (also called watchful waiting) (see Questions 9, 10, and 11).

1. What is the prostate?

The prostate is a gland in the male reproductive system. The prostate makes and stores a component of semen and is located near the bladder and the rectum. The prostate surrounds part of the urethra, the tube that empties urine from the bladder. A healthy prostate is about the size of a walnut. If the prostate grows too large, the flow of urine can be slowed or stopped.

2. What is prostate cancer?

Except for skin cancer, cancer of the prostate is the most common malignancy in American men. It is estimated that nearly 221,000 men in the United States will be diagnosed with prostate cancer in 2003. In most men with prostate cancer, the disease grows very slowly. The majority of men with low-grade, early prostate cancer (confined to the gland) live a long time after their diagnosis. Even without treatment, many of these men will not die of the prostate cancer, but rather will live with it until they eventually die of some other, unrelated cause. Nevertheless, nearly 29,000 men will die of prostate cancer in 2003.

3. Who is at risk for prostate cancer?

All men are at risk. The most common risk factor is age. More than 70 percent of men diagnosed with prostate cancer each year are over the age of 65. African American men have a higher risk of prostate cancer than white men. Dramatic differences in the incidence of prostate cancer are also seen in different countries, and there is some evidence that a diet higher in fat, especially animal fat, may account for some of these differences. Genetic factors also appear to play a role, particularly for families in whom the diagnosis is made in men under 60 years of age. The risk of prostate cancer rises with the number of close relatives who have the disease.

4. What are the symptoms of prostate cancer?

Prostate cancer often does not cause symptoms for many years. By the time symptoms occur, the disease may have spread beyond the prostate. When symptoms do occur, they may include:

- Frequent urination, especially at night
- Inability to urinate
- Trouble starting or holding back urination
- A weak or interrupted flow of urine

- Painful or burning urination
- Blood in the urine or semen
- Painful ejaculation
- Frequent pain in the lower back, hips, or upper thighs

These can be symptoms of cancer, but more often they are symptoms of noncancerous conditions. It is important to check with a doctor.

5. **What other prostate conditions can cause symptoms like these?**

   As men get older, their prostate may grow bigger and block the flow of urine or interfere with sexual function. This common condition, called benign prostatic hyperplasia (BPH), is not cancer, but can cause many of the same symptoms as prostate cancer. Although BPH may not be a threat to life, it may require treatment with medicine or surgery to relieve symptoms. An infection or inflammation of the prostate, called prostatitis, may also cause many of the same symptoms as prostate cancer. Again, it is important to check with a doctor.

6. **Can prostate cancer be found before a man has symptoms?**

   Yes. Two tests can be used to detect prostate cancer in the absence of any symptoms. One is the digital rectal exam (DRE), in which a doctor feels the prostate through the rectum to find hard or lumpy areas. The other is a blood test used to detect a substance made by the prostate called prostate specific antigen (PSA). Together, these tests can detect many "silent" prostate cancers, those that have not caused symptoms.

   At present, however, it is not known whether routine screening saves lives. The benefits of screening and local therapy (surgery or radiation) remain unclear for many patients. Because of this uncertainty, the National Cancer Institute is currently supporting research to learn more about screening men for prostate cancer. Currently, researchers are conducting a large study to determine whether screening men using a blood test for PSA and a DRE can help reduce the death rate from this disease. They are also assessing the risks of screening. Full results from this study, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial or PLCO, are expected by 2015.

7. **How reliable are the screening tests for prostate cancer?**

   Neither of the screening tests for prostate cancer is perfect. Most men with mildly elevated PSA levels do not have prostate cancer, and many men with prostate cancer have normal levels of PSA. Also, the DRE can miss many prostate cancers. The DRE and PSA test together are better than either test alone in detecting prostate cancer.

8. **How is prostate cancer diagnosed?**

   The diagnosis of prostate cancer can be confirmed only by a biopsy. During a biopsy, a urologist (a doctor who specializes in diseases of urinary and sex organs in men, and urinary organs in women) removes tissue samples, usually with a needle. This is generally done in the doctor's office with local anesthesia. Then a pathologist (a doctor who identifies diseases by studying tissues under a microscope) checks for cancer cells.

Prostate cancer is described by both grade and stage.

- Grade describes how closely the tumor resembles normal prostate tissue. Based on the microscopic appearance of tumor tissue, pathologists may describe it as low-, medium-, or high-grade cancer. One way of grading prostate cancer, called the Gleason system, uses scores of 2 to 10. Another system uses G1 through G4. In both systems, the higher the score, the higher the grade of the tumor. High-grade tumors generally grow more quickly and are more likely to spread than low-grade tumors.

- Stage refers to the extent of the cancer. Early prostate cancer, stages I and II, is localized. It has not spread outside the gland. Stage III prostate cancer, often called locally advanced disease, extends outside the gland to the seminal vesicles. Stage IV means the cancer has spread to lymph nodes and/or to other tissues or organs.

9. **How is localized prostate cancer treated?**

Three treatment options are generally accepted for men with localized prostate cancer: radical prostatectomy, radiation therapy, and surveillance (also called watchful waiting).

- Radical prostatectomy is a surgical procedure to remove the entire prostate gland and nearby tissues. Sometimes lymph nodes in the pelvic area (the lower part of the abdomen, located between the hip bones) are also removed. Radical prostatectomy may be performed using a technique called nerve-sparing surgery that may prevent damage to the nerves needed for an erection.

- Radiation therapy involves the delivery of radiation energy to the prostate. The energy is usually delivered in an outpatient setting using an external beam of radiation. The energy can also be delivered by implanting radioactive seeds in the prostate using a needle.

- Surveillance, taking a wait-and-see approach, may be recommended for patients with early-stage prostate cancer, particularly those who are older or have other serious medical conditions. These patients have regular examinations. If there is evidence of cancer growth, active treatment may be recommended.

10. **How does a patient decide what is the best treatment option for localized prostate cancer?**

Choosing a treatment option involves the patient, his family, and one or more doctors. They will need to consider the grade and stage of the cancer, the man's age and health, and his values and feelings about the potential benefits and harms of each treatment option. Often it is useful to seek a second opinion, and patients may hear different opinions and recommendations. Because there are several reasonable options for most patients, the decision can be difficult. Patients should try to get as much information as possible and allow themselves enough time to make a decision. There is rarely a need to make a decision without taking time to discuss and understand the pros and cons of the various approaches.

11. **Where can a person find more information about prostate cancer and its treatment?**

The NCI has several other resources that readers may find helpful, including the following:

- **The *Prostate Cancer Home Page*** provides links to NCI resources about prevention, screening, treatment, clinical trials, and supportive care for this type of cancer. This page can be found on the NCI's Web site at http://www.cancer.gov/prostate/ on the **Internet.**

- ***Prostate Cancer (PDQ®): Treatment*** includes information about prostate cancer treatment, including surgery, chemotherapy, radiation therapy, and hormone therapy. This summary of information from PDQ, the NCI's comprehensive cancer information database, is available at http://www.cancer.gov/cancerinfo/pdq/treatment/prostate/patient/ on the Internet.

- ***Know Your Options: Understanding Treatment Choices for Prostate Cancer*** is designed to help a man and his family understand what a diagnosis of prostate cancer means and what treatment choices are available. This resource can be found at http://www.cancer.gov/CancerInformation/understanding-prostate-cancer-treatment on the Internet.

Prostate Cancer Trial Results

1. Saw Palmetto Fails to Improve Benign Prostatic Hyperplasia
(Posted: 02/15/2006) - An extract of the saw palmetto plant was no more effective than a placebo in reducing symptoms associated with benign prostatic hyperplasia (BPH), according to the Feb. 9, 2006, issue of the New England Journal of Medicine.

2. Higher Radiation Dose Reduces Recurrence of Local Prostate Cancer
(Posted: 10/03/2005) - Men with early-stage prostate cancer who got higher doses of radiation were half as likely to see their cancer recur in five years as men who received the conventional dose, according to the Sept. 14, 2005, issue of the Journal of the American Medical Association.

3. **Radiation After Surgery Cuts Risk of Recurrence in Prostate Cancer**
(Posted: 09/07/2005) - Men with locally advanced prostate cancer who underwent surgery to remove their prostate gland followed by radiotherapy were less likely to have their cancer return and spread than men who did not receive the additional radiotherapy, according to the August 13, 2005, issue of the Lancet.

4. Surgery Helps Relieve Spinal Cord Compression Caused by Metastatic Cancer
(Posted: 06/02/2003, Updated: 08/23/2005) - Surgery followed by radiation is more effective than radiation alone in treating spinal cord compression caused by metastatic cancer.

5. Frozen Glove Reduces Skin and Nail Damage from Docetaxel Chemotherapy
(Posted: 08/01/2005) - Patients who wore an experimental "frozen glove" to keep their hands very cold during intravenous chemotherapy with docetaxel (Taxotere®) had much less subsequent damage to the nails and skin of their hands, according to a study published in the July 1, 2005, issue of the Journal of Clinical Oncology.

Skin Cancer

General Information

Basal cell carcinoma is the most common form of skin cancer, and squamous cell carcinoma is the second most common type of skin malignancy. Although the 2 types of skin cancer are the most common of all malignancies, they account for <0.1% of patient deaths caused by cancer. Both of these types of skin cancer are more likely to occur in individuals of light complexion who have had significant exposure to sunlight, and both types of skin cancer are more common in the southern latitudes of the Northern hemisphere.

The overall cure rate for basal cell carcinoma and squamous cell carcinoma is directly related to the stage of the disease and the type of treatment used. Since neither basal cell carcinoma nor squamous cell carcinoma are reportable diseases, precise 5-year cure rates are not known.

Although basal cell carcinoma and squamous cell carcinoma are by far the most frequent types of skin tumors, the skin can also be the site of a large variety of malignant neoplasms. Other types of malignant disease include malignant melanoma, cutaneous T-cell lymphomas (e.g., mycosis fungoides), Kaposi's sarcoma, extramammary Paget's disease, apocrine carcinoma of the skin, and metastatic malignancies from various primary sites. Guidelines for the care of cutaneous squamous cell carcinoma have been published.

Merkel Call Carcinoma Treatment

General Information

Merkel cell carcinoma (MCC), or neuroendocrine carcinoma of the skin, is an uncommon and often aggressive malignancy that has a poor prognosis. More than 400 new cases of MCC occur in the United States each year, and the mortality rate is approximately 25%. MCC is predominantly a tumor of the elderly, and most reported cases have occurred in white subjects. It occurs most frequently in the head and neck region and the extremities and has a predilection for the periocular region. People treated with methoxsalen and ultraviolet A for psoriasis and people who are immunocompromised have an increased incidence of developing MCC.

The Merkel cell is located in or near the basal layer of the epidermis and is closely associated with terminal axons. While MCC may be difficult to diagnose, it usually presents as a painless, indurated, solitary dermal nodule with a slightly erythematous to deeply violaceous color. MCC frequently involves regional lymph nodes (10%–45% at initial presentation), and between 50% and 75% of patients will develop regional lymph node metastases at some time during the course of their disease. Distant metastases eventually occur in as many as 50% of patients, with lymph nodes, the liver, bone, brain, lung, and skin the most common sites of distant involvement. MCC may progress rapidly, similar to aggressive melanoma. After primary tumor excision, local recurrence develops in 25% to 44% of patients; this has been attributed to inadequate surgical margins.

Cryosurgery in Cancer Treatment: Questions and Answers

Key Points

- **Cryosurgery is a technique for freezing and killing abnormal cells. It is used to treat some kinds of cancer and some precancerous or noncancerous conditions, and can be used both inside the body and on the skin (see Question 1).**
- **Cryosurgery is an alternative to surgery for liver cancer that has not spread, for cancer that has spread to the liver from another site, for prostate cancer confined to the prostate**

gland, for a precancerous condition of the cervix, and for cancerous and noncancerous tumors of the bone (see Questions 2, 3, and 4).

- **Cryosurgery may have fewer side effects than other types of treatments, and is less expensive and requires shorter recovery times (see Questions 5 and 6).**
- **The technique is still under study, and its long-term effectiveness is not known (see Questions 7 and 8).**

1. What is cryosurgery?

Cryosurgery (also called cryotherapy) is the use of extreme cold produced by liquid nitrogen (or argon gas) to destroy abnormal tissue. Cryosurgery is used to treat external tumors, such as those on the skin. For external tumors, liquid nitrogen is applied directly to the cancer cells with a cotton swab or spraying device.

Cryosurgery is also used to treat tumors inside the body (internal tumors and tumors in the bone). For internal tumors, liquid nitrogen or argon gas is circulated through a hollow instrument called a cryoprobe, which is placed in contact with the tumor. The doctor uses ultrasound or MRI to guide the cryoprobe and monitor the freezing of the cells, thus limiting damage to nearby healthy tissue. (In ultrasound, sound waves are bounced off organs and other tissues to create a picture called a sonogram.) A ball of ice crystals forms around the probe, freezing nearby cells. Sometimes more than one probe is used to deliver the liquid nitrogen to various parts of the tumor. The probes may be put into the tumor during surgery or through the skin (percutaneously). After cryosurgery, the frozen tissue thaws and is either naturally absorbed by the body (for internal tumors), or it dissolves and forms a scab (for external tumors).

2. What types of cancer can be treated with cryosurgery?

Cryosurgery is used to treat several types of cancer, and some precancerous or noncancerous conditions. In addition to prostate and liver tumors, cryosurgery can be an effective treatment for the following:

- Retinoblastoma (a childhood cancer that affects the retina of the eye). Doctors have found that cryosurgery is most effective when the tumor is small and only in certain parts of the retina.
- Early-stage skin cancers (both basal cell and squamous cell carcinomas).
- Precancerous skin growths known as actinic keratosis.
- Precancerous conditions of the cervix known as cervical intraepithelial neoplasia (abnormal cell changes in the cervix that can develop into cervical cancer).

Cryosurgery is also used to treat some types of low-grade cancerous and noncancerous tumors of the bone. It may reduce the risk of joint damage when compared with more extensive surgery, and help lessen the need for amputation. The treatment is also used to treat AIDS-related Kaposi's sarcoma when the skin lesions are small and localized.

Researchers are evaluating cryosurgery as a treatment for a number of cancers, including breast, colon, and kidney cancer. They are also exploring cryotherapy in combination with other cancer treatments, such as hormone therapy, chemotherapy, radiation therapy, or surgery.

3. **In what situations can cryosurgery be used to treat prostate cancer? What are the side effects?**

   Cryosurgery can be used to treat men who have early-stage prostate cancer that is confined to the prostate gland. It is less well established than standard prostatectomy and various types of radiation therapy. Long-term outcomes are not known. Because it is effective only in small areas, cryosurgery is not used to treat prostate cancer that has spread outside the gland, or to distant parts of the body.

   Some advantages of cryosurgery are that the procedure can be repeated, and it can be used to treat men who cannot have surgery or radiation therapy because of their age or other medical problems.

   Cryosurgery for the prostate gland can cause side effects. These side effects may occur more often in men who have had radiation to the prostate.

   - Cryosurgery may obstruct urine flow or cause incontinence (lack of control over urine flow); often, these side effects are temporary.
   - Many men become impotent (loss of sexual function).
   - In some cases, the surgery has caused injury to the rectum.

4. In what situations can cryosurgery be used to treat primary liver cancer or liver metastases (cancer that has spread to the liver from another part of the body)? What are the side effects?

   Cryosurgery may be used to treat primary liver cancer that has not spread. It is used especially if surgery is not possible due to factors such as other medical conditions. The treatment also may be used for cancer that has spread to the liver from another site (such as the colon or rectum). In some cases, chemotherapy and/or radiation therapy may be given before or after cryosurgery. Cryosurgery in the liver may cause damage to the bile ducts and/or major blood vessels, which can lead to hemorrhage (heavy bleeding) or infection.

5. **Does cryosurgery have any complications or side effects?**

   Cryosurgery does have side effects, although they may be less severe than those associated with surgery or radiation therapy. The effects depend on the location of the tumor. Cryosurgery for cervical intraepithelial neoplasia has not been shown to affect a woman's fertility, but it can cause cramping, pain, or bleeding. When used to treat skin cancer (including Kaposi's sarcoma), cryosurgery may cause scarring and swelling; if nerves are damaged, loss of sensation may occur, and, rarely, it may cause a loss of pigmentation and loss of hair in the treated area. When used to treat tumors of the bone, cryosurgery may lead to the destruction of nearby bone tissue and result in fractures, but these effects may not be seen for some time after the initial treatment and can often be delayed with other treatments. In rare cases, cryosurgery may interact badly with certain types of chemotherapy. Although the side effects of surgery may be less severe than those associated with conventional surgery or radiation, more studies are needed to determine the long-term effects.

6. **What are the advantages of cryosurgery?**

   Cryosurgery offers advantages over other methods of cancer treatment. It is less invasive than surgery, involving only a small incision or insertion of the cryoprobe through the skin. Consequently, pain, bleeding, and other complications of surgery are minimized. Cryosurgery is less expensive than other treatments and requires shorter recovery time and a shorter hospital stay, or no hospital stay at all. Sometimes cryosurgery can be done using only local anesthesia.

   Because physicians can focus cryosurgical treatment on a limited area, they can avoid the destruction of nearby healthy tissue. The treatment can be safely repeated and may be used along with standard treatments such as surgery, chemotherapy, hormone therapy, and radiation. Cryosurgery may offer an option for treating cancers that are considered inoperable or that do not respond to standard treatments. Furthermore, it can be used for patients who are not good candidates for conventional surgery because of their age or other medical conditions.

7. **What are the disadvantages of cryosurgery?**

   The major disadvantage of cryosurgery is the uncertainty surrounding its long-term effectiveness. While cryosurgery may be effective in treating tumors the physician can see by using imaging tests (tests that produce pictures of areas inside the body), it can miss microscopic cancer spread. Furthermore, because the effectiveness of the technique is still being assessed, insurance coverage issues may arise.

8. **What does the future hold for cryosurgery?**

   Additional studies are needed to determine the effectiveness of cryosurgery in controlling cancer and improving survival. Data from these studies will allow physicians to compare cryosurgery with standard treatment options such as surgery, chemotherapy, and radiation. Moreover, physicians continue to examine the possibility of using cryosurgery in combination with other treatments.

9. **Where is cryosurgery currently available?**

   Cryosurgery is widely available in gynecologists' offices for the treatment of cervical neoplasias. A limited number of hospitals and cancer centers throughout the country currently have skilled doctors and the necessary technology to perform cryosurgery for other noncancerous, precancerous, and cancerous conditions. Individuals can consult with their doctors or contact hospitals and cancer centers in their area to find out where cryosurgery is being used.

Lasers in Cancer Treatment: Questions and Answers

Key Points

- Laser light is a light of such high intensity and narrow beam that it can be used to do precise surgery to remove cancer or precancerous growths or to relieve symptoms of cancer. It is used

most often to treat cancers on the surface of the body or the lining of internal organs (see Questions 1 and 2).

- Laser therapy is often given through a thin tube called an endoscope. An endoscope can be inserted in openings in the body to treat cancer or precancerous growths inside the trachea (windpipe), esophagus, stomach, or colon (see Questions 2 and 3).
- Laser therapy causes less bleeding and damage to normal tissue than standard surgical tools, and there is a lower risk of infection (see Question 5).
- However, laser therapy is extremely expensive and the effects of the surgery may not be permanent, so the surgery may have to be repeated (see Question 6).

1. **What is laser light?**

   The term "laser" stands for light amplification by stimulated emission of radiation. Ordinary light, such as that from a light bulb, has many wavelengths and spreads in all directions. Laser light, on the other hand, has a specific wavelength. It is focused in a narrow beam and creates a very high-intensity light. This powerful beam of light may be used to cut through steel or to shape diamonds. Because lasers can focus very accurately on tiny areas, they can also be used for very precise surgical work or for cutting through tissue (in place of a scalpel).

2. **What is laser therapy, and how is it used in cancer treatment?**

   Laser therapy uses high-intensity light to treat cancer and other illnesses. Lasers can be used to shrink or destroy tumors. Lasers are most commonly used to treat superficial cancers (cancers on the surface of the body or the lining of internal organs) such as basal cell skin cancer and the very early stages of some cancers, such as cervical, penile, vaginal, vulvar, and non-small cell lung cancer.

   Lasers also may be used to relieve certain symptoms of cancer, such as bleeding or obstruction. For example, lasers can be used to shrink or destroy a tumor that is blocking a patient's trachea (windpipe) or esophagus. Lasers also can be used to remove colon polyps or tumors that are blocking the colon or stomach.

   Laser therapy can be used alone, but most often it is combined with other treatments, such as surgery, chemotherapy, or radiation therapy. In addition, lasers can seal nerve endings to reduce pain after surgery and seal lymph vessels to reduce swelling and limit the spread of tumor cells.

3. **How is laser therapy given to the patient?**

   Laser therapy is often given through a flexible endoscope (a thin, lighted tube used to look at tissues inside the body). The endoscope is fitted with optical fibers (thin fibers that transmit light). It is inserted through an opening in the body, such as the mouth, nose, anus, or vagina. Laser light is then precisely aimed to cut or destroy a tumor.

   Laser-induced interstitial thermotherapy (LITT) (or interstitial laser photocoagulation) also uses lasers to treat some cancers. LITT is similar to a cancer treatment called hyperthermia, which uses heat to shrink tumors by damaging or killing cancer cells. (More information about hyperthermia is available in the National Cancer Institute (NCI) fact sheet *Hyperthermia in*

Cancer Treatment: Questions and Answers, which can be found at http://www.cancer.gov/cancertopics/factsheet/Therapy/hyperthermia on the Internet.) During LITT, an optical fiber is inserted into a tumor. Laser light at the tip of the fiber raises the temperature of the tumor cells and damages or destroys them. LITT is sometimes used to shrink tumors in the liver.

Photodynamic therapy (PDT) is another type of cancer treatment that uses lasers. In PDT, a certain drug, called a photosensitizer or photosensitizing agent, is injected into a patient and absorbed by cells all over the patient's body. After a couple of days, the agent is found mostly in cancer cells. Laser light is then used to activate the agent and destroy cancer cells. Because the photosensitizer makes the skin and eyes sensitive to light for approximately 6 weeks, patients are advised to avoid direct sunlight and bright indoor light during that time

4. **What types of lasers are used in cancer treatment?**

   Three types of lasers are used to treat cancer: carbon dioxide (CO_2) lasers, argon lasers, and neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers. Each of these can shrink or destroy tumors and can be used with endoscopes. CO_2 and argon lasers can cut the skin's surface without going into deeper layers. Thus, they can be used to remove superficial cancers, such as skin cancer. In contrast, the Nd:YAG laser is more commonly applied through an endoscope to treat internal organs, such as the uterus, esophagus, and colon. Nd:YAG laser light can also travel through optical fibers into specific areas of the body during LITT. Argon lasers are often used to activate the drugs used in PDT.

5. **What are the advantages of laser therapy?**

   Lasers are more precise than standard surgical tools (scalpels), so they do less damage to normal tissues. As a result, patients usually have less pain, bleeding, swelling, and scarring. With laser therapy, operations are usually shorter. In fact, laser therapy can often be done on an outpatient basis. It takes less time for patients to heal after laser surgery, and they are less likely to get infections. Patients should consult with their health care provider about whether laser therapy is appropriate for them.

6. **What are the disadvantages of laser therapy?**

   Laser therapy also has several limitations. Surgeons must have specialized training before they can do laser therapy, and strict safety precautions must be followed. Also, laser therapy is expensive and requires bulky equipment. In addition, the effects of laser therapy may not last long, so doctors may have to repeat the treatment for a patient to get the full benefit.

7. **What does the future hold for laser therapy?**

   In clinical trials (research studies), doctors are using lasers to treat cancers of the brain and prostate, among others. To learn more about clinical trials, call the NCI's Cancer Information Service at the telephone number listed below or visit the clinical trials page of the NCI's Web site at http://www.cancer.gov/clinicaltrials on the Internet.

Skin Cancer Prevention

Summary of Evidence

Nonmelanoma skin cancer

Squamous Cell Carcinoma

There is inadequate evidence to determine whether the use of sunscreen reduces the incidence of squamous cell carcinoma of the skin.

Description of the Evidence

- Study design**: One randomized controlled trial (RCT) with tumor incidence as the outcome and one RCT with actinic keratosis as the outcome.**
- Internal Validity**: Fair.**
- Consistency**: Good.**
- Magnitude of Effects on Health Outcomes**: 39% point estimate reduction in tumor incidence (from one study).**
- External Validity**: Fair.**

Basal Cell Carcinoma

There is inadequate evidence to determine whether the use of sunscreen reduces the incidence of basal cell carcinoma of the skin.

Description of the Evidence

- Study design**: Evidence of association obtained from cohort studies.**
- Internal Validity**: N/A**
- Consistency**: N/A**
- Magnitude of Effects on Health Outcomes**: N/A**
- External Validity**: N/A**

Cutaneous melanoma

There is inadequate evidence to determine whether the avoidance of sunburns alters the incidence of cutaneous melanoma.

Description of the Evidence

- Study Design**: Evidence of association only obtained from cohort or case-control studies.**
- Internal Validity**: Inadequate.**
- Consistency**: Poor.**
- Magnitude of Effects on Health Outcomes**: N/A**
- External Validity**: N/A**

Thyroid Cancer

General Information

Note: Estimated new cases and deaths from thyroid cancer in the United States in 2006:

- New cases: 30,180.
- Deaths: 1,500.

Carcinoma of the thyroid gland is an uncommon cancer but is the most common malignancy of the endocrine system. Differentiated tumors (papillary or follicular) are highly treatable and usually curable. Poorly differentiated tumors (medullary or anaplastic) are much less common, are aggressive, metastasize early, and have a much poorer prognosis. Thyroid cancer affects women more often than men and usually occurs in people between the ages of 25 and 65 years. The incidence of this malignancy has been increasing over the last decade. Thyroid cancer commonly presents as a cold nodule. The overall incidence of cancer in a cold nodule is 12% to 15%, but it is higher in people younger than 40 years and in people with calcifications present on preoperative ultrasonography.

Risk factors

Patients with a history of radiation administered in infancy and childhood for benign conditions of the head and neck, such as enlarged thymus, acne, or tonsillar or adenoidal enlargement, have an increased risk of cancer as well as other abnormalities of the thyroid gland. In this group of patients, malignancies of the thyroid gland first appear beginning as early as 5 years following radiation and may appear 20 or more years later. Radiation exposure as a consequence of nuclear fallout has also been associated with a high risk of thyroid cancer, especially in children. Other risk factors for the development of thyroid cancer include a history of goiter, family history of thyroid disease, female gender, and Asian race.

Prognostic factors

The prognosis for differentiated carcinoma is better for patients younger than 40 years without extracapsular extension or vascular invasion. Age appears to be the single most important prognostic factor. The prognostic significance of lymph node status is controversial. One retrospective surgical series of 931 previously untreated patients with differentiated thyroid cancer found that female gender, multifocality, and regional node involvement are favorable prognostic factors. Adverse factors included age older than 45 years, follicular histology, primary tumor >4 cm (T2-3), extrathyroid extension (T4), and distant metastases. Other studies, however, have shown that regional lymph node involvement had no effect or even an adverse effect on survival. Diffuse, intense immunostaining for vascular endothelial growth factor in patients with papillary cancer has been associated with a high rate of local recurrence and distant metastases. An elevated serum thyroglobulin level correlates strongly with recurrent tumor when found in patients with differentiated thyroid cancer during postoperative evaluations. Serum thyroglobulin levels are most sensitive when patients are hypothyroid and have elevated serum thyroid-stimulating hormone levels. Expression of the tumor suppressor gene *p53* has also been associated with an adverse prognosis for patients with thyroid cancer.

Patients considered to be low risk by the age, metastases, extent, and size (AMES) risk criteria include women younger than 50 years and men younger than 40 years without evidence of distant metastases. Also included in the low-risk group are older patients with primary tumors <5 cm and papillary cancer without evidence of gross extrathyroid invasion or follicular cancer without either major capsular invasion or blood vessel invasion. Using these criteria, a retrospective study of 1,019 patients showed

that the 20-year survival rate is 98% for low-risk patients and 50% for high-risk patients. The 10-year overall relative survival rates for patients in the United States are 93% for papillary cancer, 85% for follicular cancer, 75% for medullary cancer, and 14% for undifferentiated/anaplastic cancer.

The thyroid gland may occasionally be the site of other primary tumors, including sarcomas, lymphomas, epidermoid carcinomas, and teratomas and may be the site of metastasis from other cancers, particularly of the lung, breast, and kidney.

Thyroid Cancer Trial Results

1. Surgery May Prevent Rare Thyroid Cancer in At-Risk Children
(Posted: 09/28/2005) - Forty-four of 50 children who carried a genetic mutation that causes a rare type of thyroid cancer, but who had no symptoms of the disease, remained disease-free five or more years after preventive surgery to remove the thyroid gland, according to the Sept. 15, 2005, issue of the New England Journal of Medicine.

At this point in the course, we should take a closer look at the two major types of cancer treatment employed today: radiation therapy, and chemotherapy:

The Basics of Radiation Therapy

The use of radiation for diagnostic and treatment purposes was a revolutionary step in the evolution of medicine. Without it, we wouldn't be able to diagnose numerous conditions and diseases, and we wouldn't be able to treat cancer with radiation. (NOTE: Use of the word “we” here is meant to mean medicine in general.) Diagnostic x-rays allow us to view the inside of the body without invading it -- literally bringing the inside out. Therapeutic radiation takes the technology one step further and allows us to treat cancer in various organs without opening up the body. For some kinds of cancer, radiation is the predominant form of treatment. For other types, it is used in conjunction with surgery and/or chemotherapy.

Because we are able to detect some cancers earlier than we used to, an aggressive combined treatment approach aimed at curing the cancer often has been found to be more effective than using only one or another treatment. For example, early detection of breast cancer by means of mammography has for many women meant less drastic surgery along with radiation to treat the breast. Chemotherapy may also be administered to decrease the possibility of distant spread.

The rapid advances in radiation and computer technology have resulted in improvements in treatment accuracy and results. At the same time, there are fewer and less severe side effects than experienced even a few years ago.

How Does Cancer Develop?

Cancers begin as a cluster of cells multiplying in an out-of-control manner, unlike the body's normal cycle of cell destruction and replenishment. Particular abnormal genes (oncogenes) that influence this uncontrolled growth have been identified in some cancer cells.

Scientists believe that once a cluster of cancer cells has arisen in an organ, there is a step-by-step progressive pattern in cancer growth and spread. At first, the body's immune system resists the growth

of the invader, a process that may take years. Once the battle tips in favor of the cancer, local growth proceeds. At some point, and this point is thought to vary among cancers as well as individuals, the cancer spreads locally into surrounding tissues. The next step is for cancer cells to attach themselves to and penetrate the neighboring blood-vessel and lymph-vessel walls.

Once the cancer cells have penetrated the blood-vessel wall, they enter the bloodstream and the lymph system of the body. Cells traveling in the lymph system settle in the lymph nodes. The cancer cells then travel throughout the body, but must reattach to and penetrate the vessel wall at a distant site. The organs into which these cells settle are generally those richly endowed with blood vessels and with nutrient materials. Thus, the bones, the liver, the lungs, and the brain are common sites for metastases.

How Does Radiation Treatment Work?

The effects of radiation on tissues and their cells are very complex. For the sake of simplicity, the principles can be explained as the ability of radiation to injure the genetic material (DNA) in the center (nucleus) of the cell. The results of the biochemical effects, which *do not* make the body radioactive, is to either destroy the cell or alter its metabolism so as to hinder its ability to function normally.

Radiation may be administered in the form of gamma rays or x-rays (as discussed later). They differ only in their origin, but not in their ultimate biological effects.

Radiation therapy is administered to those cancers where there is a selective ability for the radiation to destroy cancer cells while allowing the adjacent normal cells to repair themselves from the injury.

The reason that the treatment course for some cancers is so relatively long is to allow for normal tissue repair and to minimize permanent injury. *Relatively* small doses given over a long period of time allow for normal tissues to recover at the expense of the cancer cell. (Tissue repair can also be helped by proper nutrition and patients' mental state.) The daily dose must also be great enough to destroy the cancer cell while "sparing" the normal tissues. This "balancing act" forms the basis of modern radiation therapy, which has been further complicated in recent years because, in many cases, chemotherapy, which also harms normal tissues, is used in combination with radiation.

Patients often ask why some cancers can be destroyed by radiation while others don't respond to this treatment. Simply stated, cancer cells vary in their sensitivity to destruction by x-rays. This sensitivity largely depends on the origin of the cancer. For example, a skin cancer is generally more sensitive, meaning more easily destroyed, than a cancer originating in the brain.

The sensitivity may also vary in the same cancer site. One patient with cancer of the uterus may respond much better to radiation than another patient with the same cancer because the uterus contains more than one cell type. Each cell type varies in its ability to be destroyed by radiation therapy. Thus, cancer cells arising from the lining of the uterine cavity are more sensitive to radiation than those arising from its muscle cells. As a result, a relatively small amount of radiation may be necessary to effectively treat one patient, whereas much higher doses are necessary for another.

In addition, cancer cells in the same tumor may vary in their sensitivity to radiation depending on their *location* in the mass. Generally the outer areas of the tumor are more sensitive. This is related to the amount of oxygen reaching the cancer. The peripheral regions are better oxygenated and are destroyed more easily than tumor cells at the center.

When we talk about *resistance* we mean the opposite of sensitivity. Some cancers, such as melanoma, a type of skin cancer, are usually resistant to radiation therapy and little or no benefit is achieved by using it.

Treatment Planning

The decision to use radiation therapy for the individual patient's cancer was arrived at after consultations between the pathologist, surgeon, internist, and chemotherapist, all of whom are part of the patient's treatment team.

Some cancers respond better to surgical treatment or chemotherapy (treatment using drugs or other chemical agents). Nowadays, improvement in cancer survival often involves treatments that combine surgery, radiation, and chemotherapy. But each situation is individualized -- or tailored -- to the particular patient. In addition to the type and location of the cancer, age and general physical condition guide the choice of treatment procedures used.

Organs are composed of different cell types -- each type can lead to a different cancer. For example, cancer cells arising from the air sacs of the lungs lead to a different type of cancer than those arising from the bronchial tubes. The cell type provides the information that allows a radiation oncologist to predict the tumor's response to radiation. Thus, a prognosis, or educated opinion, about the probable effectiveness of radiation therapy is determined.

The individual cell type may vary in its ability to spread. This degree of aggressiveness is referred to as cell *grade.*

Clinicians also look at the extent to which the cancer is present. Is it *localized,* meaning limited to the organ of origin, or has it spread to neighboring or distant sites in the body? The evaluation of the extent of the cancer is referred to as the *staging* of the tumor. This involves using various diagnostic x-ray tests. CT scans and nuclear scans, ultrasound examinations, and simple x-ray tests are often used to assess the entire situation. Obviously, the goal is to correctly treat the tumor while minimizing any negative effects on the surrounding normal tissues.

Clinicians use the three parameters of grade, type, and staging to evaluate how much radiation will be necessary and for what period of time. This is known as the *dose-time* relationship of treatment. The *dose* levels and length of treatment are guidelines. The treatment schedules have been arrived at by the cumulative experience of major treatment centers, using large numbers of patients. *However, every person's case is individualized, sp treatment dose and time may vary from those described here.*

Radiation oncologists won't treat a patient's cancer as an isolated event. He or she generally works closely with the referring physician before and during treatment, jointly evaluating the impact of the therapy on the entire medical condition. For example, other diseases and disorders may coexist with cancer, or the patient may have medical problems that could be aggravated by radiation therapy. These conditions must be carefully monitored.

In addition to delivering treatment, the radiation oncologist is also responsible for treating the side effects of the treatments with appropriate medications. The patient's nutritional status is monitored, and he/she will be given advice about certain food groups that should be avoided and those that should be emphasized. In other words, the radiation oncologist is involved with patients's overall well-being during and after radiation therapy.

Consulting with The Radiation Oncologist

A radiation oncologist (RO) is a physician, specifically a radiologist, who is specially trained in not only the science, but the art, of administering radiation treatments. Some radiologists are certified in both diagnostic and therapeutic radiology. With the current emphasis on subspecialization, most radiologists are either diagnostic or therapeutic radiologists. A radiation oncologist is trained to evaluate which patients may undergo radiation therapy by determining if the tumor will respond to radiation.

When a patient and/or family members first meet with the radiation oncologist, they should be sure to tell him or her what they already know about the illness. The RO generally ask patients, "What do you understand about your disease?" He will also tell them that by the time they leave his office they should have a complete understanding of their cancer and its treatment. Patients should leave the radiation oncologist's office with the knowledge that they are part of the treatment team.

Patients should write questions down before their office visit, because the issues they want to discuss might slip their mind when actually in the office. This is understandable because the first visit is often emotionally charged for both the patient and family members. If additional questions when they return home, they should call the physician and get answers. All this information will alleviate fear, lower anxiety, and therefore boost the therapeutic effect of radiation.

Patients should NOT be afraid to ask the radiation oncologist or other physicians/nurses about the likely outcome of the disease. Such issues should be dealt with realistically. The radiation oncologist's response should be based on current statistics for the specific cancer and its stage. However, it's just as important to discuss individual variation. Often the RO mentions cures that he has seen in his practice even when, according to the statistics, the outlook was grim. As Norman Cousins wrote in his book *Head First,* "Don't deny the diagnosis, just the verdict that is supposed to go with it."

No preparation is necessary before going to the radiation oncologist's office. It's important, however, to have as many records available as possible. These include previous history and medical examinations related to the cancer and other conditions as well as any available X-rays and other tests. If these can't be directly obtained, then the patient should make sure they have been sent to the radiation oncologist's office beforehand. This will save a lot of time.

During the initial consultation, the radiation oncologist will review the pathology report and all x-ray tests available, and evaluate and determine an appropriate field (portal) of treatment. This is drawn on the skin with indelible ink. This ink may wash off with time, and the patient will be instructed not to scrub at the marks but to shower or bathe normally. A simulator machine will ensure that the portal will include the cancer and its potential areas of spread.

This phase of treatment planning is known as *simulation.* Thus, the treatment process is set up, checked, and rechecked to guarantee that the *actual* treatment will be as precise as possible. In addition, any questions about the treatment plan can be resolved with the patient and treatment team, including the nurses and technical staff, who are an important part of delivering radiation therapy.

When patients discuss their condition with their physicians, they need to bear in mind that treatment plans for cancer can't be isolated from a person's age, general physical condition, or even his or her psychological makeup. An older person who is suffering from cancer in addition to having an underlying chronic health problem -- a lung condition, for example -- will be treated differently than a person 20 years younger with a similar cancer but without other physical disabilities. Although there's no universally accepted definition of quality of life, it certainly enters into decisions about radiation dose levels, length of treatment, and size of treatment areas.

The radiation oncologist will probably be involved in the case for an average of two to eight weeks. The time to build a comfortable relationship with this person is at the beginning of treatment.

Treatment Procedure

Radiation treatments do not involve pain or any other sensation. Although patients are afraid they will feel intense heat, there is no heat, light, or sound associated with the treatment. (The fact that treatment is "silent" may produce anxieties of its own.) However, the information in this section will help alleviate any anxieties the patient may have.

The patient lies on a treatment couch for a few minutes. The exact length of time depends on body size, the location of the tumor, and the size of the area being treated. The area subject to the treatment is known as the *treatment field.*

The treatment equipment unit the patient sees is mostly shield and/or circuitry. When the machine is turned on, the beam is of a predetermined size to pass through to the desired site.

Patients can breathe normally during treatment. This is surprising to some patients, but ordinary breathing does not significantly alter the position of the organs. Physical restraints are generally not used unless a patient is disoriented and unaware of his or her surroundings and therefore lacks normal judgment. Young children, senile older persons, and severely ill patients may require some immobilization devices or tranquilizers.

Today's treatment rooms look pleasant and cheerful. Some patients wish to have music piped in the room during the few minutes of treatment to break the silence. In general, every effort is made to keep the patient comfortable and relaxed. Patients are usually relieved after the first treatment because they see how painless and easy the actual treatments are.

Patients too ill to travel on their own should arrange for friends, relatives, or an ambulance service to take them to the radiation therapy facility. Naturally, inpatients will go to the facility by direct in-hospital transportation.

Patients may wonder whether they can drive back home after the first treatment or subsequent treatments. They may also be concerned about feeling very sick after the first treatment. Except where there is a physical disability to preclude driving, there is no need to make unusual arrangements. (However, those people having radiation therapy to the brain are advised not to drive because, by virtue of the cancer itself, these patients are at risk for a sudden turn for the worse.) Unless told not to, patients can drive themselves home after the first treatment and usually after subsequent treatments.

Portals, or areas of treatment, vary in size depending on the staging of the tumor and a person's body size and shape. A heavier person will require a longer daily treatment time than will a small person because of the greater amount of tissue present between the skin surface and the tumor. However, the treatment course is the same. Treatment times average just a few minutes, depending upon the dose necessary. Two to four minutes is standard, although it may be even shorter.

Treatments are usually administered through both the front and the back of the body, or as a single treatment through front, back, or side. Alternatively, multiple-angle treatments are sometimes necessary, as well as rotation of the machine around the body. Some patients require a combination of these different treatment approaches. This depends on the particular clinical situation and is determined by the radiation oncologist.

Treatments are, as a rule, given five consecutive days each week, and the entire treatment course lasts several weeks. On average, the treatment course time will vary from two to eight weeks. Patients will receive a total dose of radiation, which is then referred to in terms of daily dose. The concept of daily doses is medically known as *fractionation.*

The neck, chest, abdomen, and pelvis (soft tissues) generally can't tolerate more than 900 to 1,000 units per week, 180 to 200 units per day. The bones of the arms and legs can easily tolerate daily doses of 250 to 300 units. (Radiation units are technically called Grays or Centigrays.) More rapid treatment may lead to severe short- or long-term side effects. Conversely, lower doses or a longer course may result in decreased effectiveness of radiation therapy. Thus, there is an optimal dose and time schedule for treating various types of tumors.

The length of treatment courses and the radiation doses have been established through extensive clinical trials. Modification of this time-dose may be necessary if problems arise because of complications with the cancer itself, the side effects of radiation, or a person's general physical condition.

Following an initial consultation, a letter is mailed to the doctors on the treatment team to summarize the patient's condition, describe the treatment plan and expected side effects, and make recommendations for further tests if indicated. Periodic letters and telephone calls follow during the treatment course when indicated. Depending on their condition, patients are usually examined by the radiation oncologist many times a week.

After the radiation therapy is completed, a discharge letter is mailed to the patient's various doctors describing the side effects; possible problems; progress; and recommendations. Many radiation oncologists, see patients for one or more follow-up visits after treatment is completed. Remaining problems and side effects can be addressed, and patients have an opportunity to ask additional questions. Patients feel less abandoned and are able to easily make the transition from radiation treatment to general medical care when they know that a connection to the radiation oncologist can continue.

Patients have a right to feel both physically attended to and emotionally supported during the course of treatment. The technicians working with them, as well as the radiation oncologist, should be available to answer questions and help with the "mechanics" of treatment. If, at any time, the patient believes that he/she is not being given the kind of information and help they need, then by all means they need to speak up!

This advice applies to family members, too. If a loved one is undergoing radiation treatment, they may be better equipped to ask questions and retain information than the patient. In addition, if they will be caring for a family member, much sound advice can be directed to them. Confusion about diet, sleep patterns, activity levels, treatment of side effects, and so on can be avoided when all who are involved with the patient are aware of medical advice and suggestions. Furthermore, fears may be alleviated by taking an active role in their loved one's treatment.

Equipment and Dosage

Most common x-ray tests are performed with x-ray energies measured in thousands of volts. Radiation treatments, by comparison, usually involve energies of over one million electron volts.

In the past 25 years, new machines have been designed to increase the power, or energy, of the x-ray beams. Prior to the early 1960s, x-ray treatment units had powers of approximately 200,000 volts.

These earlier x-ray therapy treatments were accompanied by many untoward side effects. One of the worst was skin damage.

The new so-called super voltage therapy units fall into two main categories. The first, Cobalt 60, is an isotope. It is a radioactive substance emitting approximately one million electron volts of energy in the form of gamma rays. The second is the Linear accelerator machines, which deliver an energy range of 6 million to 18 million volts of x-rays.

In the interest of clarity and to keep these explanations as simple as possible, the Cobalt 60 and Linear accelerator units can be considered as one entity, both being super voltage machines. This is appropriate because their ultimate therapeutic properties are similar. And for the sake of simplicity, I refer to the dosages of radiation as units. However, these are technically known as Grays (Gy). For example, 10 Grays (Gy) equal 1000 Centigrays (CGy).

Super voltage units have some definite characteristics important to treatment. For one, they are "skin sparing," meaning that little radiation affects the skin surface. Most of the x-ray energy goes to the tumor. However, the tissues in the path of the x-ray beam are also irradiated.

Secondly, with the modern equipment, there is minimal *scatter* of x-ray energy outside the treatment beam. By scatter, we mean the presence of radiation in the body outside the field of treatment. Picture a beam of light from a powerful flashlight projected on a wall, the visible beam of the light is well defined (equivalent to the radiation beam) with only a slight halo of light around the edges (equivalent to the scatter). In radiation therapy, a sharply defined x-ray beam minimizes the side effects of treatment because only small amounts of radiation travel to other parts of the body.

With Linear accelerator machines, the sharpness of the beam edge allows for very precise treatment, and adjacent tissues are spared unnecessary radiation during treatment. The precision a radiologist can achieve with these machines is similar to that necessary in surgical procedures. Lastly, the Linear accelerator may be programmed to treat with electrons rather than x-rays for special situations.

The Support Staff

Radiation therapy is delivered with the assistance of a team of specialists who assist the radiation oncologist. *Radiation physicists* accurately determine the radiation doses and precisely assess the risk of injury to normal tissues. Radiation physicists are experts in medical computer technology, and with today's complex treatments, this expertise is essential in treatment planning.

Radiation therapists operate the complex treatment machines, position the patient for treatment, and verify that treatments are precisely reproduced daily. They combine their technical and scientific skill with compassionate "hands on" involvement with the patient.

Oncology nurses are nurses whose specialty is working with cancer patients. They have received extensive training in order to deal with the multitude of concerns patients have, including such things as fears about treatment, controlling side effects, changing dressings, intravenous feedings, and so on.

These three disciplines are an integral part of today's radiation treatment, and patients should feel free to ask questions about the role they will play in the care.

Modern Treatment

At one time, radiation therapy caused more severe side effects than it does today. Much technological progress has been made over the past decades, and now advances in radiation therapy have contributed

to improvement in the cure rates for many cancers. Still, patient apprehension is normal and expected, and they should not be satisfied until all their concerns are addressed and questions answered. The radiation oncologist is there to help during treatment course, and patients should ask about all aspects of the treatment.

What Is Chemotherapy?

To doctors, nurses, pharmacists, and health professionals, the word *chemotherapy* means any drug (such as aspirin or penicillin) used for treating people with any disease. Most of us, however, think of medicines to treat cancer when we hear the term chemotherapy. Two other medical terms often used to describe cancer chemotherapy are *antineoplastic* (meaning anticancer) therapy and *cytotoxic* (cell-killing) therapy.

History of Chemotherapy

The first drug used for cancer chemotherapy was not originally intended for that purpose. Mustard gas was used as a chemical warfare agent during World War I and was studied further during World War II. During a military operation in World War II, a group of people were accidentally exposed to mustard gas and were later found to have very low white blood cell counts. It was reasoned that an agent that damaged the rapidly growing white blood cells might have a similar effect on cancer. Therefore, in the 1940s, several patients with advanced lymphomas (cancers of certain white blood cells) were given the drug by vein, rather than by breathing the irritating gas. Their improvement, although temporary, was remarkable. That experience started researchers studying other substances that might have similar effects against cancer. As a result, many other drugs have been developed to treat cancer.

Why Chemotherapy Is Different From Other Treatments

Chemotherapy is sometimes the first choice for treating many cancers. It differs from surgery or radiation in that it is almost always used as a *systemic* treatment. This means the medicines travel throughout the whole body rather than being confined to one area such as the breast, lung, or colon. This is important because chemotherapy can reach cancer cells that may have spread to other parts of the body.

More than 100 drugs are currently used for chemotherapy – either alone or in combination with other drugs or treatments. Many more drugs are expected to become available. These medicines vary widely in their chemical composition, how they are taken, their usefulness in treating specific forms of cancer, and their side effects. New medicines are first developed through research in test tubes and animals. Then, their safety and effectiveness are tested in clinical trials in humans.

Chemotherapy in Clinical Trials

Clinical trials are studies of new or experimental medicines (or other new treatments). The studies are done when there is a reason to believe a new drug or a new combination of drugs may be of value in curing or controlling cancer.

If you wish to take part in a clinical trial, the researchers will fully explain to you and your family what is required. You always have the chance to refuse to take part in the study or to leave the study at a

later time if you change your mind. Being in a clinical trial does not keep you from getting other medical or nursing care that you need. People who take part in clinical trials make an important contribution to medical care because the study results will also help future patients.

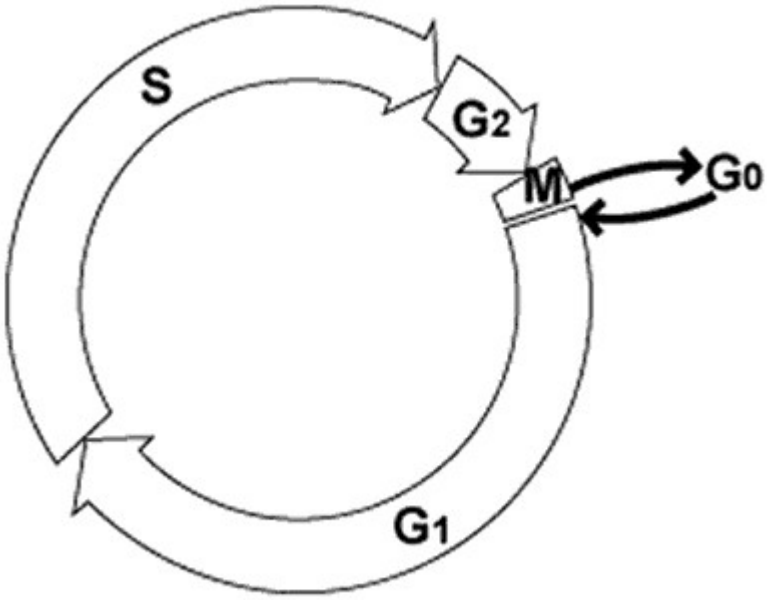
How Does Chemotherapy Work?

To understand how chemotherapy works as a treatment, it is helpful to understand the normal life cycle of a cell in the body. All living tissue is composed of cells. Cells grow and reproduce to replace cells lost during injury or normal "wear and tear." The cell cycle is a series of steps that both normal cells and cancer cells go through in order to grow and reproduce to form new cells.

This discussion is somewhat technical, but it can help you understand how doctors predict which drugs are likely to work well together and how doctors decide how often doses of each drug should be given.

There are 5 phases in the cell cycle, designated by letters and numbers:

G_0 = Resting stage
G_1 = RNA and protein synthesis
S = DNA synthesis
G_2 = Construction of mitotic apparatus
M = Mitosis



The Cell Cycle

G_0 phase (resting stage): Cells have not yet started to divide. Cells spend much of their lives in this phase. Depending on the type of cell, it can last for a few hours to a few years. When the cell is signaled to reproduce, it moves into the G1 phase.

G_1 phase: During this phase, the cell starts making more proteins to get ready to divide. This phase lasts about 18 to 30 hours.

S phase: In the S phase, the chromosomes containing the genetic code (DNA) are copied so that both of the new cells formed will have the right amount of DNA. This phase lasts about 18 to 20 hours.

G_2 phase: The G2 phase is just before the cell starts splitting into two cells. It lasts from 2 to 10 hours.

M phase (mitosis): In this phase, which lasts only 30 to 60 minutes, the cell actually splits into 2 new cells.

This cell cycle is important to cancer doctors (oncologists) because many chemotherapy drugs work only on actively reproducing cells (not on cells in the resting phase, G0). Some of these drugs specifically attack cells in a particular phase of the cell cycle (the M or S phases, for example). Understanding how these drugs function helps oncologists predict which drugs are likely to work well together. Doctors can also effectively plan how often doses of each drug should be given.

Although chemotherapy drugs attack reproducing cells, they cannot tell the difference between reproducing cells of normal tissues (that are replacing worn-out normal cells) and cancer cells. The damage to normal cells can result in side effects.

Each time chemotherapy is given, it involves trying to balance between destroying the cancer cells (in order to cure or control the disease) and sparing the normal cells (to lessen undesirable side effects).

What are the goals of treatment with chemotherapy?

There are 3 possible goals for chemotherapy treatment.

- **Cure:** If possible, chemotherapy is used to cure the cancer, meaning that the tumor or cancer disappears and does not return.
- **Control:** If cure is not possible, the goal is to control the disease (stop the cancer from growing and spreading) in order to extend life and provide the best quality of life.
- **Palliation:** Sometimes control is unlikely if the cancer is at an advanced stage. At this point the goal is called palliation. This means that chemotherapy drugs may be used to relieve symptoms caused by the cancer, thereby improving the quality of life, even though the drugs may not lengthen life.

For some people, chemotherapy is the only treatment used in an attempt to cure, control, or palliate their cancer. In other cases, chemotherapy may be given along with other treatments. It may be used as neoadjuvant therapy (before surgery or radiation), or as adjuvant therapy (after surgery or radiation).

- **Neoadjuvant chemotherapy** may be used to shrink a large tumor so that it can then be removed by surgery (with a less extensive operation) or can be treated more effectively with radiation.
- **Adjuvant chemotherapy** is given to prevent the growth of stray cancer cells remaining in the body after surgery or radiation. In most cases, these cells cannot be seen on routine tests such as CT scans but may still be present.

What are the different types of chemotherapy drugs?

Chemotherapy drugs are divided into several groups based on how they affect specific chemical substances within cancer cells, which cellular activities or processes the drug interferes with, and which specific phases of the cell cycle the drug affects. Knowing this helps oncologists decide which

drugs are likely to work well together and, if more than one drug will be used, plan exactly when each of the drugs should be given (in which order and how often).

Alkylating Agents

Alkylating agents work directly on DNA to prevent the cancer cell from reproducing. As a class of drugs, these agents are not phase-specific (in other words, they work in all phases of the cell cycle). These drugs are active against chronic leukemias, non-Hodgkin lymphoma, Hodgkin disease, multiple myeloma, and lung, breast, ovarian, and certain other cancers.

Some examples of alkylating agents include busulfan, cisplatin, carboplatin, chlorambucil, cyclophosphamide, ifosfamide, dacarbazine (DTIC), mechlorethamine (nitrogen mustard), melphalan, and temozolomide.

Nitrosoureas

Nitrosoureas act in a similar way to alkylating agents. They interfere with enzymes that help repair DNA. Unlike many other drugs, these agents are able to travel from the blood to the brain, so they are often used to treat brain tumors. They may also be used to treat non-Hodgkin lymphomas, multiple myeloma, and malignant melanoma.

Examples of nitrosoureas include carmustine (BCNU) and lomustine (CCNU).

Antimetabolites

Antimetabolites are a class of drugs that interfere with DNA and RNA growth. These agents work during the S phase and are commonly used to treat leukemias, tumors of the breast, ovary, and the gastrointestinal tract, as well as other cancers.

Examples of antimetabolites include 5-fluorouracil, capecitabine, 6-mercaptopurine, methotrexate, gemcitabine, cytarabine (ara-C), fludarabine, and pemetrexed.

Anthracyclines and Related Drugs

Anthracyclines interfere with enzymes involved in DNA replication. These agents work in all phases of the cell cycle. Thus, they are widely used for a variety of cancers. A major concern when giving these drugs is the effect they can have on heart muscle.

Examples include daunorubicin, doxorubicin (Adriamycin), epirubicin, idarubicin, and mitoxantrone.

Topoisomerase nhibitors

These drugs interfere with enzymes called topoisomerases, which are important in DNA replication. They are used to treat certain leukemias, and lung, ovarian, gastrointestinal, and other cancers.

Examples of topoisomerase I inhibitors include topotecan and irinotecan.
Examples of topoisomerase II inhibitors include etoposide (VP-16) and teniposide.

Mitotic Inhibitors

Mitotic inhibitors are plant alkaloids and other compounds derived from natural products. They can stop mitosis or inhibit enzymes from making proteins needed for reproduction of the cell. These work during the M phase of the cell cycle.

Examples of mitotic inhibitors include the taxanes (paclitaxel, docetaxel) and the vinca alkaloids (vinblastine, vincristine, and vinorelbine).

Corticosteroid Hormones

Steroids are natural hormones and hormone-like drugs that are useful in treating some types of cancer (lymphoma, leukemias, and multiple myeloma) as well as other illnesses. When these drugs are used to kill cancer cells or slow their growth, they are considered chemotherapy drugs. They are often combined with other types of chemotherapy drugs to increase their effectiveness.

Examples include prednisone and dexamethasone.

Miscellaneous Chemotherapy Drugs

Some chemotherapy drugs act in slightly different ways and do not fit well into any of the other categories.

Examples include such drugs as L-asparaginase, dactinomycin, thalidomide, and tretinoin.

Other Types of Cancer Drug Therapies

Some other drugs and biological treatments are used to treat cancer but are not usually considered to be "chemotherapy." While chemotherapy drugs take advantage of the fact that cancer cells divide rapidly, these other drugs target different properties that set cancer cells apart from normal cells. They often have less serious side effects than those commonly caused by chemotherapy drugs. Some are even used in combination with chemotherapy.

Targeted therapies: As researchers have come to learn more about the inner workings of cancer cells in recent years, they have begun to create new drugs that attack cancer cells more specifically than standard chemotherapy drugs can. Most attack cells with mutant versions of certain genes, or cells that express too many copies of these genes.

Only a handful of these drugs are available at this time. Examples include imatinib (Gleevec), gefitinib (Iressa), erlotinib (Tarceva), rituximab (Rituxan), and bevacizumab (Avastin). There will likely many more in the future.

Sex hormones: Sex hormones, or hormone-like drugs, alter the action or production of female or male hormones. They are used to slow the growth of breast, prostate, and endometrial (uterine) cancers, which normally grow in response to hormone levels in the body. These hormones do not work in the same ways as standard chemotherapy drugs.

Examples include anti-estrogens (tamoxifen, fulvestrant), aromatase inhibitors (anastrozole, exemestane, letrozole), progestins (megestrol acetate), anti-androgens (bicalutamide, flutamide), and LHRH agonists (leuprolide, goserelin).

Immunotherapy: Some drugs are given to people with cancer to stimulate their immune systems to more effectively recognize and attack cancer cells. These drugs offer a unique method of treatment, and are often considered to be separate from "chemotherapy."

Selecting which drugs to use for chemotherapy

In some cases, the best choice of doses and schedules for giving each drug are relatively clear, and most oncologists would recommend the same treatment. In other cases, less may be known about the best way to treat people with certain types and stages of cancer. Different cancer doctors might choose different drug combinations with different schedules.

Factors to consider in choosing which drugs to use for a chemotherapy regimen include:

- type of cancer
- stage of the cancer (how far it has spread)
- age
- general state of health
- other serious health problems (such as liver or kidney diseases)
- other types of anticancer treatments given in the past

Doctors take these factors into account, along with information published in medical journals and textbooks describing the outcomes of similar patients treated with chemotherapy.

Chemotherapy regimens or treatment plans may use a single drug or a combination of drugs. Oncologists usually recommend a combination of drugs for most people with cancer. This is often more effective than a single drug, as the cancer cells can be attacked in several different ways. Doctors must also consider side effects of each drug and any potential interactions among the drugs.

Side Effects

Different drugs may have different side effects, so it is often better to use moderate doses that cause bearable side effects rather than very high doses of a single drug that might cause severe side effects and possible permanent damage to an important organ. However, there are important exceptions to this rule, and a single chemotherapy drug may be the best option for some people with certain types of cancer.

Doctors try to give chemotherapy at levels high enough to cure or control the cancer, while keeping side effects at a minimum. They also try to avoid drugs with similar and additive side effects.

Drug Interactions

In addition to considering how to best combine 2 or more chemotherapy drugs, doctors must also consider potential interactions between chemotherapy drugs and other medications, including vitamins and nonprescription medicines. In some cases, these interactions may make side effects worse. In others they may interfere with the effectiveness of the chemotherapy. Therefore, it is important that you tell your doctor about all medicines, including vitamins, dietary supplements, and nonprescription medicines that you are taking.

For example, many chemotherapy drugs temporarily slow down the bone marrow’s production of blood platelets (clotting cells). Aspirin or related drugs can weaken blood platelets. This is not a problem for healthy people with normal platelet counts. But, for people with low platelet counts due to chemotherapy, this interaction may increase the risk of a serious bleeding problem.

Vitamins: Many people want to take an active role in improving their general health in order to help their body's natural defenses fight the cancer and to speed up their recovery from the side effects of chemotherapy.

Because most people think of vitamins as a safe way to improve health, it is not surprising that many people with cancer take high doses of one or more vitamins. But few realize that some vitamins might make their chemotherapy less effective.

Certain vitamins, such as A, E, and C act as antioxidants. This means that they can prevent formation of ions that damage DNA. This damage is thought to have an important role in causing cancer. There is some evidence that getting enough of these vitamins (through a balanced diet and, perhaps, by taking vitamin supplements) may help reduce the risk of developing some types of cancer.

On the other hand, some chemotherapy drugs (and radiation) work by producing these same types of ions to severely damage the DNA of cancer cells, so the cells are unable to grow and reproduce. Some scientists believe that taking high doses of antioxidant vitamins during treatment may make chemotherapy or radiation less effective. Few studies have been done to thoroughly test this theory. Until we know more about the effects of vitamins on chemotherapy drugs, many oncologists recommend the following during chemotherapy:

- If your doctor has not prescribed vitamins for a specific reason, it is best not to take any on your own.
- A simple multivitamin is probably acceptable for people who want to take a vitamin supplement, but check with your doctor first.
- It is safest to avoid taking high doses of antioxidant vitamins during chemotherapy treatment. Ask your doctors when it might be safe to start such vitamins after treatment is finished.
- If you are concerned about nutrition, you can usually get plenty of vitamins by eating a well-balanced diet.

Planning drug doses and schedules

Some drugs, especially those available to people without a prescription, have a fairly wide *therapeutic index*. This means that wide ranges of doses can be used effectively and safely. For example, the label on a bottle of aspirin may suggest taking 2 tablets for a mild headache. But one tablet (half the dose) will probably help many people.

Most chemotherapy drugs, on the other hand, are strong medicines that have a fairly narrow range of safe and effective doses. Taking too little of a drug will not effectively treat the cancer and taking too much may cause life-threatening side effects. For this reason, doctors must calculate chemotherapy doses very precisely.

Doses

Depending on the drug(s) to be given, there are different ways to determine chemotherapy doses. Most chemotherapy doses are measured in milligrams (mg).

The overall dose is sometimes based on a person's body weight in kilograms (1 kilogram is 2.2 pounds). For instance, if the standard dose of a drug is 10 milligrams per kilogram (10 mg/kg), a person weighing 50 kilograms (110 pounds) would receive 500 mg (50 kg x 10 mg/kg).

Some chemotherapy doses are determined based on body surface area (BSA), which doctors calculate using your height and weight and which is expressed in meters squared (m2).

Dosages for children and adults differ, even after BSA is taken into account. This is because children's bodies process drugs differently. They may have different levels of sensitivity to the drugs as well. For similar reasons, dosages of some drugs may also be adjusted for people who:

- are elderly
- have poor nutritional status
- have already taken or are currently taking other medications
- have already received or are currently receiving radiation therapy
- have low blood cell counts
- have liver or kidney diseases

Schedule (Cycles)

Chemotherapy is generally given at regular intervals called cycles. A cycle may involve one dose followed by several days or weeks without treatment. This allows normal cells in the body time to recover from the drug's side effects. Alternatively, doses may be given several days in a row, or every other day for several days, followed by a period of rest. Some drugs work best when given continuously over several days.

Different drugs work best on different schedules. If more than one drug is used, the treatment plan will specify how often and exactly when each drug should be given. The number of cycles you receive may be determined before treatment starts (based on the type and stage of cancer) or may be flexible, in order to take into account how the treatment affects the cancer.

Changes in Doses and Schedules

In most cases, the most effective doses and schedules of drugs to treat specific cancers have been determined by testing them in clinical trials. It is important whenever possible to receive the full course of chemotherapy and to keep the cycles on schedule, as this will give you the best chance to benefit from treatment.

There may be times, though, when certain serious side effects require doctors to adjust the chemotherapy plan (dosage and/or schedule) to allow your body time to recover. In some cases, supportive medicines such as growth factors (discussed below) may help the body recover more quickly. Again, the key is to give enough medicine to affect the cancer without causing serious problems.

Where are chemotherapy treatments given?

Chemotherapy treatments may be given in the following locations:

- hospital
- doctor's office
- outpatient clinic
- home
- workplace

Both convenience and how the drugs are to be given must be considered in deciding the best place to give chemotherapy. For example, a chemotherapy regimen that requires placement of a special intravenous catheter and infusion over 24 hours or longer may need to be done in a hospital. The specific drugs and their doses, as well as your general state of health, will determine the expected side effects and whether you need to be monitored more closely during treatment.

What are the different ways to take chemotherapy?

Drugs used in chemotherapy regimens can be given in many ways:

- oral (PO) – taken by mouth (usually as pills)
- topical – applied to the skin as a cream or lotion
- intravenous (IV) – injected into a vein
- intramuscular (IM) – injected into a muscle
- subcutaneous (SQ) – injected under the skin
- intra-arterial – injected into an artery
- intrathecal – infused into the central nervous system via the cerebrospinal fluid
- intrapleural – infused into the chest cavity
- intraperitoneal – infused into the abdominal cavity
- intravesical – infused into the bladder
- intralesional/intratumoral – injected directly into the tumor

Some chemotherapy drugs are never taken by mouth because the digestive system can't absorb them or because they are very irritating to the digestive system. Even when a drug is available in an oral form (such as a pill), this method may not be the best choice. For example, some people with certain symptoms (severe nausea, vomiting, or diarrhea) can't swallow liquids or pills, and some people may have trouble remembering when or how many pills to take.

The term *parenteral* is used to describe drugs given intravenously, intramuscularly, or subcutaneously. The IV route is the most common. Intramuscular and subcutaneous injections are less frequently used because many drugs can be very irritating or even damaging to the skin or muscle tissue.

The IV route gets the drug quickly throughout the body. IV therapy may be given through a vein in the arm or hand or through a vascular access device (VAD), which includes a catheter implanted into a larger vein in the chest, neck, or arm.

There are different types of VADs with different types of catheters and implantable ports. VADs are used for these reasons:

- to give several drugs at one time
- for long-term therapy (to reduce the number of needle sticks)
- for continuous infusion chemotherapy
- to give drugs that can cause serious damage to skin and muscle tissue if they leak outside of a vein (drugs that are vesicants). Delivering them through a VAD provides more stable access in a vein than a regular IV, thus reducing the risk of the drug leaking outside of the vein.

The type of VAD used is based on the length of chemotherapy planned, your preference and what your doctor may suggest, the care required to maintain the VAD, and its cost.

Types of Vascular Access Devices

Type of Device	Comments
PICC (peripherally inserted central catheter) **(Per-Q-Cath, Groshong PICC)**	Placed in a vein in the arm and threaded up near the heart. Allows for continuous access to peripheral vein for several weeks. No surgery needed. Care of catheter needed.
Midline catheter **(Per-Q-Cath Midline, Groshong Midline)**	Also placed in a vein in the arm, but the catheter is not inserted as far as a PICC. Used for intermediate length therapy when a regular peripheral IV is not advisable or available. No surgery needed. Care of catheter needed.
TCVC (Tunneled Central Venous Catheter) **(Hickman, Broviac, Groshong)**	Catheter with multiple lumens (openings). Surgically placed in large central vein in the chest. The catheter is tunneled under the skin, but the lumens remain outside the body. Care of catheter needed.
Implantable Venous Access Port (Port-A-Cath, BardPort, PassPort, Medi-port)	A port of plastic, stainless steel, or titanium with a silicone septum. It is surgically placed under the skin of the

	chest or arm. The catheter extends into a large or central vein. The port is accessed by a needle to give chemotherapy.
Implantable pump	A titanium pump with an internal power source surgically implanted to give continuous infusion chemotherapy, usually at home. There is a refillable reservoir for continuous infusions.

Chemotherapy for Specific Areas of the Body (Regional Chemotherapy)

When there is a need to give high doses of chemotherapy to a specific area of the body, it may be given by a regional method. Regional chemotherapy involves directing the anticancer drugs into the tumor-bearing part of the body. The purpose is to achieve greater exposure to the cancer than could be achieved by chemotherapy drugs that go to all parts of the body, while minimizing side effects elsewhere. Examples of regional chemotherapy include drugs given into the body through these routes:

- intra-arterial (into an artery)
- intravesical (into the bladder)
- intrapleural (into the chest)
- intraperitoneal (into the abdomen)
- intrathecal (into the central nervous system via spinal fluid)

Intra-arterial infusions gained some popularity during the 1980s. An intra-arterial infusion allows a chemotherapy drug to be given directly through a catheter in an artery to an organ such as the liver (isolated hepatic perfusion) or to an extremity such as the leg (isolated limb perfusion). The catheter is attached to an implanted or portable pump. Although this approach sounds like a good idea for increasing effectiveness and reducing side effects, most studies have not found it to be as useful as was anticipated. Clinical trials continue to improve this approach to chemotherapy, but it is not widely used except in these studies.

Intracavitary is a broad term used to describe chemotherapy given directly into a body cavity such as intravesical (into the bladder), intraperitoneal (abdominal cavity), or intrapleural (chest cavity) chemotherapy. The drug is given through a catheter placed directly into one of these areas.

Intravesical chemotherapy is especially effective for early stage bladder cancer. The chemotherapy is usually given weekly for 4 to 12 weeks. For each treatment a urinary catheter is placed into the bladder to give the drug. The drug is kept in the bladder for about 2 hours and then drained. The urinary catheter is removed after each treatment.

Intrapleural and *intraperitoneal* chemotherapy are not used very often but are useful for some people with mesothelioma (cancer that develops in the lining of the lung), ovarian cancer that has spread to the peritoneum, and lung or breast cancers that have spread to the pleura.

Intrapleural chemotherapy is given through large or small chest catheters that may be connected to an implantable port. These catheters can be used to give drugs as well as to drain fluid that often accumulates in the pleural or peritoneal cavity when cancer has spread to these areas.

Intraperitoneal chemotherapy is given through a Tenckhoff catheter (a catheter specially designed for removing or adding large amounts of fluid from or into the peritoneum) or through an implanted port. Cancers of the appendix that spread extensively within the abdomen are sometimes treated with intraperitoneal chemotherapy.

Intrathecal chemotherapy is given directly into the cerebrospinal fluid (fluid that surrounds the brain and spinal cord) and can reach cancer cells in the central nervous system. Most chemotherapy drugs that are given into veins are unable to cross the barrier between the bloodstream and the central nervous system (brain and spinal cord), called the blood-brain barrier. Intrathecal chemotherapy may be necessary for some people with leukemia or other cancers that have spread to the brain or spinal cord.

Intrathecal chemotherapy may use one of 2 methods:

- In one method, chemotherapy is given by a *lumbar puncture* (spinal tap) daily or weekly into the space around the spinal cord.
- The second method uses a special device called an *Ommaya reservoir,* which is placed into the skull and has a catheter inserted into a ventricle (a space inside the brain filled with cerebrospinal fluid).

Safety Precautions for Healthcare Professionals

Many chemotherapy drugs are considered hazardous, so the nurses and doctors who give chemotherapy will take precautions to avoid direct contact with the drugs while giving them to you.

Some chemotherapy drugs are dangerous to others in these ways:

- They can cause abnormal changes in DNA (mutagenic).
- They may be able to alter development of a fetus or embryo, leading to birth defects (teratogenic).
- They may be able to cause another type of cancer (carcinogenic).
- Some may cause localized skin irritation or damage.

Nurses may wear special gloves and gowns when preparing and giving you the chemotherapy drugs. Additionally, pharmacists or nurses prepare the drugs in areas with special ventilation systems.

If you are hospitalized, nurses and health care professionals may take special precautions in handling your urine and stool for a few days after treatment, as they may contain the drugs. If you are receiving chemotherapy drugs at home, you will be given special instructions and precautions to ensure the safety of caregivers in the home.

Special procedures are used for disposing of materials after mixing and administering the drugs. There are separate plastic containers to dispose of sharp items, syringes, IV tubing, and medication bags. Gowns and gloves are disposed of in special bags. If any drug leaks or spills, special precautions are used to clean up the drugs.

Possible side effects of chemotherapy

Although chemotherapy is given to kill cancer cells, it also can damage normal cells. Most likely to be damaged are normal cells that divide rapidly:

- bone marrow/blood cells
- cells of hair follicles
- cells in the reproductive and digestive tracts

Damage to these cells accounts for many of the side effects of chemotherapy drugs. Side effects are different for each chemotherapy drug, and they also differ based on the dosage, the route the drug is given, and how the drug affects you individually.

If after reading this section you want more information about managing the side effects of chemotherapy, please call the American Cancer Society at 1-800-ACS-2345 and ask for the booklet "Understanding Chemotherapy: A Guide for Patients and their Families."

Bone Marrow Suppression

The bone marrow is the inner part of some bones that produces white blood cells (WBCs), red blood cells (RBCs), and blood platelets. Damage to the blood cell-producing tissues of the bone marrow is called bone marrow suppression, or myelosuppression, and is one of the most common side effects of chemotherapy.

Cells produced in the bone marrow tissue are growing rapidly and are sensitive to the effects of chemotherapy. Until your bone marrow cells recover from this damage, you may have abnormally low numbers of WBCs, RBCs, and/or blood platelets.

While you are getting chemotherapy your blood will be tested regularly, sometimes daily when necessary, so the numbers of these cells can be counted. This test is often called a complete blood count (CBC). Bone marrow samples may also be taken periodically to check on the blood-forming marrow cells that develop into WBCs, RBCs, and blood platelets.

The decrease in blood cell counts does not occur right at the start of chemotherapy because the drugs do not destroy the cells already in the bloodstream (which are not dividing rapidly). Instead, the drugs affect the formation of new blood cells by the bone marrow.

As blood cells normally wear out, they are constantly replaced by the bone marrow. Following chemotherapy, as these cells wear out, they are not replaced as they would be normally, and the blood cell levels will begin to drop. The type and dose of the chemotherapy will influence how low the blood cell counts will drop and how long it will take for the drop to occur.

Each type of blood cell has a different life span:

- white blood cells live for an average of 6 hours
- platelets average 10 days
- red blood cells average 120 days

The lowest count that blood cell levels fall to is called the *nadir.* The nadir for each blood cell type will occur at different times but usually WBCs and platelets will reach their nadir within 7-14 days. RBCs live longer and will not reach a nadir for several weeks.

Knowing what the 3 types of blood cells normally do can help you understand the effects of low blood cell counts.

- White blood cells help the body fight off infections.
- Platelets help prevent bleeding by forming plugs to seal up damaged blood vessels.
- Red blood cells bring oxygen to cells throughout the body so they can turn certain nutrients into energy.

The side effects caused by low blood cell counts will likely be at their worst when the WBC, RBC, and platelets are at their nadirs or lowest value.

Low white blood cell counts: The medical term for a low WBC count is *leukopenia.* Blood normally has between 4,000 and 10,000 WBCs per cubic millimeter. WBCs are divided into 2 main categories, based on how they appear under the microscope:

- ***Granulocytes,*** which contain granules (visible specks) in the cytoplasm of the cell, include 3 subtypes -- neutrophils, eosinophils, and basophils.
- ***Agranulocytes,*** which do not contain granules in the cytoplasm of the cell, include 3 subtypes -- lymphocytes, monocytes, and macrophages.

Granulocytes, especially neutrophils, provide an important defense against infections and are the most numerous type of WBC. *Neutropenia,* an abnormally low number of neutrophils, is the most common factor that puts people with cancer at risk for infection. The normal range of neutrophils is between 2,500 and 6,000 cells per cubic millimeter. Your doctor will likely watch your neutrophil count closely during chemotherapy.

To determine how likely someone is to develop an infection, health care providers look at the number of neutrophils in the blood, called the *absolute neutrophil count* (ANC). Someone with an ANC of 1,000 or less is *neutropenic* and at risk of developing an infection. An ANC lower than 500 is considered severe neutropenia.

Having a low WBC count or neutrophil count does not mean you will definitely have an infection. But you need to watch for these signs and symptoms:

- fever
- sore throat
- new cough or shortness of breath
- nasal congestion
- burning during urination
- shaking chills

- redness, swelling, and warmth at the site of an injury

Fever is a very important sign and may be the first sign of an infection. Usually you will be instructed to call your doctor or nurse if you have a fever higher than or equal to 100.50F, any signs or symptoms of infection, or shaking chills.

Your health care team may take measures to lower your risk of infection. You may be instructed to stay away from small children or other people who are likely to be sick. When WBC counts are very low, doctors often prescribe antibiotics as a preventive measure. These anti-infection drugs may be given intravenously or by mouth.

Because of the risk of infections, further chemotherapy doses may need to be delayed when you have a very low WBC count.

In some situations, doctors may prescribe growth factors to keep the WBC from falling too low so that chemotherapy can be given on schedule. Your body normally produces several growth factors (also called colony-stimulating factors) to prompt the bone marrow to make various types of blood cells. But the levels of these factors in the body are often not enough to keep up with demands during chemotherapy. Researchers have recently learned how to make these growth factors in the lab, and they are now available as drugs.

The growth factors that stimulate production of WBCs are granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim, Leukine) and granulocyte colony-stimulating factor (G-CSF, filgrastim, Neupogen). These drugs are often given daily, starting the day after you receive chemotherapy, for up to 2 weeks. A newer, longer lasting form of G-CSF (pegfilgrastim, Neulasta) is now available and may need to be given only once each chemotherapy cycle.

These drugs help bone marrow recover more quickly and reduce your risk of getting a serious infection. They are given intravenously (IV) or as injections under the skin (SQ). Nurses give the injections if you are in the hospital or at the doctor's office, but you or your family members can learn how to give these injections at home.

Low red blood cell counts: Not having enough red blood cells is called *anemia.* Doctors use 2 measurements to determine if you have enough RBCs.

- The red pigment in RBCs that carries oxygen is *hemoglobin.* If there are not enough RBCs, the blood hemoglobin concentration will be less than its usual range of 12 to 16 grams per deciliter (g/dL) in women or 14 to 18 g/dL in men.
- *Hematocrit* is the percentage of total blood volume occupied by red blood cells. Its normal range is between 37% and 52%. Levels are normally higher for men than for women.

With anemia, you may have the following symptoms:

- fatigue (described below)
- dizziness
- headaches
- irritability
- shortness of breath

- an rise in heart rate or breathing rate (or both)

Anemia caused by chemotherapy is usually temporary. But bleeding caused by surgery or by the cancer (a common occurrence with colorectal cancers, for example) can make anemia even worse.

If the symptoms are severe, blood transfusions may be needed until the bone marrow is healthy enough to replace worn-out RBCs. Because blood transfusions have some risks, doctors use this procedure only if there are serious signs and symptoms, such as shortness of breath and/or very low RBC counts. Other factors will also affect this decision. For example, people with heart or lung diseases are more sensitive to anemia.

A newer option for treating anemia caused by chemotherapy is epoetin (EPO, Procrit, Epogen). This drug is a manmade version of a naturally occurring growth factor that prompts bone marrow cells to make more RBCs. It can relieve symptoms of anemia and reduce the need for blood transfusions, but it may take a few weeks to work. Epoetin is generally given 3 times per week by injection under the skin (SQ) until the hemoglobin level rises to an acceptable level. A newer, longer lasting form, known as darbepoetin (Aranesp), may only need to be given every 1 to 2 weeks.

Low platelet counts: The normal range for platelet counts is between 150,000 and 450,000 per cubic millimeter. The medical term for a low platelet count is *thrombocytopenia.*

If your platelet count is low, you may show these signs:

- bruise easily
- bleed longer than usual after minor cuts or scrapes
- have bleeding gums or nose bleeds
- develop petechiae (small purple spots on the skin)
- have serious internal bleeding if the platelet count is very low

Although low platelet counts resulting from chemotherapy are temporary, they can cause serious blood loss. This can lead to damage in internal organs.

Sometimes a low platelet count will delay necessary surgery because doctors are concerned about blood loss during surgery.

If platelet counts are very low (below 10,000) or if a person with moderately low counts has greater than normal bleeding or bruising, platelet transfusions may be given. Transfused platelets last only a few days, and some people who have received many platelet transfusions can develop an immune reaction that destroys donor platelets.

A platelet growth factor called oprelvekin (Neumega) can be given as a drug for people with severe thrombocytopenia. This lowers their need for platelet transfusions and can lessen the risk of bleeding. The drug is given under the skin every day.

Nausea and Vomiting

Many patients getting chemotherapy worry about nausea and vomiting more than other side effects. New medicines can help prevent or treat nausea and vomiting, making it less prevalent than in the past, but it is still a possible effect of chemotherapy. Chemotherapy agents cause nausea and vomiting for a variety of reasons. One reason is they irritate the lining of the stomach and duodenum (the first section of the small intestine). This stimulates certain nerves that lead to the vomiting center in the brain.

Nausea is an unpleasant wavelike sensation in the stomach and back of throat. It can be accompanied by symptoms such as sweating, light-headedness, dizziness, and weakness. It can lead to retching, vomiting, or both.

Retching is a rhythmic movement of the diaphragm and stomach muscles that are controlled by the vomiting center.

Vomiting is a process controlled by the vomiting center that causes the contents of the stomach to be forced out through the mouth.

Vomiting can occur at various times. It can be *acute,* occurring within minutes to hours after chemotherapy, or *delayed,* developing or continuing for 24 hours after chemotherapy and sometimes lasting for days.

Anticipatory vomiting occurs when you have had a bad experience with nausea and vomiting in the past that was not treated. As a result, you develop nausea and vomiting when placed in the same situation (for example, before receiving the next chemotherapy treatment).

Although it is not possible to predict the onset, severity, or duration of nausea and vomiting for any one person, certain chemotherapy drugs are more likely to cause nausea and vomiting. Some examples of these are:

- cisplatin
- carboplatin
- dacarbazine
- mechlorethamine
- daunorubicin
- streptozocin
- cytarabine (high doses)
- doxorubicin
- carmustine
- cyclophosphamide
- ifosfamide
- procarbazine
- lomustine

- dactinomycin
- pentostatin
- irinotecan

Other factors that may affect the amount and severity of nausea and vomiting include:

- prior experiences with motion sickness
- previous bad experience with nausea and vomiting
- anxiety during treatment
- heavy alcohol intake (currently or in the past)
- being a woman of menstrual age (at greatest risk for severe and long-lasting nausea and vomiting)

The key to effective control of nausea and vomiting is to prevent it before it occurs whenever possible. Many drugs are used alone or in combination to prevent or decrease nausea and vomiting. They include:

- lorazepam
- prochlorperazine
- promethazine
- metoclopramide
- dexamethasone
- ondansetron
- granisetron
- dolasetron
- palonosteron
- aprepitant

Consideration may also be given to non-drug methods to help with nausea and vomiting, such as:

- ginger in tablets or in ginger ale
- relaxation exercises
- guided imagery
- soothing music

Hair Loss

Some chemotherapy drugs affect the rapidly growing cells of hair follicles. Your hair may become brittle and break off at the surface of the scalp, or it may simply fall out from the hair follicle.

Basic facts about hair loss:

- Whether or not hair loss occurs depends on which drugs are given, their doses, and the length of treatment. Hair loss can be very individual. Some people may have complete loss of hair while others may see just a thinning of their hair. Loss of eyebrows, eyelashes, pubic hair, and body hair is usually less severe because the growth is less active in these hair follicles than in the scalp.
- If hair is going to be affected, you may see it start 2 to 3 weeks after treatment begins.
- Hair loss from chemotherapy is almost always temporary. When your hair grows back, its color or texture may be different. Hair may start to grow again near the end of your treatment or after the treatment is completed.
- Unlike some other side effects of chemotherapy, hair loss is never life threatening. But it may have a substantial impact on your quality of life. Hair loss may cause depression, loss of self-confidence, and grief reactions.

Appetite and Weight Loss

Most chemotherapy medicines cause some degree of *anorexia,* a decrease in or complete loss of appetite. Loss of appetite, as well as weight loss, may also result directly from effects of the cancer on the body's metabolism.

Anorexia may be mild, or it may lead to cachexia, a form of malnutrition. Proper nutrition helps strengthen the body to fight the disease and cope with cancer treatments.

Decreased appetite is generally temporary and returns when chemotherapy is finished. It may take a few weeks after chemotherapy is finished for your appetite to recover. Some chemotherapy may cause more severe loss of appetite.

Talk with your doctor or nurse if you experience anorexia or cachexia. Medicines can be prescribed to help improve these conditions.

Taste Changes

Cancer treatments and the cancer itself can change the way some food tastes. Taste changes can contribute to anorexia and malnutrition. With taste changes caused by chemotherapy, you may notice:

- either a dislike for or an increased desire for sweet foods
- dislike of foods with bitter tastes
- dislike for tomatoes and tomato products
- dislike for beef or pork
- constant metallic or medicinal taste in your mouth

These changes occur because chemotherapy drugs can change the taste receptor cells in your mouth that tell you what flavor you are tasting. Changes in taste and smell may continue as long as chemotherapy treatments continue, or longer. Several weeks after chemotherapy has ended, taste and smell sensations usually (but not always) return to normal.

Sores in the Mouth or Throat

Some chemotherapy drugs can cause sores to develop in the mouth or throat. These drugs affect the rapidly dividing cells that line these areas.

Stomatitis refers to the inflammation and sores within your mouth that may result from chemotherapy. Similar changes in the throat are called *pharyngitis* and in the esophagus (the tube that leads from the throat to the stomach) are called *esophagitis.* The term *mucositis* is used to refer to inflammation of the lining layer of the mouth, throat, and esophagus.

The first signs of mouth sores occur when the lining of the mouth appears pale and dry. Later, the mouth, gums, and throat may feel sore and become red and inflamed. The tongue may be "coated" and swollen, leading to trouble swallowing, eating, or talking. Stomatitis, pharyngitis, and esophagitis can lead to bleeding, painful ulcers, and infection.

Mouth, throat, and esophagus sores are temporary and usually develop 5 to 14 days after receiving chemotherapy. They will heal completely once chemotherapy is finished.

Constipation

Constipation is the passage (usually with discomfort) of infrequent, hard, dry stool. If you have constipation, you may also notice bloating, increased gas, cramping, or pain. Constipation affects about half of people with cancer and about 3 out of 4 of those with advanced disease.

Risk factors for developing constipation include:

- taking opioid pain medicines
- lack of physical activity
- poor diet
- decreased fluid intake and dehydration
- bed rest
- depression
- getting certain chemotherapy drugs (such as vincristine and vinblastine)

If constipation develops, your doctor will try to determine the cause then take appropriate measures to treat the problem. For more information, please see the American Cancer Society document, "Understanding Chemotherapy: A Guide for Patients and their Families."

Diarrhea

Diarrhea is the passage of loose or watery stools several times a day with or without discomfort. Along with diarrhea, you may have gas, cramping, and bloating. Diarrhea occurs in about 3 out of 4 people who receive chemotherapy because of the damage to the rapidly dividing cells in the digestive (gastrointestinal) tract.

Factors affecting diarrhea during chemotherapy:

- receiving drugs that cause diarrhea (examples include irinotecan, 5-fluorouracil, methotrexate, docetaxel, and dactinomycin)
- drug dose
- length of treatment
- having a stomach tumor
- receiving both radiation and chemotherapy
- being lactose intolerant (can't drink milk, for example)

Diarrhea can be serious and become life threatening if it leads to dehydration, malnutrition, and electrolyte imbalances. It is important to report any diarrhea to your doctor or nurse so that it can be treated promptly. Keep a record of the number of times you have diarrhea, the amount, and the appearance and give this information to your doctor.

Fatigue

Fatigue is a common side effect of cancer and chemotherapy. It can be one of the most debilitating side effects people experience. With fatigue caused by chemotherapy, you may experience these feelings:

- weariness
- weakness
- lack of energy
- decreased ability for physical and mental work
- trouble thinking and concentrating
- forgetfulness

The fatigue a person with cancer feels is different from the fatigue of everyday life. It is unrelated to activity and may not be resolved with rest or sleep. Fatigue can be prolonged and affect your quality of life.

Heart Damage

Certain chemotherapy drugs can damage the heart. The most common ones are the anthracyclines, such as daunorubicin and doxorubicin (Adriamycin), but other drugs may cause it as well. This occurs in about 1 in 10 people who receive these drugs and usually involves changes to the heart muscles.

If the heart is damaged by chemotherapy, it may not be able to pump blood through the body as well. This can lead to fluid buildup and other problems. You may feel these symptoms:

- puffiness or swelling in the hands and feet
- shortness of breath
- dizziness
- erratic heartbeat
- dry cough

If you have had radiation to the mid-chest area before, existing heart problems, uncontrolled high blood pressure, or are a smoker, you will be at higher risk for heart damage.

Before chemotherapy is started, your doctor will check your heart function to make sure that there are no major problems. Your heart function will also be checked during treatment to ensure that no changes have occurred. Tests such as an electrocardiogram (EKG), an echocardiogram, or a MUGA scan are done to check for any changes in heart function. An echocardiogram is an ultrasound of the heart. With a MUGA scan, you receive a radioactive substance that is then traced through your heart with a special scanner.

If problems develop, the chemotherapy drug will be stopped to prevent further permanent damage. Tell your doctor or nurse right away if you notice changes in your heart rhythm, shortness of breath, weight gain, or fluid retention.

Nervous System Changes

Some chemotherapy drugs can cause direct or indirect changes in the central nervous system (brain and spinal cord), the cranial nerves, or peripheral nerves. The cranial nerves are connected directly to the brain and are important for movement and touch sensation of the head, face, and neck. Cranial nerves are also important for vision, hearing, taste, and smell. Peripheral nerves lead to and from the rest of the body and are important in movement, touch sensation, and regulating activities of some internal organs.

Side effects that are the result of nerve damage caused by chemotherapy can occur soon after chemotherapy or years later. Changes in the *central nervous system* could produce these symptoms:

- stiff neck
- headache
- nausea and vomiting
- lethargy or sleepiness
- fever
- confusion
- depression
- seizures

Damage to the *cranial nerves* may cause these symptoms:

- visual problems (such as blurred vision or double vision)
- increased sensitivity to odors
- hearing loss or ringing in the ears
- dry mouth

Peripheral nervous system changes usually affect the hands and feet and can include:

- numbness
- tingling
- decreased sensation

These may make you feel clumsy and cause difficulty in daily activities such as opening jars or squeezing toothpaste tubes.

Some of the most commonly used drugs that cause peripheral nerve damage include the mitotic inhibitors (vincristine, paclitaxel, docetaxel, etc.) and cisplatin. If the chemotherapy dose is lowered or treatment is stopped, the symptoms will usually decrease or disappear. However, there are times when the damage may be permanent.

Changes in Thinking and Memory

Recent research has shown that chemotherapy can also affect the way your brain functions many years after treatment. This occurs in a small number of patients and is often worse with larger doses of chemotherapy agents. Some of the brain's activities that are affected are concentration, memory, comprehension (understanding), and reasoning.

The changes that have been found in patients are subtle, but the people who have problems notice the differences in their thinking. Patients who have had chemotherapy and have this cognitive impairment call this experience "chemo brain" or "chemo fog." Researchers are not sure exactly why chemotherapy affects the brain in this way or exactly how much chemotherapy (or in what combinations) it takes to cause a problem.

Researchers are currently studying the problem to get more information to help prevent and treat cognitive impairment for chemotherapy patients. If you have problems with thinking that interfere with daily life, there are programs that can help you improve your memory and problem-solving abilities. Simply being aware that problems with thinking can occur may help patients and their family members feel less isolated and alone.

Lung Damage

It is possible for some chemotherapy drugs, such as bleomycin, to cause irreversible damage to the lungs. The chance of this occurring is higher if you receive radiation to the chest along with chemotherapy. Age seems to be an important factor in the development of lung damage. For example, people over 70 years old have about 3 times the risk of developing lung problems from the drug bleomycin.

Lung damage may cause symptoms such as shortness of breath, a nonproductive (dry) cough, and possibly fever. If the chemotherapy drug is stopped early enough, the lung tissue can regenerate. Because early lung changes may not show up on a chest x-ray, your doctor may assess your lungs through pulmonary function tests and arterial blood gas tests.

Reproduction and Sexuality

Reproductive and sexual problems can occur after you receive chemotherapy. Which, if any, problems develop depends on your age when you are treated, the dose and duration of the chemotherapy, and the chemotherapy drug(s) that are given.

Most men on chemotherapy still have normal erections. A few, however, may develop problems.

Sexual changes men may experience:

- Erections and sexual desire often decrease just after a course of chemotherapy but usually recover in a week or two. A few chemotherapy drugs, for example, cisplatin or vincristine, can permanently damage parts of the nervous system. Although it is not yet proven, these drugs may interfere with the nerves that control erection.
- Chemotherapy can sometimes affect sexual desire and erections by slowing down the amount of testosterone produced. Some of the medications used to prevent nausea during chemotherapy can also upset a man's hormonal balance, but hormone levels should return to normal after treatments have ended.
- Many chemotherapy drugs can affect sperm and the parts of the body that produce them. Some of these effects may be permanent. Freezing sperm prior to chemotherapy is one option for men who wish to father children later in life. Although it is possible to conceive during chemotherapy, the toxicity of some drugs may cause birth defects. Therefore, it is suggested that all men and women take precautions and use a reliable type of birth control if they are sexually active.
- Chemotherapy may suppress your immune system. If you have had genital herpes or genital wart infections in the past, you may have flare-ups during chemotherapy.

For more information, please see the American Cancer Society document, "Sexuality & Cancer: For the Man Who Has Cancer and His Partner."

Sexual changes women may experience:

- Many chemotherapy drugs can either temporarily or permanently damage a woman’s ovaries, reducing their output of hormones. This affects a woman's fertility and libido. Ovarian function is less likely to return in women over age 30, and they are therefore more likely to go into menopause. Symptoms of early menopause include hot flashes, vaginal dryness and tightness during intercourse, and irregular or no menstrual periods. As the lining of the vagina thins, light spotting of blood after intercourse becomes common. Even though menstrual cycles may be disrupted or stopped with chemotherapy, it may still be possible to get pregnant at this time. If you do not want to become pregnant, always use birth control.
- Some chemotherapy drugs irritate all mucous membranes in the body. This includes the lining of the vagina, which often becomes dry and inflamed.

- Vaginal infections are common during chemotherapy, particularly in women taking steroids or the powerful antibiotics used to prevent bacterial infections. Yeast cells are a natural part of the vagina's cleansing system. If too many grow, however, you may notice itching inside your vagina, a whitish discharge that often looks like cottage cheese,or a burning sensation during sexual intercourse. Yeast infections can often be prevented by not wearing pantyhose, nylon panties, and tight pants. Loose clothing and cotton panties let the vagina breathe. The doctor may also prescribe a vaginal cream or suppository to reduce yeast cells or other organisms that grow in the vagina. It is very important to have a vaginal infection treated if you are taking chemotherapy. Your body's immune system is not as strong because of the treatment, and any infection may be a more serious problem.
- If you have had genital herpes or genital wart infections in the past, you may have flare-ups during chemotherapy.
- Chemotherapy is often given through an IV tube into the bloodstream. However, new ways have been developed to bring drugs directly to a tumor. For cancer of the bladder, for example, a liquid is placed directly into the bladder through a catheter in the urethra. Such a treatment has only a minor effect on a woman's sex life. You may notice some pain if you have intercourse too soon after the treatment. This is because the bladder and urethra are still irritated.

For more information, please see the American Cancer Society document, "Sexuality & Cancer: For the Woman Who Has Cancer and Her Partner."

Liver Damage

The liver is the organ that breaks down (metabolizes) most of the chemotherapy drugs that enter the body. Unfortunately, some drugs can cause liver damage, including methotrexate, cytarabine (ara-C), vincristine, and streptozocin. Most often the damage is temporary, and the liver recovers a few weeks after the drug is stopped.

Signs of liver damage include:

- yellowing of the skin and the whites of the eyes (jaundice)
- fatigue
- pain under the lower part of the right ribs
- swelling of the abdomen or in the feet

Blood tests may be needed to watch for possible liver damage. People who are older or who have hepatitis may be more likely to develop liver damage.

Kidney and Urinary System Damage

Many of the breakdown products of chemotherapy drugs are excreted through the kidneys. These drug byproducts can damage the kidneys, ureters, and bladder. If you have a history of kidney problems, you may be at a higher risk for kidney damage.

Certain chemotherapy drugs such as cisplatin, high-dose methotrexate, ifosfamide, and streptozocin are more likely to cause kidney and urinary damage than other medications.

Signs of possible kidney problems:

- headache
- pain in the lower back
- fatigue
- weakness
- nausea
- vomiting
- high blood pressure
- increased breathing rate
- change in how often you urinate
- change in color of urine
- swelling or puffiness of the body

Blood tests to measure kidney function are done regularly to watch for any changes.

Long-term Side Effects of Chemotherapy

For many people with cancer, chemotherapy is the best option for controlling their disease. You may be faced, however, with long-term side effects related to your chemotherapy treatments.

In some cases, side effects related to specific chemotherapy drugs can continue after the treatment is completed. These effects can progress and become chronic, or new side effects may occur. Long-term side effects depend on the specific drugs received and whether you received other treatments such as radiation therapy.

- **Permanent organ damage:** Certain chemotherapy drugs may permanently damage the body's organs. If the damage is detected during treatment, the drug will be stopped. However, some of the side effects may remain. Damage to some organs and systems, such as the reproductive system, may not show up until after chemotherapy is finished.
- **Delayed development in children:** When young children receive chemotherapy for cancer treatment, it may affect their growth and their ability to learn. Several factors affect long-term side effects, including the age of the child, the specific drugs that are given, the dosage and length of treatment, and if chemotherapy is used along with other types of treatment such as radiation.
- **Nerve damage:** Nervous system changes can develop months or years after treatment with some drugs. Signs of nerve damage may include hearing loss or tinnitus (ringing in the ears), changes in sensations in the hands and feet, personality changes, sleepiness, impaired memory, shortened attention span, and seizures.

- **Blood in the urine:** Hemorrhagic cystitis (blood in the urine), a side effect of cyclophosphamide and ifosfamide, can continue for some time after the drug is stopped, and symptoms may become worse.

- **Another cancer:** Development of a second cancer is a great concern for cancer survivors. Some chemotherapy drugs raise the risk of developing another type of cancer later on. This risk is affected by many factors, including the age of the patient and whether or not other treatments like radiation were used. The most commonly reported secondary cancers are leukemias, lymphomas, and some solid tumors. Follow-up care after all treatment is finished is an essential component of cancer care for all cancer survivors.

What is new in chemotherapy research?

Over the years, many people have been successfully treated with chemotherapy drugs thanks to ongoing research into their use. Yet despite the best treatments, some cancers will still come back.

Several exciting uses of chemotherapy and other agents hold even more promise for curing or controlling cancer. New drugs, new combinations of chemotherapy drugs, and new delivery techniques will improve our ability to cure or control cancer and improve the quality of life for people with cancer. There are many expected advances in coming years:

- ***New classes of chemotherapy*** medicines and combinations of medicines are being developed.

- ***New ways to give the drugs*** are being studied, such as using smaller amounts over longer periods of time or giving them continuously with special pumps.

- Some new medicines are specifically developed to attack a particular target on cancer cells. These drugs may have fewer side effects than standard chemotherapy drugs and may eventually be used along with them. Several drugs, such as imatinib mesylate (Gleevec), are already approved for use against certain cancers, and other *targeted drugs* are now under study.

- Other approaches to targeting drugs more specifically at the cancer cells, such as attaching drugs to *monoclonal antibodies,* may make them more effective and cause fewer side effects. Monoclonal antibodies, which are special types of proteins made in the lab, can be designed to guide chemotherapy medicines directly to the tumor. Such antibodies (without attached chemotherapy) can also be used as immunotherapy drugs, to strengthen the body's immune response against cancer cells.

- ***Liposomal therapy*** involves using chemotherapy drugs that have been packaged inside liposomes (synthetic fat globules). The liposome helps the drug penetrate the cancer cells more selectively and decreases possible side effects (such as hair loss and nausea and vomiting). Examples of liposomal medicines already in use are Doxil (the encapsulated form of doxorubicin) and DaunoXome (the encapsulated form of daunorubicin).

- ***Chemoprotective agents*** are being developed to protect against specific side effects of certain chemotherapy drugs. For example, dexrazoxane helps prevent heart damage, amifostine helps protect the kidneys, and mesna protects the bladder.

- Some new agents may be given along with chemotherapy to help *overcome drug resistance.* Cancer cells often become resistant to chemotherapy by developing the ability to pump the

drugs out of the cells. These new agents inactivate the pumps, allowing the chemotherapy to remain in the cancer cells longer and hopefully making it more effective.

Cancer Course Post-Test

Select the best answer to each of the following items. Mark your responses on the Answer Form.

1. Cancer is the second among fatal diseases, next to _____, in the industrialized countries and third fatal disease in India.

a. stroke
b. cardiovascular diseases
c. C0PD
d. diabetes

2. Cancer is a broad term used for identifying a large number of diseases. Perhaps the only common feature of these diseases is the ability of uncontrolled cell proliferation that cannot be checked by the normal cell kinetics regulators.

a. True
b. False

3. About _____ of all cancers are attributed to life style, e.g.. diet, tobacco habits and alcohol consumption, and exposure to industrial toxins.

a. 20%
b. 50%
c. 70%
d. 90%

4. . The concept of multi-stage carcinogenesis was first proposed in 1948 and supported by later studies. Present day oncology recognizes these main phases:

a. promotion
b. initiation
c. progression
d. All of the above

5. The _____ sequences responsible for transformation are called oncogenes.

a. human DNA
b. primary
c. genetic
d. None of the above

6. Normal cells may bear the seeds of their own destruction in the form of cancer genes. The activities of these genes may represent the final common pathway by which many carcinogens act.

a. True
b. False

7. Cancer genes may not be unwanted guests but essential constituents of the cell's genetic apparatus, betraying the cell only when their structure or control is distributed by _____.

a. blood flow
b. synaptic action
c. carcinogens
d. None of the above

8. Expression of the initial mutation will depend not only on interaction with other oncogenic mutations but also on factors that may temporarily change the patterns of specific gene expression, e.g. _____.

a. cytokines
b. lipid metabolites
c. certain phorbol esters
d. All of the above

9. Cancer metastasis consists of a number of steps; the main steps are common for all tumors. The progress of the neoplastic disease depends on metastatic changes that facilitate:_____.

a. invasion of local normal tissues
b. entry and transit of neoplastic cells in the blood and lymphatic systems
c. subsequent establishment of secondary tumor growth at distant sites
d. All of the above

10. Tumor growth depends on the supply of growth factors and efficient removal of toxic molecules, which comes through _____.

a. special diet
b. antioxidants
c. an adequate blood supply
d. None of the above

11. Two classes of regulatory genes are directly involved in carcinogenesis, the oncogenes and the antioncogenes.

a. True

b. False

12. A number of intrinsic (biological) and external factors are associated with the development of cancers. The intrinsic factors include _____.

a. the age and hormonal status of the individual
b. familial history
c. genetic predisposition
d. All of the above

13. The extraneous factors include _____.

a. diet and life style
b. individual's habits like smoking and alcohol use
c. exposure to toxic chemicals and radiation
d. All of the above

14. Tumor markers are used in the detection, diagnosis, and management of some types of cancer. Although an abnormal tumor marker level may suggest cancer, this alone is usually enough to diagnose cancer.

a. True
b. False

15. It is difficult to state unequivocally "X causes cancer"; in reality, "X" probably allows other factors to engage in the development of a cancer.

a. True
b. False

16. Not all tumors are cancerous. Benign (noncancerous) tumors do not spread (metastasize) to other parts of the body and, with very rare exceptions, are life threatening.

a. True
b. False

17. Anyone can get cancer at any age; however, about _____% of all cancers are diagnosed in people age of 55 and older.

a. 25
b. 40
c. 55
d. 77

18. It is important to know what some of the general (non-specific) signs and symptoms of cancer are. They include _____.

a. fever
b. unexplained weight loss
c. changes in the skin
d. All of the above

19. _____ is a period of time when the cancer is responding to treatment or is under control.

a. Transgression
b. Remission
c. Metastasis
d. None of the above

20. The major types of treatment for cancer include: _____.

a. surgery
b. radiation
c. biologic therapies
d. All of the above

21. Biologic therapy is an effective treatment for certain cancers. It is sometimes called immunotherapy, biotherapy, or biological response modifier therapy. Biologic therapies use the body's immune system to fight cancer or to lessen the side effects of some cancer treatments.

a. True
b. False

22. Chemotherapy is given in cycles, each followed by a recovery period. The total course of chemotherapy is often about six months, usually ranging from three to nine months.

a. True
b. False

23. Enrollment in any clinical trial is completely up to the individual patient. Their doctors and nurses explain the study to in detail and provide forms to read and sign indicating the patient's desire to take part. This process is known as_____.

a. patient accountability
b. DNR order
c. informed consent
d. None of the above

24. Complementary and alternative therapies are a diverse group of health care practices, systems, and products that are not part of usual medical treatment. They may include products/procedures such as _____.

a. acupuncture
b. vitamins
c. dietary supplements
d. All of the above

25. Alternative medicines are defined as those that are used instead of your regular medical care. Some of them have been proven not to be useful or even to be harmful, but are still promoted as "cures."

a. True
b. False

26. Pain is one of the reasons people fear cancer so much. It is normal to be afraid of witnessing pain. In fact, there are some cancers, which cause no physical pain at all.

a. True
b. False

27. Fatigue is one of the most common side effects of chemotherapy. It can range from mild lethargy to feeling completely wiped out. Fatigue tends to be the worst at the beginning and at the end of a treatment cycle.

a. True
b. False

28. The most common type of cancer on the list is non-melanoma skin cancer, with more than 1,000,000 new cases expected in the United States in 2006. Non-melanoma skin cancers represent about _____of all cancers diagnosed in this country.

a. 25%
b. one-third
c. half
d. 90%

29. The cancer on the list with the lowest incidence is _____. The estimated number of new cases of it for 2006 is 30,180.

a. skin
b. thyroid cancer
c. ovarian
d. None of the above

30. Bladder cancer usually originates in the bladder lining, which consists of a mucous layer of surface cells that expand and deflate (transitional epithelial cells), smooth muscle, and a fibrous layer.

a. True
b. False

31. Bladder cancer, with over _____ estimated new cases this year, is both one of the more common cancers and one that has a high recurrence rate.

a. 10,000
b. 24,000
c. 30,000
d. 60,000

32. Studies of promising new or experimental treatments in patients are known as clinical trials. A clinical trial is only done when there is some reason to believe that the treatment being studied may be valuable to the patient.

a. True
b. False

33. Tumor markers are substances produced by tumor cells or by other cells of the body in response to cancer or certain benign (noncancerous) conditions. These substances can be found in the _____.

a. urine
b. blood
c. tumor tissue
d. All of the above

34. Some people have a greater chance of developing certain types of cancer because of a change, known as a mutation or alteration, in specific genes. The presence of such a change is sometimes called a risk marker.

a. True
b. False

35. Treatment for bladder cancer depends on the stage of the disease, the type of cancer, and the patient's age and overall health. Options include _____.

a. surgery
b. immunotherapy
c. chemotherapy
d. All of the above

36. Radiation uses high-energy x-rays to destroy cancer cells. External beam radiation is emitted from a machine outside the body and internal radiation is emitted from radioactive "seeds" implanted into the tumor.

a. True
b. False

37. Breast cancer is diagnosed by pathologic review of a fixed specimen of breast tissue. The breast tissue can be obtained from a symptomatic area or from an area identified by a screening test, usually _____.

a. an X-ray
b. mammography
c. CT-scan
d. None of the above

38. Cancer of the _____ is a highly treatable and often curable disease when localized to the bowel. Surgery is the primary form of treatment and results in cure in approximately 50% of patients. Recurrence following surgery is a major problem and is often the ultimate cause of death.

a. breast
b. colon
c. kidney
d. None of the above

39. Cancer of the rectum is a highly treatable and often curable disease when localized. Surgery is the primary treatment and results in cure in approximately _____% of all patients.

a. 15
b. 27
c. 45
d. 85

40. The American Joint Committee on Cancer and a National Cancer Institute-sponsored panel recommended that at least _____ lymph nodes be examined in patients with colon and rectal cancer to confirm the absence of nodal involvement by tumor.

a. 4
b. 7
c. 12
d. None of the above

41. There is inadequate evidence to suggest that a diet low in fat and high in fiber, fruits, and vegetables decreases the risk of colorectal cancer.

a. True
b. False

42. Cancer of the endometrium is the most common gynecologic malignancy and accounts for _____% of all cancers in women. It is a highly curable tumor.

a. 6
b. 12
c. 25
d. 76

43. Based on solid evidence, giving progestin in combination with estrogen therapy eliminates the excess risk of _____ cancer associated with unopposed estrogen among postmenopausal women who have a uterus and are taking hormone therapy.

a. ovarian
b. endometrial
c. thyroid
d. None of the above

44. _____ cancer, also called renal adenocarcinoma, or hypernephroma, can often be cured if it is diagnosed and treated when still localized to the kidney and to immediately surrounding tissue.

a. Renal cell
b. Endometrial
c. Thyroid
d. None of the above

45. Genetic testing may also be sought by people affected with cancer, both newly diagnosed individuals and survivors of earlier cancers. Testing may be desired to define personal cancer etiology, to clarify risk to offspring, to define the appropriateness of particular surveillance approaches, or to aid in decision-making about risk-reducing prophylactic surgery.

a. True
b. False

46. Genetic counseling has been defined by the American Society of Human Genetics as "a communication process which deals with the human problems associated with the occurrence or risk of occurrence of a genetic disorder in a family.

a. True
b. False

47. Interferons (IFNs) are types of cytokines that occur naturally in the body. They were the first cytokines produced in the laboratory for use as BRMs. There are three major types of interferons—interferon alpha, interferon beta, and interferon gamma; interferon alpha is the type most widely used in cancer treatment.

a. True
b. False

48. Researchers are evaluating the effectiveness of certain antibodies made in the laboratory called monoclonal antibodies (MOABs or MoABs). These antibodies are produced by a single type of cell and are specific for a particular antigen. Researchers are examining ways to create MOABs specific to the antigens found on the surface of various cancer cells.

a. True
b. False

49. Cancer vaccines are another form of biological therapy currently under study. Vaccines for infectious diseases, such as measles, mumps, and tetanus, are injected into a person before the disease develops. These vaccines are effective because they expose the body's immune cells to weakened forms of antigens that are present on the surface of the infectious agent.

a. True
b. False

50. Gene therapy is an experimental treatment that involves introducing genetic material into a person's cells to fight disease. Researchers are studying gene therapy methods that can improve a patient's immune response to cancer. For example, a gene may be inserted into an immune cell to enhance its ability to recognize and attack cancer cells. In another approach, scientists inject cancer cells with genes that cause the cancer cells to produce cytokines and stimulate the immune system.

a. True
b. False

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