

Common Cancer Types:

Breast, Lung and Blood



Micheline Royal

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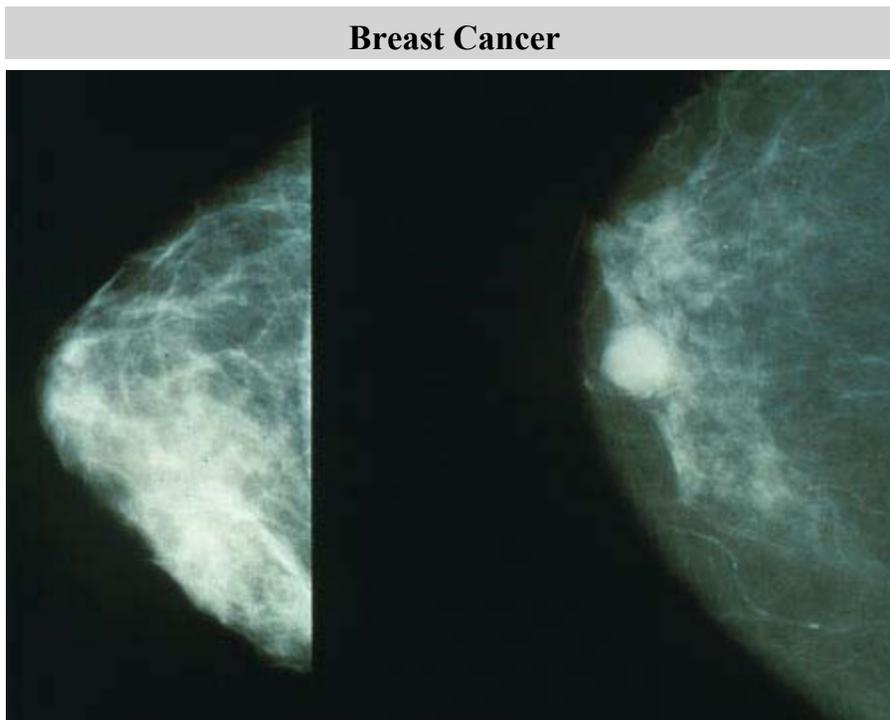
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Chapter 1

Breast Cancer



Mammograms showing a normal breast (left) and a breast cancer (right).

ICD-10	C50.
ICD-9	174-175,V10.3
OMIM	114480
DiseasesDB	1598
MedlinePlus	000913
MeSH	D001943

Breast cancer (malignant breast neoplasm) is cancer originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk. Cancers originating from ducts are known as ductal carcinomas; those originating from lobules are known as lobular carcinomas.

Prognosis and survival rate varies greatly depending on cancer type and staging. Computerized models are available to predict survival. With best treatment and dependent on staging, 10-year disease-free survival varies from 98% to 10%. Treatment includes surgery, drugs (hormonal therapy and chemotherapy), and radiation.

Worldwide, breast cancer comprises 10.4% of all cancer incidence among women, making it the most common type of non-skin cancer in women and the fifth most common cause of cancer death. In 2004, breast cancer caused 519,000 deaths worldwide (7% of cancer deaths; almost 1% of all deaths). Breast cancer is about 100 times more common in women than in men, although males tend to have poorer outcomes due to delays in diagnosis.

Some breast cancers are sensitive to hormones such as estrogen and/or progesterone, which makes it possible to treat them by blocking the effects of these hormones in the target tissues. Estrogen and progesterone receptor positive tumors have better prognosis and require less aggressive treatment than hormone negative cancers.

Breast cancers without hormone receptors, or which have spread to the lymph nodes in the armpits, or which express certain genetic characteristics, are higher-risk, and are treated more aggressively. One standard regimen, popular in the U.S., is cyclophosphamide plus doxorubicin (Adriamycin), known as CA; these drugs damage DNA in the cancer, but also in fast-growing normal cells where they cause serious side effects. Sometimes a taxane drug, such as docetaxel, is added, and the regime is then known as CAT; taxane attacks the microtubules in cancer cells. An equivalent treatment, popular in Europe, is cyclophosphamide, methotrexate, and fluorouracil (CMF). Monoclonal antibodies, such as trastuzumab (Herceptin), are used for cancer cells that have HER2/neu overexpressed. Radiation is usually added to the surgical bed to control cancer cells that were missed by the surgery, which usually extends survival, although radiation exposure to the heart may cause damage and heart failure in the following years.

Classification

Breast cancers can be classified by different schemata. Every aspect influences treatment response and prognosis. Description of a breast cancer would optimally include multiple classification aspects, as well as other findings, such as signs found on physical exam. Classification aspects include stage (TNM), pathology, grade, receptor status, and the presence or absence of genes as determined by DNA testing:

- Stage. The TNM classification for breast cancer is based on the size of the tumor (T), whether or not the tumor has spread to the lymph nodes (N) in the armpits,

and whether the tumor has metastasized (M) (i.e. spread to a more distant part of the body). Larger size, nodal spread, and metastasis have a larger stage number and a worse prognosis.

The main stages are:

Stage 0 is a pre-malignant disease or marker (sometimes called DCIS, Ductal Carcinoma in situ or LCIS, lobular carcinoma in situ) .

Stages 1–3 are defined as 'early' cancer with a good prognosis.

Stage 4 is defined as 'advanced' and/or 'metastatic' cancer with a bad prognosis.

- Histopathology. Breast cancer is usually classified primarily by its histological appearance. Most breast cancers are derived from the epithelium lining the ducts or lobules, and these cancers are classified as ductal or lobular carcinoma.

Carcinoma in situ is growth of low grade cancerous or precancerous cells in particular tissue compartment such as the mammary duct without invasion of the surrounding tissue. In contrast, *invasive carcinoma* does not confine itself to the initial tissue compartment and invades the surrounding tissue.

- Grade (Bloom-Richardson grade). When cells become differentiated, they take different shapes and forms to function as part of an organ. Cancerous cells lose that differentiation. In cancer grading, tumor cells are generally classified as well differentiated (low grade), moderately differentiated (intermediate grade), and poorly differentiated (high grade). Poorly differentiated cancers have a worse prognosis.
- Receptor status. Cells have receptors on their surface and in their cytoplasm and nucleus. Chemical messengers such as hormones bind to these receptors, and this causes changes in the cell. Breast cancer cells may or may not have three important receptors: estrogen receptor (ER), progesterone receptor (PR), and HER2/neu.

ER+ cancer cells depend on estrogen for their growth, so they can be treated with drugs to block estrogen effects (e.g. tamoxifen), and generally have a better prognosis.

HER2+ breast cancer had a worse prognosis, but HER2+ cancer cells respond to drugs such as the monoclonal antibody, trastuzumab, (in combination with conventional chemotherapy) and this has improved the prognosis significantly.

Cells with none of these receptors are called basal-like or triple negative.

- DNA assays of various types including DNA microarrays have compared normal cells to breast cancer cells. The specific changes in a particular breast cancer can be used to classify the cancer in several ways, and may assist in choosing the most effective treatment for that DNA type.

Signs and symptoms



Breast cancer showing an inverted nipple, lump, skin dimpling

The first noticeable symptom of breast cancer is typically a lump that feels different from the rest of the breast tissue. More than 80% of breast cancer cases are discovered when the woman feels a lump. The earliest breast cancers are detected by a mammogram. Lumps found in lymph nodes located in the armpits can also indicate breast cancer.

Indications of breast cancer other than a lump may include changes in breast size or shape, skin dimpling, nipple inversion, or spontaneous single-nipple discharge. Pain ("mastodynia") is an unreliable tool in determining the presence or absence of breast cancer, but may be indicative of other breast health issues.

Inflammatory breast cancer is a special type of breast cancer which can pose a substantial diagnostic challenge. Symptoms may resemble a breast inflammation and may include pain, swelling, nipple inversion, warmth and redness throughout the breast, as well as an orange-peel texture to the skin referred to as *peau d'orange*.

Another reported symptom complex of breast cancer is Paget's disease of the breast. This syndrome presents as eczematoid skin changes such as redness and mild flaking of the nipple skin. As Paget's advances, symptoms may include tingling, itching, increased sensitivity, burning, and pain. There may also be discharge from the nipple. Approximately half of women diagnosed with Paget's also have a lump in the breast.

In rare cases, what initially appears as a fibroadenoma (hard movable lump) could in fact be a phyllodes tumor. Phyllodes tumors are formed within the stroma (connective tissue) of the breast and contain glandular as well as stromal tissue. Phyllodes tumors are not staged in the usual sense; they are classified on the basis of their appearance under the microscope as benign, borderline, or malignant.

Occasionally, breast cancer presents as metastatic disease, that is, cancer that has spread beyond the original organ. Metastatic breast cancer will cause symptoms that depend on the location of metastasis. Common sites of metastasis include bone, liver, lung and brain. Unexplained weight loss can occasionally herald an occult breast cancer, as can symptoms of fevers or chills. Bone or joint pains can sometimes be manifestations of metastatic breast cancer, as can jaundice or neurological symptoms. These symptoms are "non-specific", meaning they can also be manifestations of many other illnesses.

Most symptoms of breast disorder do not turn out to represent underlying breast cancer. Benign breast diseases such as mastitis and fibroadenoma of the breast are more common causes of breast disorder symptoms. The appearance of a new symptom should be taken seriously by both patients and their doctors, because of the possibility of an underlying breast cancer at almost any age.

Risk factors

The primary risk factors for breast cancer are sex, age, lack of childbearing or breastfeeding, higher hormone levels, race, economic status and dietary iodine deficiency.

Most cases of breast cancer cannot be prevented through any action on the part of the affected person. The World Cancer Research Fund estimated that 38% of breast cancer cases in the US are preventable through reducing alcohol intake, increasing physical activity levels and maintaining a healthy weight. It also estimated that 42% of breast cancer cases in the UK could be prevented in this way, as well as 28% in Brazil and 20% in China.

Smoking tobacco also increases the risk of breast cancer with the greater the amount smoking and the earlier in life smoking begins the higher the risk.

In a study of attributable risk and epidemiological factors published in 1995, later age at first birth and not having children accounted for 29.5% of U.S. breast cancer cases, family history of breast cancer accounted for 9.1% and factors correlated with higher income contributed 18.9% of cases. Attempts to explain the increased incidence (but

lower mortality) correlated with higher income include epidemiologic observations such as lower birth rates correlated with higher income and better education, possible overdetection and overtreatment because of better access to breast cancer screening, and the postulation of as yet unexplained lifestyle and dietary factors correlated with higher income. One such factor may be past hormone replacement therapy, which was typically more widespread in higher income groups.

Genetic factors usually increase the risk slightly or moderately; the exception is women and men who are carriers of BRCA mutations. These people have a very high lifetime risk for breast and ovarian cancer, depending on the portion of the proteins where the mutation occurs. Instead of a 12 percent lifetime risk of breast cancer, women with one of these genes have a risk of approximately 60 percent.

In more recent years, research has indicated the impact of diet and other behaviors on breast cancer. These additional risk factors include a high-fat diet, alcohol intake, obesity, and environmental factors such as tobacco use, radiation, endocrine disruptors and shiftwork. Although the radiation from mammography is a low dose, the cumulative effect can cause cancer.

In addition to the risk factors specified above, demographic and medical risk factors include:

- Personal history of breast cancer: A woman who had breast cancer in one breast has an increased risk of getting a second breast cancer.
- Family history: A woman's risk of breast cancer is higher if her mother, sister, or daughter had breast cancer, the risk becomes significant if at least two close relatives had breast or ovarian cancer. The risk is higher if her family member got breast cancer before age 40. An Australian study found that having other relatives with breast cancer (in either her mother's or father's family) may also increase a woman's risk of breast cancer and other forms of cancer, including brain and lung cancers.
- Certain breast changes: Atypical hyperplasia and lobular carcinoma in situ found in benign breast conditions such as fibrocystic breast changes are correlated with an increased breast cancer risk.

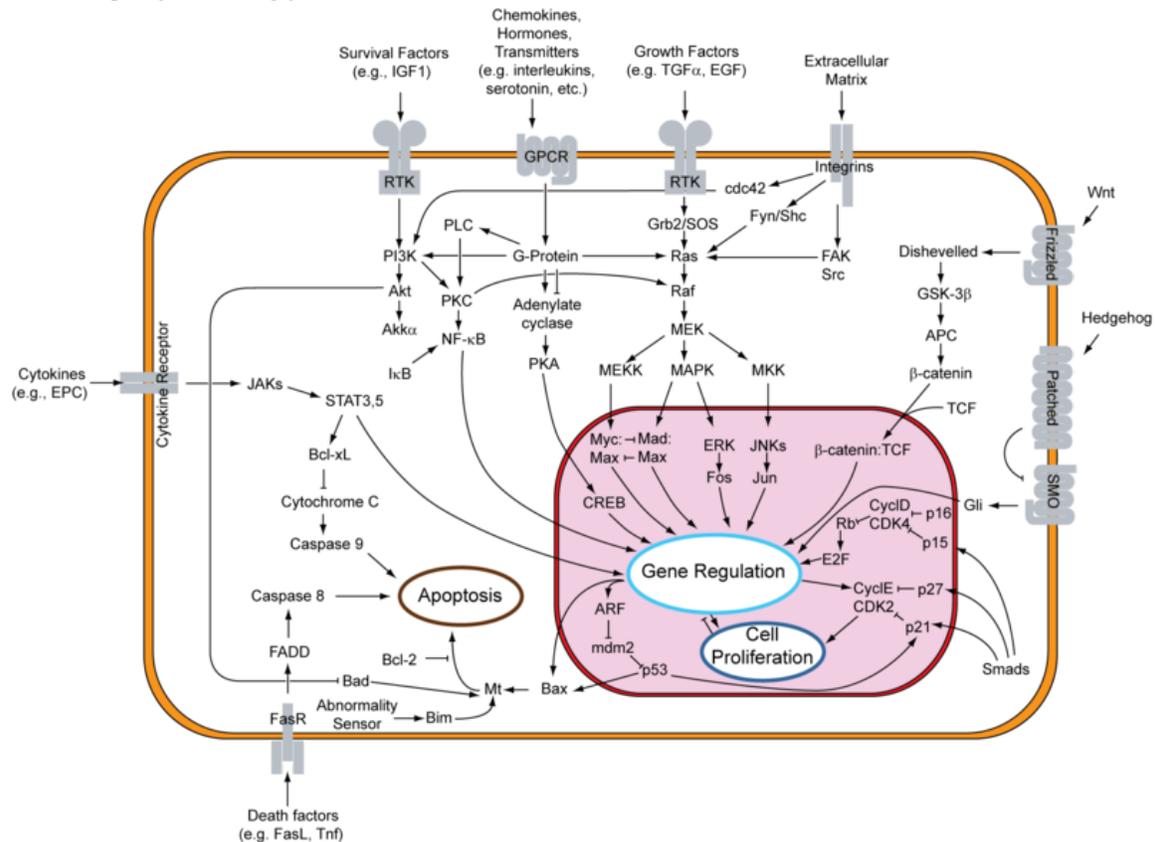
Those with a normal body mass index at age 20 who gained weight as they aged had nearly double the risk of developing breast cancer after menopause in comparison to women who maintained their weight. The average 60-year-old woman's risk of developing breast cancer by age 65 is about 2 percent; her lifetime risk is 13 percent.

Prevention

Exercise may decrease breast cancer risk. Also avoiding alcohol and obesity. Prophylactic bilateral mastectomy may be considered in patients with BRCA1 and BRCA2 mutations. A 2007 report concluded that women can somewhat reduce their risk

by maintaining a healthy weight, drinking less alcohol, being physically active and breastfeeding their children.

Pathophysiology



Overview of signal transduction pathways involved in apoptosis. Mutations leading to loss of apoptosis can lead to tumorigenesis.

Breast cancer, like other cancers, occurs because of an interaction between the environment and a defective gene. Normal cells divide as many times as needed and stop. They attach to other cells and stay in place in tissues. Cells become cancerous when mutations destroy their ability to stop dividing, to attach to other cells and to stay where they belong. When cells divide, their DNA is normally copied with many mistakes. Error-correcting proteins fix those mistakes. The mutations known to cause cancer, such as p53, BRCA1 and BRCA2, occur in the error-correcting mechanisms. These mutations are either inherited or acquired after birth. Presumably, they allow the other mutations, which allow uncontrolled division, lack of attachment, and metastasis to distant organs. Normal cells will commit cell suicide (apoptosis) when they are no longer needed. Until then, they are protected from cell suicide by several protein clusters and pathways. One of the protective pathways is the PI3K/AKT pathway; another is the RAS/MEK/ERK pathway. Sometimes the genes along these protective pathways are mutated in a way that turns them permanently "on", rendering the cell incapable of committing suicide when it is no longer needed. This is one of the steps that causes cancer in combination with other

mutations. Normally, the PTEN protein turns off the PI3K/AKT pathway when the cell is ready for cell suicide. In some breast cancers, the gene for the PTEN protein is mutated, so the PI3K/AKT pathway is stuck in the "on" position, and the cancer cell does not commit suicide.

Mutations that can lead to breast cancer have been experimentally linked to estrogen exposure.

Failure of immune surveillance, the removal of malignant cells throughout one's life by the immune system.

Abnormal growth factor signaling in the interaction between stromal cells and epithelial cells can facilitate malignant cell growth.

In the United States, 10 to 20 percent of patients with breast cancer and patients with ovarian cancer have a first- or second-degree relative with one of these diseases. Mutations in either of two major susceptibility genes, breast cancer susceptibility gene 1 (BRCA1) and breast cancer susceptibility gene 2 (BRCA2), confer a lifetime risk of breast cancer of between 60 and 85 percent and a lifetime risk of ovarian cancer of between 15 and 40 percent. However, mutations in these genes account for only 2 to 3 percent of all breast cancers.

Diagnosis

While screening techniques (which are further discussed below) are useful in determining the possibility of cancer, a further testing is necessary to confirm whether a lump detected on screening is cancer, as opposed to a benign alternative such as a simple cyst.

Very often the results of noninvasive examination, mammography and additional tests that are performed in special circumstances such as ultrasound or MR imaging are sufficient to warrant excisional biopsy as the definitive diagnostic and curative method.

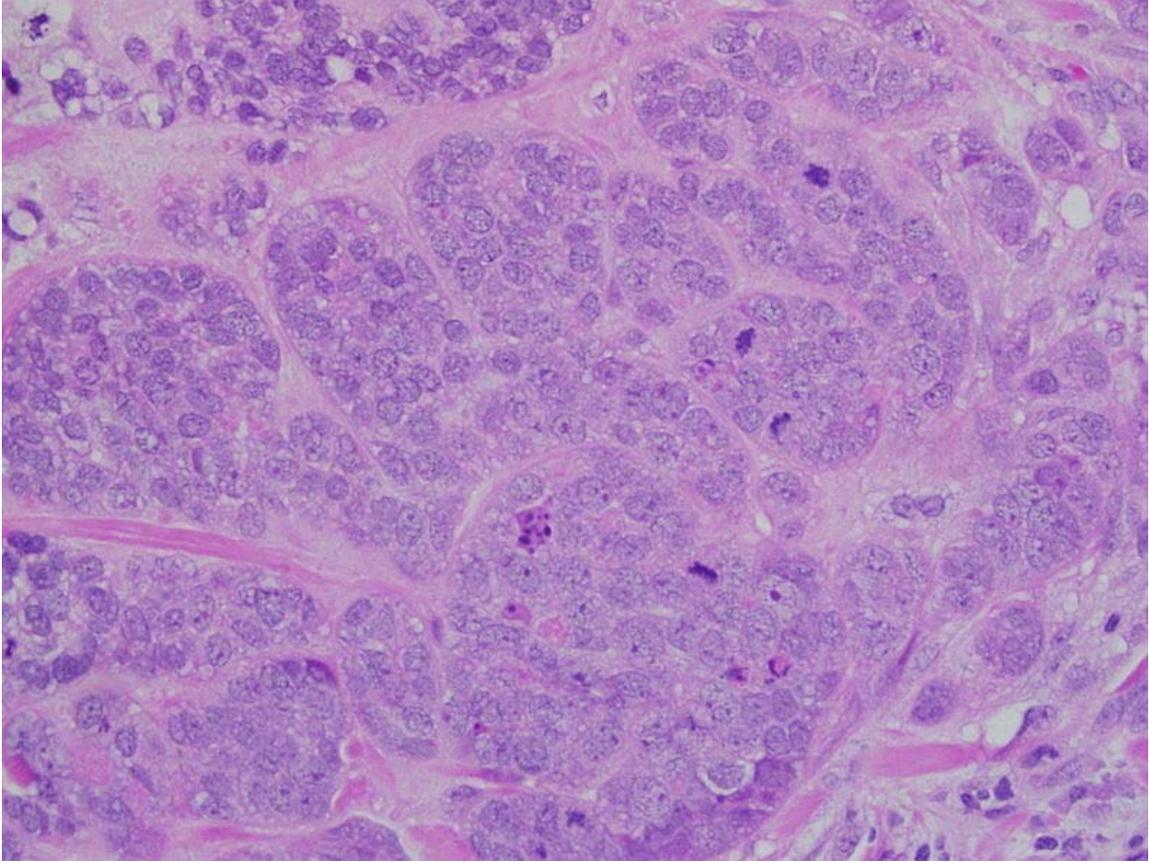
Both mammography and clinical breast exam, also used for screening, can indicate an approximate likelihood that a lump is cancer, and may also detect some other lesions. When the tests are inconclusive Fine Needle Aspiration and Cytology (FNAC) may be used. FNAC may be done in a GP's office using local anaesthetic if required, involves attempting to extract a small portion of fluid from the lump. Clear fluid makes the lump highly unlikely to be cancerous, but bloody fluid may be sent off for inspection under a microscope for cancerous cells. Together, these three tools can be used to diagnose breast cancer with a good degree of accuracy.

Other options for biopsy include core biopsy, where a section of the breast lump is removed, and an excisional biopsy, where the entire lump is removed.

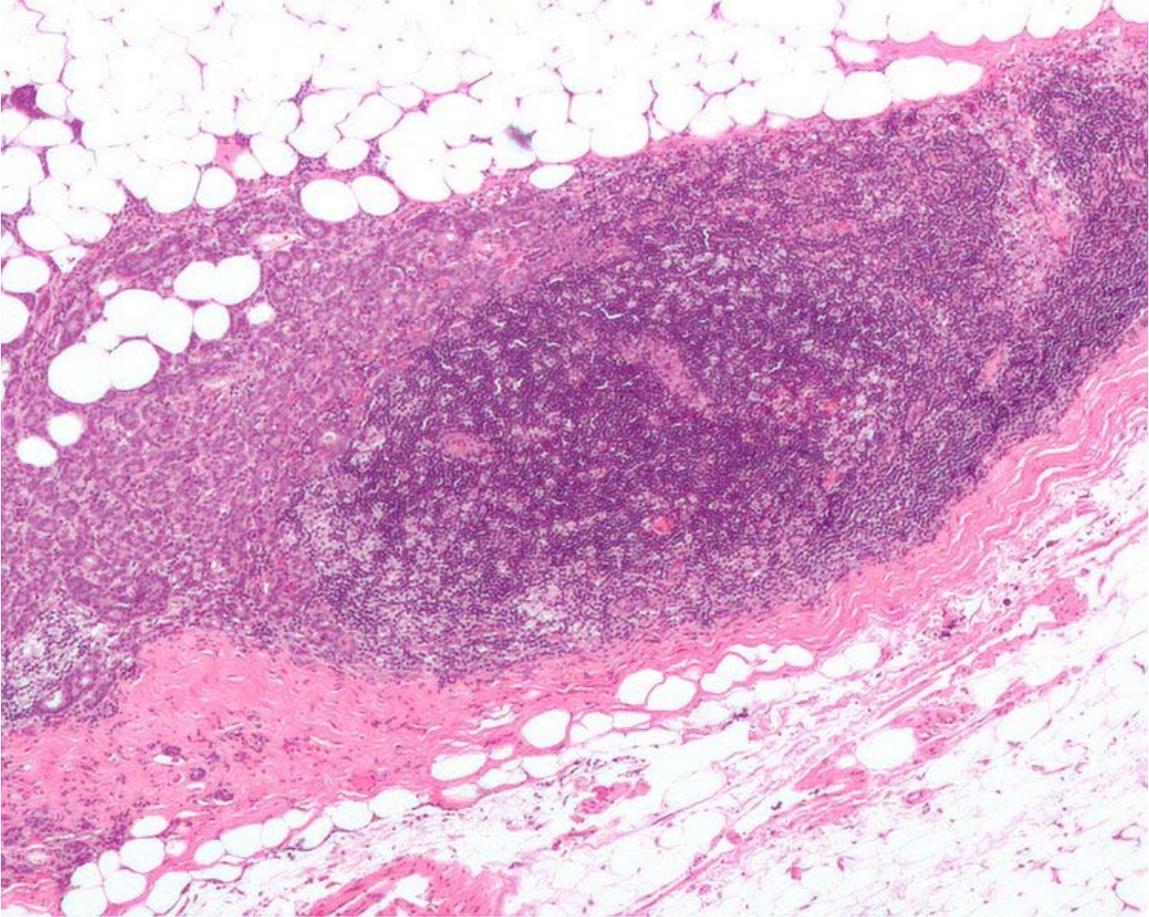
In addition vacuum-assisted breast biopsy (VAB) may help diagnose breast cancer among patients with a mammographically detected breast in women.



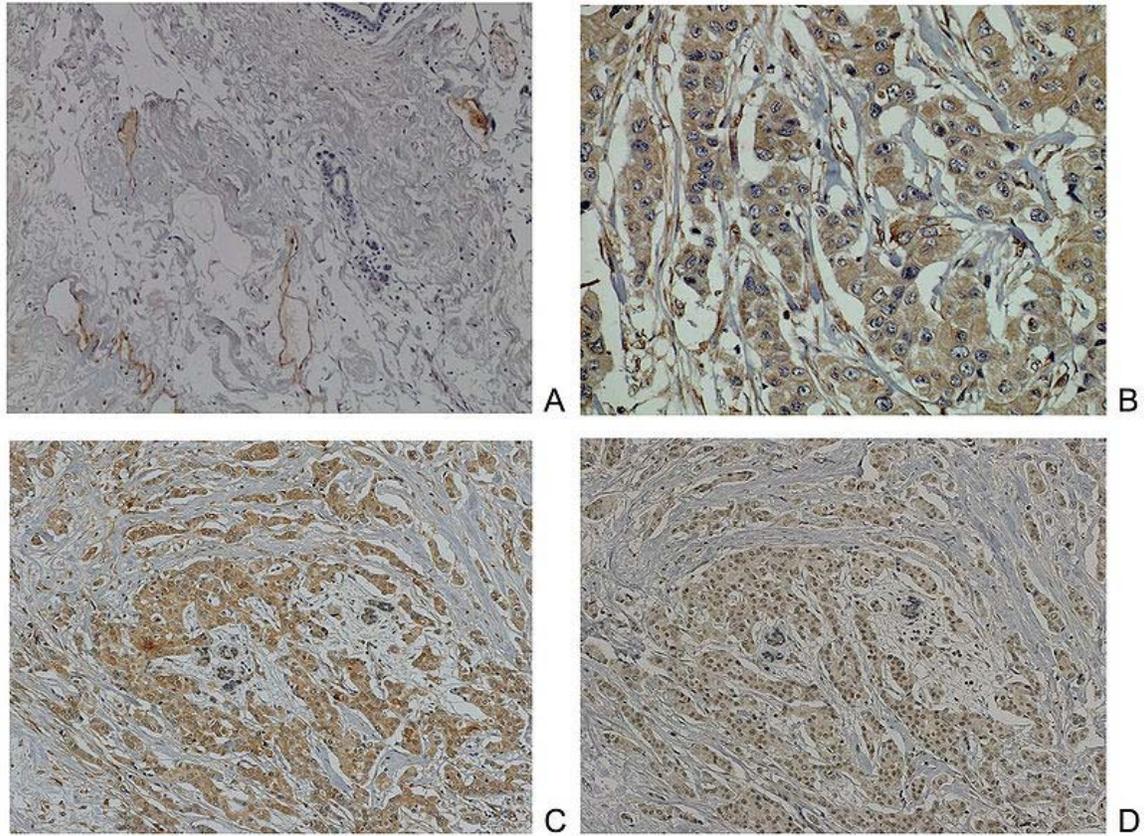
Excised human breast tissue, showing an irregular, dense, white stellate area of cancer 2 cm in diameter, within yellow fatty tissue.



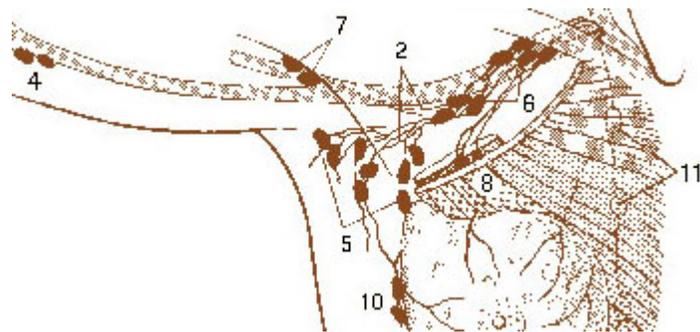
High grade invasive ductal carcinoma, with minimal tubule formation, marked pleomorphism, and prominent mitoses, 40x field.



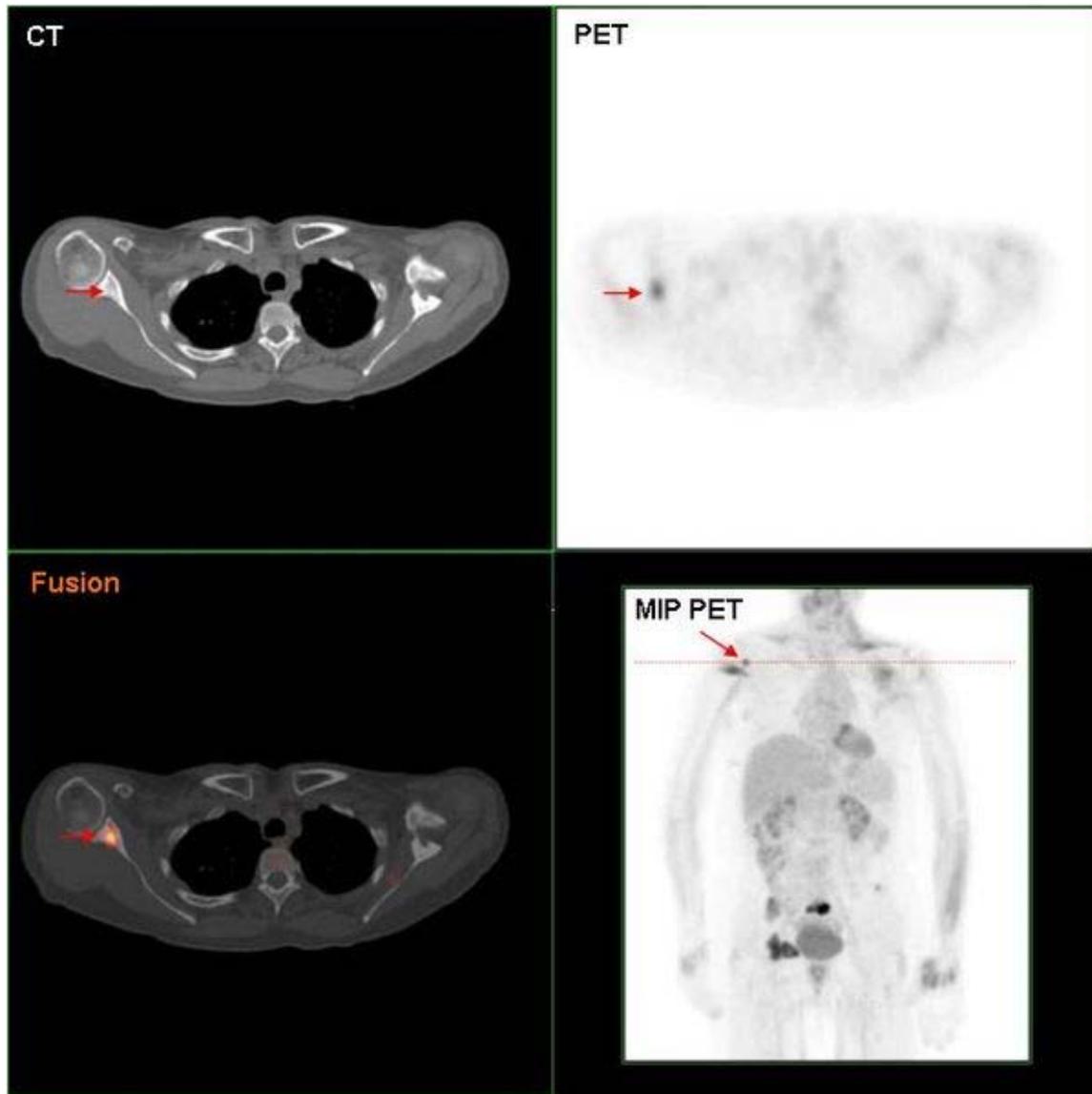
Micrograph showing a lymph node invaded by ductal breast carcinoma and with extranodal extension of tumour.



Neuropilin-2 expression in normal breast and breast carcinoma tissue



Lymph nodes which drain the breast



F-18 FDG PET/CT: Metastasis of a mamma carcinoma in the right scapula

Screening

Breast cancer screening refers to testing otherwise-healthy women for breast cancer in an attempt to achieve an earlier diagnosis. The assumption is that early detection will improve outcomes. A number of screening test have been employed including: clinical and self breast exams, mammography, genetic screening, ultrasound, and magnetic resonance imaging.

A clinical or self breast exam involves feeling the breast for lumps or other abnormalities. Research evidence does not support the effectiveness of either type of breast exam, because by the time a lump is large enough to be found it is likely to have been growing for several years and will soon be large enough to be found without an exam.

Mammographic screening for breast cancer uses x-rays to examine the breast for any uncharacteristic masses or lumps. The Cochrane collaboration in 2009 concluded that mammograms reduce mortality from breast cancer by 15 percent but also result in unnecessary surgery and anxiety, resulting in their view that it is not clear whether mammography screening does more good or harm. Many national organizations recommend regular mammography, nevertheless. For the average woman, the U.S. Preventive Services Task Force recommends mammography every two years in women between the ages of 50 and 74. The Task Force points out that in addition to unnecessary surgery and anxiety, the risks of more frequent mammograms include a small but significant increase in breast cancer induced by radiation.

In women at high risk, such as those with a strong family history of cancer, mammography screening is recommended at an earlier age and additional testing may include genetic screening that tests for the BRCA genes and / or magnetic resonance imaging.

Treatment

Breast cancer is *usually* treated with surgery and then possibly with chemotherapy or radiation, or both. Hormone positive cancers are treated with long term hormone blocking therapy. Treatments are given with increasing aggressiveness according to the prognosis and risk of recurrence.

Stage 1 cancers (and DCIS) have an excellent prognosis and are generally treated with lumpectomy and sometimes radiation. HER2+ cancers should be treated with the trastuzumab (Herceptin) regime, chemotherapy is uncommon for other types of stage 1 cancers.

Stage 2 and 3 cancers with a progressively poorer prognosis and greater risk of recurrence are generally treated with surgery (lumpectomy or mastectomy with or without lymph node removal), chemotherapy (plus trastuzumab for HER2+ cancers) and sometimes radiation (particularly following large cancers, multiple positive nodes or lumpectomy).

Stage 4, metastatic cancer, (i.e. spread to distant sites) has poor prognosis and is managed by various combination of all treatments from surgery, radiation, chemotherapy and targeted therapies. 10 year survival rate is 5% without treatment and 10% with optimal treatment.

Medications



Nolvadex (tamoxifen) 20 mg tablets (UK)

Drugs used after and in addition to surgery are called adjuvant therapy. Chemotherapy prior to surgery is called neo-adjuvant therapy. There are currently 3 main groups of medications used for adjuvant breast cancer treatment:

- Hormone Blocking Therapy
- Chemotherapy
- Monoclonal Antibodies

One or all of these groups can be used.

Hormone Blocking Therapy: Some breast cancers require estrogen to continue growing. They can be identified by the presence of estrogen receptors (ER+) and progesterone receptors (PR+) on their surface (sometimes referred to together as hormone receptors). These ER+ cancers can be treated with drugs that either block the receptors, e.g. tamoxifen, or alternatively block the production of estrogen with an aromatase inhibitor, e.g. anastrozole (Arimidex) or letrozole (Femara). Aromatase inhibitors, however, are only suitable for post-menopausal patients.

Chemotherapy: Predominately used for stage 2-4 disease, being particularly beneficial in estrogen receptor-negative (ER-) disease. They are given in combinations, usually for 3–

6 months. One of the most common treatments is cyclophosphamide plus doxorubicin (Adriamycin), known as AC. The mechanism of action of chemotherapy is to destroy fast growing and fast replicating cancer cells either by causing DNA damage upon replication or other mechanisms; these drugs also damage fast-growing normal cells where they cause serious side effects. Damage to the heart muscle is the most dangerous complication of doxorubicin. Sometimes a taxane drug, such as docetaxel, is added, and the regime is then known as CAT; taxane attacks the microtubules in cancer cells. Another common treatment, which produces equivalent results, is cyclophosphamide, methotrexate, and fluorouracil (CMF). (Chemotherapy can literally refer to any drug, but it is usually used to refer to traditional non-hormone treatments for cancer.)

Monoclonal antibodies: A relatively recent development in HER2+ breast cancer treatment. Approximately 15-20 percent of breast cancers have an amplification of the *HER2/neu* gene or overexpression of its protein product. This receptor is normally stimulated by a growth factor which causes the cell to divide; in the absence of the growth factor, the cell will normally stop growing. Overexpression of this receptor in breast cancer is associated with increased disease recurrence and worse prognosis. Trastuzumab (Herceptin), a monoclonal antibody to HER2, has improved the 5 year disease free survival of stage 1–3 HER2+ breast cancers to about 87% (overall survival 95%). Trastuzumab, however, is expensive, and approx 2% of patients suffer significant heart damage; it is otherwise well tolerated, with far milder side effects than conventional chemotherapy. Other monoclonal antibodies are also undergoing clinical trials.

A recent analysis of a subset of the Nurses' Health Study data indicated that Aspirin may reduce mortality from breast cancer.

Radiation

Radiotherapy is given after surgery to the region of the tumor bed and regional lymph nodes, to destroy microscopic tumor cells that may have escaped surgery. It may also have a beneficial effect on tumour microenvironment. Radiation therapy can be delivered as external beam radiotherapy or as brachytherapy (internal radiotherapy). Conventionally radiotherapy is given *after* the operation for breast cancer. Radiation can also be given at the time of operation on the breast cancer- intraoperatively. The largest randomised trial to test this approach was the TARGIT-A Trial which found that targeted intraoperative radiotherapy was equally effective at 4-years as the usual several weeks' of whole breast external beam radiotherapy. Radiation can reduce the risk of recurrence by 50-66% (1/2 - 2/3rds reduction of risk) when delivered in the correct dose and is considered essential when breast cancer is treated by removing only the lump (Lumpectomy or Wide local excision)

Prognosis

A prognosis is a prediction of outcome and the probability of progression-free survival (PFS) or disease-free survival (DFS). These predictions are based on experience with breast cancer patients with similar classification. A prognosis is an estimate, as patients

with the same classification will survive a different amount of time, and classifications are not always precise. Survival is usually calculated as an average number of months (or years) that 50% of patients survive, or the percentage of patients that are alive after 1, 5, 15, and 20 years. Prognosis is important for treatment decisions because patients with a good prognosis are usually offered less invasive treatments, such as lumpectomy and radiation or hormone therapy, while patients with poor prognosis are usually offered more aggressive treatment, such as more extensive mastectomy and one or more chemotherapy drugs.

Prognostic factors include staging, (i.e., tumor size, location, grade, whether disease has spread to other parts of the body), recurrence of the disease, and age of patient.

Stage is the most important, as it takes into consideration size, local involvement, lymph node status and whether metastatic disease is present. The higher the stage at diagnosis, the worse the prognosis. The stage is raised by the invasiveness of disease to lymph nodes, chest wall, skin or beyond, and the aggressiveness of the cancer cells. The stage is lowered by the presence of cancer-free zones and close-to-normal cell behaviour (grading). Size is not a factor in staging unless the cancer is invasive. For example, Ductal Carcinoma In Situ (DCIS) involving the entire breast will still be stage zero and consequently an excellent prognosis with a 10yr disease free survival of about 98%.

Grading is based on how biopsied, cultured cells behave. The closer to normal cancer cells are, the slower their growth and the better the prognosis. If cells are not well differentiated, they will appear immature, will divide more rapidly, and will tend to spread. Well differentiated is given a grade of 1, moderate is grade 2, while poor or undifferentiated is given a higher grade of 3 or 4 (depending upon the scale used). The most widely used grading system is the Nottingham Modification of the Bloom-Richardson system, which grades breast carcinomas by adding up scores for tubule formation, nuclear pleomorphism, and mitotic count, each of which is given 1 to 3 points, which add to a final score as follows: 3-5 points = Grade I; 6-7 points = Grade II; and 8-9 points = Grade III. The grading criteria is as follows:

Tubule formation

- 1 point: tubular formation in >75% of the tumor
- 2 points: tubular formation in 10 to 75% of the tumor
- 3 points: tubular formation in <10% of the tumor

Note: The overall appearance of the tumor has to be considered.

Nuclear pleomorphism

- 1 point: nuclei with minimal variation in size and shape
- 2 points: nuclei with moderate variation in size and shape
- 3 points: nuclei with marked variation in size and shape

Note: The tumor areas having cells with the greatest atypia should be evaluated.

Mitotic count

- 1 point: 0-9 mitotic counts per field under X25 objective using the Leitz Ortholux microscope, 0-5 mitotic counts per field under X40 objective using the Nikon Labophot microscope, or 0-11 mitotic counts per field under X40 objective using the Leitz Daiplan microscope
- 2 points: 10-19 mitotic counts per field under X25 objective using the Leitz Ortholux microscope, 6-10 mitotic counts per field under X40 objective using the Nikon Labophot microscope, or 12-22 mitotic counts per field under X40 objective using the Leitz Daiplan microscope
- 3 points: >19 mitotic counts per field under X25 objective using the Leitz Ortholux microscope, >10 mitotic counts per field under X40 objective using the Nikon Labophot microscope, or >22 mitotic counts per field under X40 objective using the Leitz Daiplan microscope

Note: Mitotic figures are counted only at the periphery of the tumor, and counting should begin in the most mitotically active areas.

Younger women tend to have a poorer prognosis than post-menopausal women due to several factors. Their breasts are active with their cycles, they may be nursing infants, and may be unaware of changes in their breasts. Therefore, younger women are usually at a more advanced stage when diagnosed. There may also be biologic factors contributing to a higher risk of disease recurrence for younger women with breast cancer.

The presence of estrogen and progesterone receptors in the cancer cell is important in guiding treatment. Those who do not test positive for these specific receptors will not be able to respond to hormone therapy, and this can affect their chance of survival depending upon what treatment options remain, the exact type of the cancer, and how advanced the disease is.

In addition to hormone receptors, there are other cell surface proteins that may affect prognosis and treatment. HER2 status directs the course of treatment. Patients whose cancer cells are positive for HER2 have more aggressive disease and may be treated with the 'targeted therapy', trastuzumab (Herceptin), a monoclonal antibody that targets this protein and improves the prognosis significantly. Tumors overexpressing the Wnt signaling pathway co-receptor low-density lipoprotein receptor-related protein 6 (LRP6) may represent a distinct subtype of breast cancer and a potential treatment target.

Psychological aspects

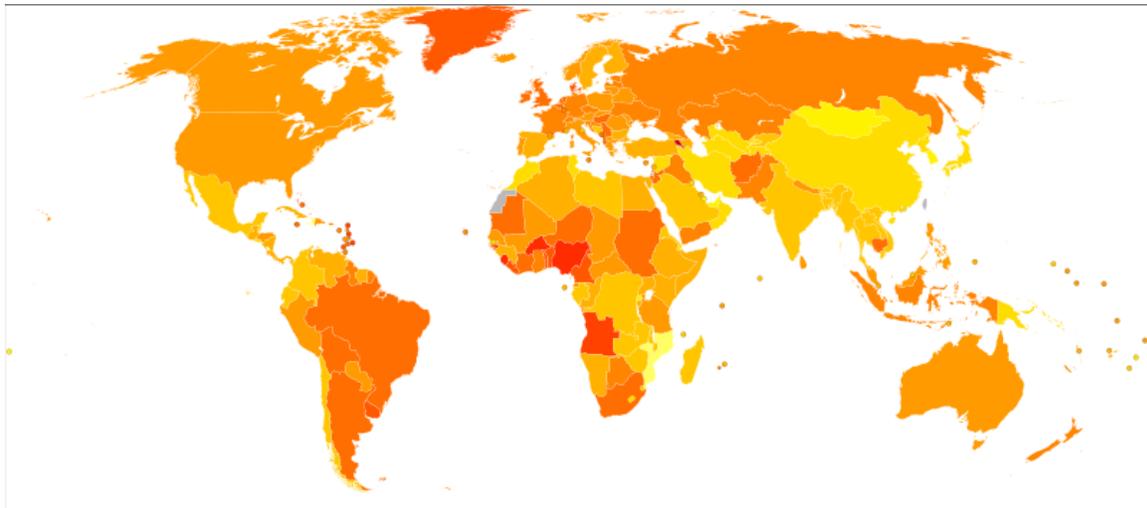
The emotional impact of cancer diagnosis, symptoms, treatment, and related issues can be severe. Most larger hospitals are associated with cancer support groups which provide a supportive environment to help patients cope and gain perspective from cancer survivors. Online cancer support groups are also very beneficial to cancer patients,

especially in dealing with uncertainty and body-image problems inherent in cancer treatment.

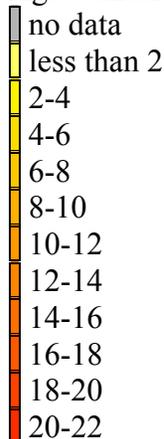
Not all breast cancer patients experience their illness in the same manner. Factors such as age can have a significant impact on the way a patient copes with a breast cancer diagnosis. Premenopausal women with estrogen-receptor positive breast cancer must confront the issues of early menopause induced by many of the chemotherapy regimens used to treat their breast cancer, especially those that use hormones to counteract ovarian function.

On the other hand, a recent study conducted by researchers at the College of Public Health of the University of Georgia showed that older women may face a more difficult recovery from breast cancer than their younger counterparts. As the incidence of breast cancer in women over 50 rises and survival rates increase, breast cancer is increasingly becoming a geriatric issue that warrants both further research and the expansion of specialized cancer support services tailored for specific age groups.

Epidemiology



Age-standardized death from breast cancer per 100,000 inhabitants in 2004.



more than 22

Worldwide, breast cancer is the most common cancer in women, after skin cancer, representing 16% of all female cancers. Mortality worldwide is 25% greater than that of lung cancer in women. In 2004, breast cancer caused 519,000 deaths worldwide (7% of cancer deaths; almost 1% of all deaths). The number of cases worldwide has significantly increased since the 1970s, a phenomenon partly attributed to the modern lifestyles.

The incidence of breast cancer varies greatly around the world: it is lowest in less-developed countries and greatest in the more-developed countries. In the twelve world regions, the annual age-standardized incidence rates per 100,000 women are as follows: in Eastern Asia, 18; South Central Asia, 22; sub-Saharan Africa, 22; South-Eastern Asia, 26; North Africa and Western Asia, 28; South and Central America, 42; Eastern Europe, 49; Southern Europe, 56; Northern Europe, 73; Oceania, 74; Western Europe, 78; and in North America, 90.

Breast cancer is strongly related to age with only 5% of all breast cancers occur in women under 40 years old.

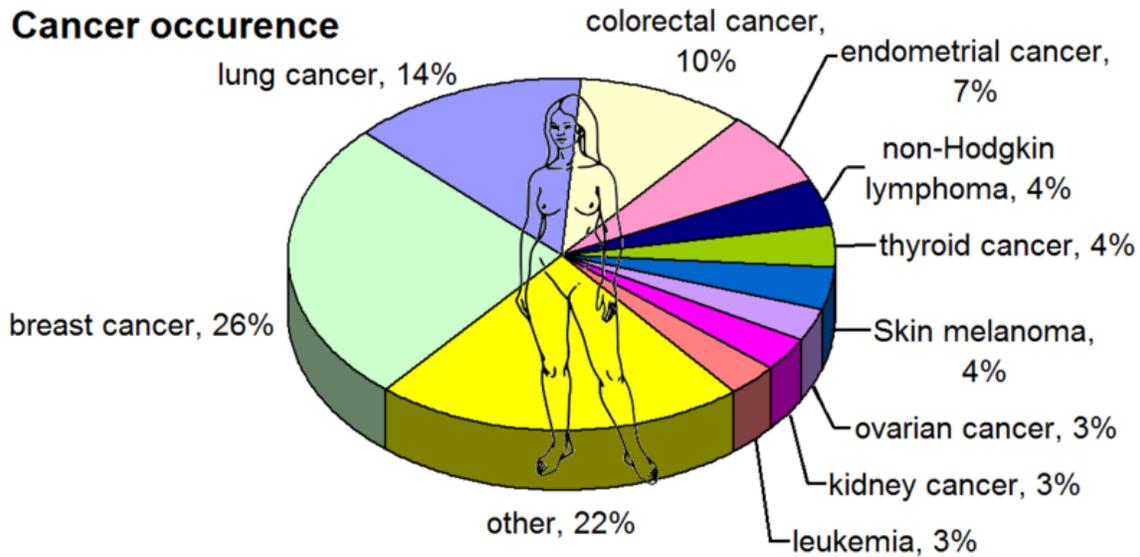
United States

The lifetime risk for breast cancer in the United States is usually given as 1 in 8 (12.5%) with a 1 in 35 (3%) chance of death. A recent analysis however has called this estimate into question when it found a risk of only 6% in healthy women.

The United States has the highest annual incidence rates of breast cancer in the world; 128.6 per 100,000 in whites and 112.6 per 100,000 among African Americans. It is the second-most common cancer (after skin cancer) and the second-most common cause of cancer death (after lung cancer). In 2007, breast cancer was expected to cause 40,910 deaths in the US (7% of cancer deaths; almost 2% of all deaths). This figure includes 450-500 annual deaths among men out of 2000 cancer cases.

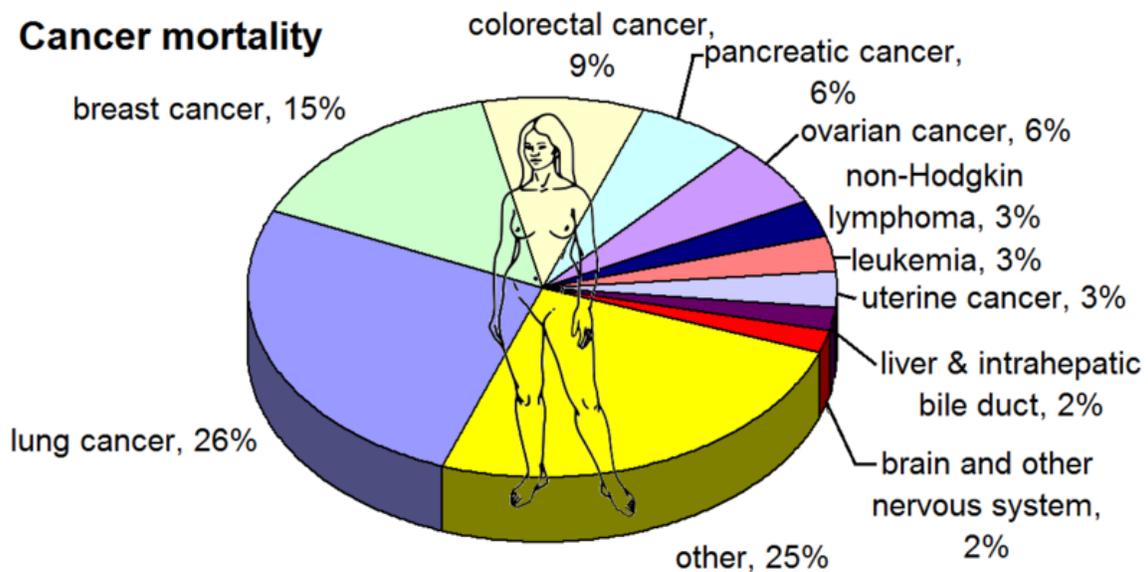
In the US, both incidence and death rates for breast cancer have been declining in the last few years in Native Americans and Alaskan Natives. Nevertheless, a US study conducted in 2005 indicated that breast cancer remains the most feared disease, even though heart disease is a much more common cause of death among women. Many doctors say that women exaggerate their risk of breast cancer.

Cancer occurrence



Cancer occurrence in females in the United States. Breast cancer is seen in light green at left.

Cancer mortality



By mortality

UK

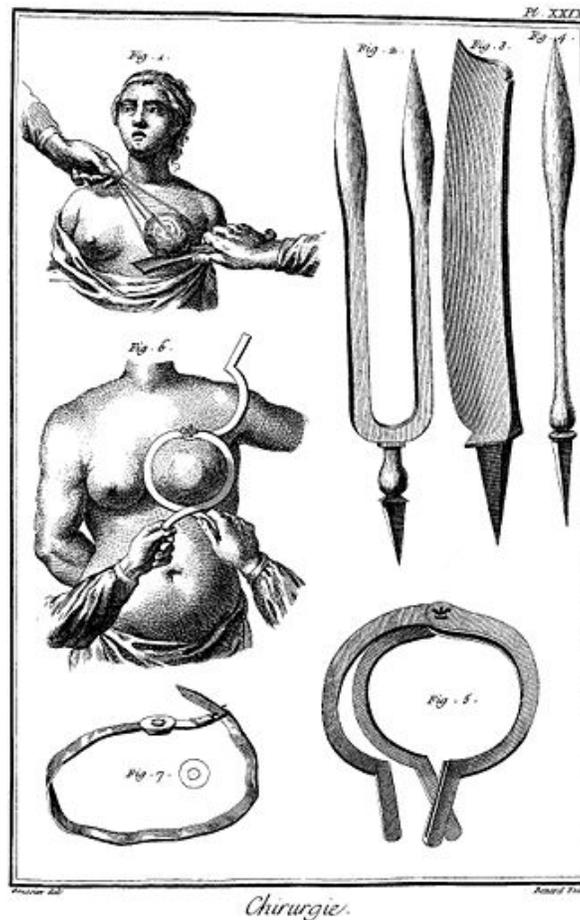
45,000 cases diagnosed and 12,500 deaths per annum.

Developing countries

As developing countries grow and adopt Western culture they also accumulate more disease that has arisen from Western culture and its habits (fat/alcohol intake, smoking,

exposure to oral contraceptives, the changing patterns of childbearing and breastfeeding, low parity). For instance, as South America has developed so has the amount of breast cancer. "Breast cancer in less developed countries, such as those in South America, is a major public health issue. It is a leading cause of cancer-related deaths in women in countries such as Argentina, Uruguay, and Brazil. The expected numbers of new cases and deaths due to breast cancer in South America for the year 2001 are approximately 70,000 and 30,000, respectively." However, because of a lack of funding and resources, treatment is not always available to those suffering with breast cancer.

History



Breast cancer surgery in the 18th century

Because of its visibility, breast cancer was the form of cancer most often described in ancient documents. Because autopsies were rare, cancers of the internal organs were essentially invisible to ancient medicine. Breast cancer, however, could be felt through the skin, and in its advanced state often developed into fungating lesions: the tumor

would become necrotic (die from the inside, causing the tumor to appear to break up) and ulcerate through the skin, weeping fetid, dark fluid.

The oldest description of cancer was discovered in Egypt and dates back to approximately 1600 BC. The Edwin Smith Papyrus describes 8 cases of tumors or ulcers of the breast that were treated by cauterization. The writing says about the disease, "There is no treatment." For centuries, physicians described similar cases in their practises, with the same conclusion. Ancient medicine, from the time of the Greeks through the 17th century, was based on humoralism, and thus believed that breast cancer was generally caused by imbalances in the fundamental fluids that controlled the body, especially an excess of black bile. Alternatively, patients often saw it as divine punishment. In the 18th century, a wide variety of medical explanations were proposed, including a lack of sexual activity, too much sexual activity, physical injuries to the breast, curdled breast milk, and various forms of lymphatic blockages, either internal or due to restrictive clothing. In the 19th century, the Scottish surgeon John Rodman said that fear of cancer caused cancer, and that this anxiety, learned by example from the mother, accounted for breast cancer's tendency to run in families.

Although breast cancer was known in ancient times, it was uncommon until the 19th century, when improvements in sanitation and control of deadly infectious diseases resulted in dramatic increases in lifespan. Previously, most women had died too young to have developed breast cancer. Additionally, early and frequent childbearing and breastfeeding probably reduced the rate of breast cancer development in those women who did survive to middle age.

Because ancient medicine believed that the cause was systemic, rather than local, and because surgery carried a high mortality rate, the preferred treatments tended to be pharmacological rather than surgical. Herbal and mineral preparations, especially involving the poisons hemlock or arsenic, were relatively common.

Mastectomy for breast cancer was performed at least as early as 548 CE, when it was proposed by the court physician Aetios of Amida to Theodora. It was not until doctors achieved greater understanding of the circulatory system in the 17th century that they could link breast cancer's spread to the lymph nodes in the armpit. The French surgeon Jean Louis Petit (1674–1750) and later the Scottish surgeon Benjamin Bell (1749–1806) were the first to remove the lymph nodes, breast tissue, and underlying chest muscle.

Their successful work was carried on by William Stewart Halsted who started performing radical mastectomies in 1882, helped greatly by advances in general surgical technology, such as aseptic technique and anesthesia. The Halsted radical mastectomy often involved removing both breasts, associated lymph nodes, and the underlying chest muscles. This often led to long-term pain and disability, but was seen as necessary in order to prevent the cancer from recurring. Before the advent of the Halsted radical mastectomy, 20-year survival rates were only 10%; Halsted's surgery raised that rate to 50%. Extending Halsted's work, Jerome Urban promoted superradical mastectomies, taking even more

tissue, until 1963, when the ten-year survival rates proved equal to the less-damaging radical mastectomy.

Radical mastectomies remained the standard of care in America until the 1970s, but in Europe, breast-sparing procedures, often followed radiation therapy, were generally adopted in the 1950s. One reason for this striking difference in approach may be the structure of the medical professions: European surgeons, descended from the barber surgeon, were held in less esteem than physicians; in America, the surgeon was the king of the medical profession. Additionally, there were far more European women surgeons: Less than one percent of American surgical oncologists were female, but some European breast cancer wards boasted a medical staff that was half female. American health insurance companies also paid surgeons more to perform radical mastectomies than they did to perform more intricate breast-sparing surgeries.

Breast cancer staging systems were developed in the 1920s and 1930s.

During the 1970s, a new understanding of metastasis led to perceiving cancer as a systemic illness as well as a localized one, and more sparing procedures were developed that proved equally effective. Modern chemotherapy developed after World War II.

The French surgeon Bernard Peyrilhe (1737–1804) realized the first experimental transmission of cancer by injecting extracts of breast cancer into an animal.

Prominent women who died of breast cancer include Anne of Austria, the mother of Louis XIV of France; Mary Washington, mother of George, and Rachel Carson, the environmentalist.

The first case-controlled study on breast cancer epidemiology was done by Janet Lane-Clayton, who published a comparative study in 1926 of 500 breast cancer cases and 500 control patients of the same background and lifestyle for the British Ministry of Health.

In the 1980s and 1990s, thousands of women who had successfully completed standard treatment then demanded and received high-dose bone marrow transplants, thinking this would lead to better long-term survival. However, it proved completely ineffective, and 15–20% of women died because of the brutal treatment.

The 1995 reports from the Nurses' Health Study and the 2002 conclusions of the Women's Health Initiative trial conclusively proved that hormone replacement therapy significantly increased the incidence of breast cancer.

Research

A considerable part of the current knowledge on breast carcinomas is based on in vivo and in vitro studies performed with breast cancer cell (BCC) lines. These provide an unlimited source of homogenous self-replicating material, free of contaminating stromal cells, and often easily cultured in simple standard media. The first line described, BT-20,

was established in 1958. Since then, and despite sustained work in this area, the number of permanent lines obtained has been strikingly low (about 100). Indeed, attempts to culture BCC from primary tumors have been largely unsuccessful. This poor efficiency was often due to technical difficulties associated with the extraction of viable tumor cells from their surrounding stroma. Most of the available BCC lines issued from metastatic tumors, mainly from pleural effusions. Effusions provided generally large numbers of dissociated, viable tumor cells with little or no contamination by fibroblasts and other tumor stroma cells. Many of the currently used BCC lines were established in the late 1970s. A very few of them, namely MCF-7, T-47D, and MDA-MB-231, account for more than two-thirds of all abstracts reporting studies on mentioned BCC lines, as concluded from a Medline-based survey.

Treatments are constantly evaluated in randomized, controlled trials, to evaluate and compare individual drugs, combinations of drugs, and surgical and radiation techniques. The latest research is reported annually at scientific meetings such as that of the American Society of Clinical Oncology, San Antonio Breast Cancer Symposium, and the St. Gallen Oncology Conference in St. Gallen, Switzerland. These studies are reviewed by professional societies and other organizations, and formulated into guidelines for specific treatment groups and risk category.

List of cell lines

Mainly based on Lacroix and Leclercq (2004).

Cell line	Primary tumor	Origin of cells	Estrogen receptors	Progesterone receptors	ERBB2 amplification	Mutated TP53	Tumorigenic in mice	Reference
600MPE	Invasive ductal carcinoma		+	-		-		
AU565	Adenocarcinoma		-	-	+	-		
BT-20	Invasive ductal carcinoma	Primary	No	No	No	Yes	Yes	
BT-474	Invasive ductal carcinoma	Primary	Yes	Yes	Yes	Yes	Yes	
BT-483	Invasive ductal carcinoma		+	+		-		
BT-549	Invasive ductal carcinoma		-	-		+		

Evsa-T	Invasive ductal carcinoma, mucin-producing, signet-ring type	Metastasis (ascites)	No	Yes	?	Yes	?
Hs578T	Carcinosarcoma	Primary	No	No	No	Yes	No
MCF-7	Invasive ductal carcinoma	Metastasis (pleural effusion)	Yes	Yes	No	No (wild-type)	Yes (with estrogen supplementation)
MDA-MB-231	Invasive ductal carcinoma	Metastasis (pleural effusion)	No	No	No	Yes	Yes
SK-BR-3	Invasive ductal carcinoma	Metastasis (pleural effusion)	No	No	Yes	Yes	No
T-47D	Invasive ductal carcinoma	Metastasis (pleural effusion)	Yes	Yes	No	Yes	Yes (with estrogen supplementation)

Chapter 2

Breast Cancer Classification

Breast cancer classification divides breast cancer into several categories according to multiple different schemes, each based on different criteria and serving a different purpose. A typical description usually considers each of these aspects in turn: the histopathological type, the grade of the tumor, the stage of the tumor, and the expression of proteins and genes. As knowledge of cancer cell biology develops these classifications are updated.

The practical purpose of classification is to describe each individual instance of breast cancer in a way that helps select which treatment approach is anticipated to have the best chance for a good outcome, with increased efficacy and low toxicity. Treatment algorithms rely on breast cancer classification to define specific subgroups that are each treated according to the best evidence available. Classification aspects must be carefully tested and validated, such that confounding effects are minimized, making them either true *prognostic factors*, which estimate disease outcomes such as disease-free or overall survival *in the absence of therapy*, or true *predictive factors*, which estimate the likelihood of response or lack of response *to a specific treatment*.

Classification of breast cancer is usually, but not always, primarily based on the histological appearance of tissue in the tumor. A variant from this approach is defined on the basis of physical exam findings, is that inflammatory breast cancer (IBC), a form of ductal carcinoma or malignant cancer in the ducts, is distinguished from other carcinomas by the inflamed appearance of the affected breast, which correlates with increased cancer aggressivity.

Schemes or aspects

Overview

Breast cancers can be classified by different schemata. Each of these aspects influences treatment response and prognosis. Description of a breast cancer would optimally include all of these classification aspects, as well as other findings, such as signs found on physical exam. A full classification includes histopathological type, grade, stage (TNM), receptor status, and the presence or absence of genes as determined by DNA testing:

- **Histopathology.** Although breast cancer has many different histologies, the considerable majority of breast cancers are derived from the epithelium lining the ducts or lobules, and are classified as mammary ductal carcinoma. *Carcinoma in situ* is proliferation of cancer cells within the epithelial tissue without invasion of the surrounding tissue. In contrast, *invasive carcinoma* invades the surrounding tissue. Perineural and/or lymphovascular space invasion is usually considered as part of the histological description of a breast cancer, and when present may be associated with more aggressive disease.
- **Grade.** Grading focuses on the appearance of the breast cancer cells compared to the appearance of normal breast tissue. Normal cells in an organ like the breast become differentiated, meaning that they take on specific shapes and forms that reflect their function as part of that organ. Cancerous cells lose that differentiation. In cancer, the cells that would normally line up in an orderly way to make up the milk ducts become disorganized. Cell division becomes uncontrolled. Cell nuclei become less uniform. Pathologists describe cells as well differentiated (low grade), moderately differentiated (intermediate grade), and poorly differentiated (high grade) as the cells progressively lose the features seen in normal breast cells. Poorly differentiated cancers have a worse prognosis.
- **Stage.** The TNM classification for breast cancer is based on the size of the cancer where it originally started in the body and the locations to which it has travelled. These cancer characteristics are described as the size of the tumor (T), whether or not the tumor has spread to the lymph nodes (N) in the armpits, neck, and inside the chest, and whether the tumor has metastasized (M) (i.e. spread to a more distant part of the body). Larger size, nodal spread, and metastasis have a larger stage number and a worse prognosis.
The main stages are:
Stage 0 is a pre-malignant disease or marker (sometimes called DCIS: Ductal Carcinoma in Situ) .
Stages 1–3 are defined as 'early' cancer and potentially curable.
Stage 4 is defined as 'advanced' and/or 'metastatic' cancer and incurable.
- **Receptor status.** Cells have receptors on their surface and in their cytoplasm and nucleus. Chemical messengers such as hormones bind to receptors, and this causes changes in the cell. Breast cancer cells may or may not have many different types of receptors, the three most important in the present classification being: estrogen receptor (ER), progesterone receptor (PR), and HER2/neu. Cells with or without these receptors are called ER positive (ER+), ER negative (ER-), PR positive (PR+), PR negative (PR-), HER2 positive (HER2+), and HER2 negative (HER2-). Cells with none of these receptors are called basal-like or triple negative.
- **DNA-based classification.** Understanding the specific details of a particular breast cancer may include looking at the cancer cell DNA by several different laboratory approaches. When specific DNA mutations or gene expression profiles are

identified in the cancer cells this may guide the selection of treatments, either by targeting these changes, or by predicting from the DNA profile which non-targeted therapies are most effective.

- Other prognostic tools. Computer models consider several traditional factors concurrently to derive individual survival predictions and calculation of potential treatment benefits. Adjuvant! was based on US cohorts and presents colored bar charts that display information that may assist in decisions regarding systemic adjuvant therapies. Successful validation was seen with Canadian and Dutch cohorts. Adjuvant! seemed less applicable to a British cohort and accordingly PREDICT is being developed in the United Kingdom.

Histopathologic types

Histopathologic classification is based upon characteristics seen upon light microscopy of biopsy specimens. The most common pathologic types of breast cancer are:

- Invasive ductal carcinoma - 55% of breast cancer incidence upon diagnosis, according to statistics from the United States in 2004
- Ductal carcinoma in situ - 13%
- Invasive lobular carcinoma - 5%

These three pathologic types represent approximately $\frac{3}{4}$ of breast cancer incidence.

The overall 5-year survival rate for both invasive ductal carcinoma and invasive lobular carcinoma were approximately 85% in 2003 according to a study in the USA. Ductal carcinoma in situ, on the other hand, is itself harmless, but untreated, approximately 60 percent of low grade DCIS lesions will become invasive at 40 years follow-up.

For an extensive list, the latest (2003) World Health Organization (WHO) classification of tumors of the breast recommends the following pathological types, which includes benign (harmless) tumors along with malignant (cancerous) tumors:

Invasive breast carcinomas

- Invasive ductal carcinoma
 - Most are "not otherwise specified"
 - The remainder are given subtypes:
 - Mixed type carcinoma
 - Pleomorphic carcinoma
 - Carcinoma with osteoclastic giant cells
 - Carcinoma with choriocarcinomatous features
 - Carcinoma with melanotic features
- Invasive lobular carcinoma

Precursor lesions

- Lobular neoplasia
 - lobular carcinoma in situ
- Intraductal proliferative lesions
 - Usual ductal hyperplasia
 - Flat epithelial hyperplasia
 - Atypical ductal hyperplasia
 - Ductal carcinoma in situ
- Microinvasive carcinoma
- Intraductal papillary neoplasms
 - Central papilloma
 - Peripheral papilloma

- Tubular carcinoma
- Invasive cribriform carcinoma
- Medullary carcinoma
- Mucinous carcinoma and other tumours with abundant mucin
 - Mucinous carcinoma
 - Cystadenocarcinoma and columnar cell mucinous carcinoma
 - Signet ring cell carcinoma
- Neuroendocrine tumours
 - Solid neuroendocrine carcinoma (carcinoid of the breast)
 - Atypical carcinoid tumour
 - Small cell / oat cell carcinoma
 - Large cell neuroendocrine carcinoma
- Invasive papillary carcinoma
- Invasive micropapillary carcinoma
- Apocrine carcinoma
- Metaplastic carcinomas
 - Pure epithelial metaplastic carcinomas
 - Squamous cell carcinoma
 - Adenocarcinoma with spindle cell metaplasia
 - Adenosquamous carcinomas
 - Mucoepidermoid carcinoma
 - Mixed epithelial/mesenchymal metaplastic carcinomas
- Lipid-rich carcinoma
- Secretory carcinoma
- Oncocytic carcinoma
- Adenoid cystic carcinoma
- Acinic cell carcinoma
- Glycogen-rich clear cell carcinoma
- Sebaceous carcinoma
- Inflammatory carcinoma
- Bilateral breast carcinoma

Mesenchymal tumors (including sarcoma)

- Haemangioma
- Angiomatosis
- Haemangiopericytoma
- Pseudoangiomatous stromal hyperplasia
- Myofibroblastoma
- Fibromatosis (aggressive)
- Inflammatory myofibroblastic tumour

- Atypical papilloma
- Intraductal papillary carcinoma
- Intracystic papillary carcinoma

Benign epithelial lesions

- Adenosis, including variants
 - Sclerosing adenosis
 - Apocrine adenosis
 - Blunt duct adenosis
 - Microglandular adenosis
 - Adenomyoepithelial adenosis
- Radial scar / complex sclerosing lesion
- Adenomas
 - Tubular adenoma
 - Lactating adenoma
 - Apocrine adenoma
 - Pleomorphic adenoma
 - Ductal adenoma

Myoepithelial lesions

- Myoepitheliosis
- Adenomyoepithelial adenosis
- Adenomyoepithelioma
- Malignant myoepithelioma

Fibroepithelial tumours

- Fibroadenoma
- Phyllodes tumour
 - Benign
 - Borderline
 - Malignant
- Periductal stromal sarcoma, low grade
- Mammary hamartoma

Tumours of the nipple

- Nipple adenoma
- Syringomatous adenoma
- Paget's disease of the nipple

Malignant lymphoma

- Lipoma
 - Angiolipoma
- Granular cell tumour
- Neurofibroma
- Schwannoma
- Angiosarcoma
- Liposarcoma
- Rhabdomyosarcoma
- Osteosarcoma
- Leiomyoma
- Leiomyosarcoma

Metastatic tumours

Tumours of the male breast

- Gynecomastia
- Carcinoma
 - In situ
 - Invasive

Grading

The Bloom-Richardson grade is the most commonly used scoring system in the US, but other schemes such as the Nottingham score have also been widely applied. Grading schemes look at the similarity of breast cancer cells to normal breast tissue, and classify the cancer as well differentiated (low grade), moderately differentiated (intermediate grade), and poorly differentiated (high grade), reflecting progressively less normal appearing cells that have a worsening prognosis.

Staging

TNM (tumor, node, metastasis) system

The TNM system classifies the cancer by several factors as described below, T for tumor, N for nodes, M for metastasis, and then aggregates TNM groups into overall stages as shown in the table. However, several factors are important when reviewing reports for individual breast cancers or when reading the medical literature- it is crucial to be aware that the criteria used in the TNM system have varied over time, sometimes fairly substantially, according to the different editions that AJCC and UICC have released. The dates of publication and adoption for use of AJCC editions is summarized here; past editions are available from AJCC for web download.

- Edition 1 published 1977 and went into effect 1978
- Edition 2 published 1983 and went into effect 1984
- Edition 3 published 1988 and went into effect 1989
- Edition 4 published 1992 and went into effect 1993
- Edition 5 published 1997 and went into effect 1998
- Edition 6 published 2002 and went into effect 2003
- Edition 7 published 2009 and went into effect 2010

As a result, a given stage may have quite a different prognosis depending on which staging edition is used, independent of any changes in diagnostic methods or treatments, an effect that has been termed "stage migration." The technologies used to assign patients

to particular categories have changed also, and it can be seen that increasingly sensitive methods tend to cause individual cancers to be reassigned to higher stages, making it improper to compare that cancer's prognosis to the historical expectations for that stage. Finally, of course, a further important consideration is the effect of improving treatments over time as well.

These descriptors refer to the 2010 edition.

Tumor - The characteristics of cancer at its primary site of origin in the breast are used to determine tumor (or T) classification values (TX, T0, Tis, T1, T2, T3 or T4) which depend on the presence or absence of invasive cancer, the dimensions of the invasive cancer, and the presence or absence of invasion outside of the breast, for example to the skin of the breast, to the muscle or to the rib cage underneath:

- TX - Primary tumor cannot be assessed.
- T0 - No evidence of primary tumor.
- Tis - Carcinoma in situ.
 - Tis (DCIS) - Ductal Carcinoma in situ.
 - Tis (LCIS) - Lobular Carcinoma in situ.
 - Tis (Paget's) - Paget's disease of the nipple with no tumor. Paget's disease of the nipple is NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted.
- T1 - Tumor 20 mm or less in its greatest dimension.
 - T1mi - Microinvasive tumor that is 1 mm or less in greatest dimension.
 - T1a - Tumor more than 1 mm but not more than 5 mm in its greatest dimension.
 - T1b - Tumor more than 5 mm but not more than 10 mm in its greatest dimension.
 - T1c - Tumor more than 10 mm but not more than 20 mm in its greatest dimension.
- T2 - Tumor more than 20 mm but not more than 50 mm in its greatest dimension.
- T3 - Tumor more than 50 mm in its greatest dimension.
- T4 - Tumor of any size with direct extension to (a) chest wall or (b) skin as described below:
 - T4a - Extension to chest wall. By definition, adherence to, or invasion of, the pectoralis muscle alone does not qualify as T4.
 - T4b - Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange of the skin confined to the same breast which does not meet the criteria for inflammatory carcinoma. By definition, invasion of the dermis alone does not qualify as T4.
 - T4c - Both T4a and T4b.
 - T4d - Inflammatory breast cancer. Inflammatory carcinoma is restricted to cases with typical skin changes involving a third or more of the skin of the

breast. While the histologic presence of invasive carcinoma invading dermal lymphatics is supportive of the diagnosis, it is not required, nor is dermal lymphatic invasion without typical clinical findings sufficient for a diagnosis of inflammatory breast cancer.

Lymph Node - The lymph node (or N) classification values (NX, N0, N1, N2 or N3) depend on the number, size and location of breast cancer cell deposits in various lymph nodes including in the armpit (axillary lymph nodes), the collar area (supraclavicular lymph nodes), and inside the chest (internal mammary lymph nodes.) Within the armpit there are three levels of axillary lymph nodes, such that Level I is the bottom or outer level, below the lower edge of the pectoralis minor muscle; Level II is lying underneath the pectoralis minor muscle; and Level III is above the pectoralis minor muscle.

- NX - regional lymph nodes cannot be assessed. Perhaps due to previous removal.
- N0 - no regional lymph node metastasis. There are several N0 subsets:
 - pN0(i-): No regional lymph node metastases histologically, negative IHC
 - pN0(i+): Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC) where Isolated Tumor Cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.
 - pN0(mol-): No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
 - pN0(mol+): Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC
- N1 - this refers to clinically staged N1 disease, defined as present in movable level I or level II axillary lymph nodes on the same side as the affected breast.
- pN1 - this refers to pathologically staged lymph nodes, that have micrometastases; or metastases in 1 to 3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected, with the following characteristics:
 - pN1mi - Micrometastases (defined as greater than 0.2 mm and/or more than 200 cells, but none greater than 2 mm) or metastases in 1 to 3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected.
 - pN1a - Metastases in 1 to 3 axillary lymph nodes, at least one metastasis greater than 2 mm

- pN1b - Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected.
- pN1c - Metastases in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected.
- N2 - (needs updated to 2010 descriptors) metastasis to fixed regional axillary lymph nodes, or metastasis to the internal mammary lymph nodes, on the same side as the affected breast.
- N3 - (needs updated to 2010 descriptors) metastasis to supraclavicular lymph nodes or infraclavicular lymph nodes or metastasis to the internal mammary lymph nodes with metastasis to the axillary lymph nodes.

Metastases - There were traditionally three metastatic classification values (MX, M0 and M1) which principally depended on the absence of adequate information, the confirmed absence, or the presence, respectively, of breast cancer cells in locations other than the breast and lymph nodes (so-called distant metastases, e.g. to bone, brain, lung.) The MX classification was used by pathologists where clinical information about spread of cancer to other body sites was not available to them at the time the cancer pathology report was written. The present TNM report forms do not include the MX option, and, indeed, there is now no pathologic M0 stage as the staging forms direct the user to apply the clinical M category to complete stage group. There are now three options:

- M0 - No clinical or radiographic evidence of distant metastases.
- cM0(i+) - No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow or other non-regional nodal tissue that are no larger than 0.2 mm and which are not causing symptoms or signs of metastases.
- M1 - Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm.

Overall stage grouping

The TNM descriptors for tumor T stage, node N involvement, and metastatic M stage can be combined into a single overall stage grouping number, also called Prognostic Group, labelled Stage 0 to IV. A summary of the AJCC and UICC 7th edition from 2010 is shown:

Tumor T Stage	Node N Stage	Metastatic M Stage	Overall Stage / Prognostic Group
Tis	N0	M0	0
T1 (includes T1mi)	N0	M0	IA
T0 or T1	N1mi	M0	IB

T0-1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T0-T2	N2	M0	IIIA
T3	N1-N2	M0	IIIA
T4	N0-N2	M0	IIIB
any T	N3	M0	IIIC
any T	any N	M1 (this does NOT include cM0(+))	IV

The following table shows historical data from a textbook with publication date 2007 May. A primary reference that details which staging edition was used and when the outcome data were collected needs to be identified.

Stages	Features	Overall 5-year survival historically
Stage 0	Ductal (DCIS) or lobular carcinoma in situ (LCIS) without microinvasion	92%
Stage I	Invasive carcinoma of 2cm or less in diameter (including invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), as well as DCIS and LCIS with microinvasion) without lymph node involvement or metastases of less than 0.02 cm in diameter Invasive carcinoma (mainly IDC and ILC)	87%
Stage II	<ul style="list-style-type: none"> of 5 cm or less in diameter with up to three involved axillary nodes, or greater than 5 cm but without lymph node involvement. 	75%

Invasive carcinoma (mainly IDC and ILC)

- Stage III**
- of 5 cm or less in diameter with four or more involved axillary lymph nodes, or
 - greater than 5 cm with any lymph node involvement, or
 - involving the ipsilateral internal mammary lymph nodes, or 46%
 - involving the skin, with e.g. edema, ulceration or satellite skin nodules, chest wall fixation
 - showing chest wall fixation
 - Clinical inflammatory carcinoma

Stage IV Any T Any N M1; Any breast cancer showing distant metastasis 13%

Receptor status

The receptor status of breast cancers has traditionally been identified by immunohistochemistry, which stains the cells based on the presence of estrogen receptors (ER), progesterone receptors (PR) and HER2 receptors. This remains the commonest method of testing for receptor status, but DNA based analyses can categorize breast cancers into groups based on gene profiles that correspond to receptor status.

Receptor status is used to divide breast cancer into several molecular classes:

1. Basal-like, which are ER-, PR- and HER2- (triple negative, TN). Most BRCA1 breast cancers are basal-like TN.
2. Luminal A, which are ER+ and low grade
3. Luminal B, which are ER+ but often high grade
4. HER2+, which have amplified ERBB2
5. Claudin-low, a more recently described class that is often triple-negative but which may be distinct in that this subset of TN also has low cell-cell junction protein and has frequent lymphocytic infiltration.

Receptor status is a critical assessment for all breast cancers as it determines the suitability of using targeted treatments such as tamoxifen and or trastuzumab. These treatments are now some of the most effective adjuvant treatments of breast cancer. Estrogen receptor positive (ER+) cancer cells depend on estrogen for their growth, so they can be treated with drugs to reduce either the effect of estrogen (e.g. tamoxifen) or the actual level of estrogen (e.g. aromatase inhibitors), and generally have a better prognosis. Generally, prior to modern treatments, HER+ had a worse prognosis, however HER2+ cancer cells respond to drugs such as the monoclonal antibody, trastuzumab, (in combination with conventional chemotherapy) and this has improved the prognosis significantly. Conversely, triple negative cancer (i.e. no positive receptors), lacking targeted treatments now has a comparatively poor prognosis.

Other immunohistochemical tests

Among many immunohistochemical tests that may further stratify prognosis, BCL2 has shown promise in preliminary studies.

DNA classification

Traditional DNA classification was based on the general observation that cells that are dividing more quickly have a worse prognosis, and relied on either the presence of protein Ki67 or the percentage of cancer cell DNA in S phase. These methods, and scoring systems that used DNA ploidy, are used much less often now, as their predictive and prognostic power was less substantial than other classification schemes such as the TNM stage. In contrast, modern DNA analyses are increasingly relevant in defining underlying cancer biology and in helping choose treatments.

HER2/neu status can be analyzed by fluorescent in-situ hybridization (FISH) assays, which have a higher correlation than receptor immunohistochemistry with response to trastuzumab, a targeted therapy.

DNA microarrays have compared normal cells to breast cancer cells and found differences in the expression of hundreds of genes. Although the significance of many of those genetic differences is unknown, independent analyses by different research groups has found that certain groups of genes have a tendency to co-express. These co-expressing clusters have included hormone receptor-related genes, HER2-related genes, a group of basal-like genes, and proliferation genes. As might therefore be anticipated, there is considerable similarity between the receptor and microarray classifications, but assignment of individual tumors is by no means identical. By way of illustration, some analyses have suggested that approximately 75% of receptor classified triple-negative (TN) basal-like tumors have the expected DNA expression profile, and a similar 75% of tumors with a typical basal-like DNA expression profile are receptor TN as well. This means that 25% of triple-negative (TN) basal-like tumors as defined by one or other classification are excluded from the alternative classification's results. Which classification scheme more reliably sorts patients to effective therapies is under investigation.

Several commercially marketed DNA microarray tests analyze clusters of certain genes and may help decide which possible treatment is most effective for a particular cancer. These tests are presently of potential use mainly in estrogen-receptor positive cancers, and their use in that subset of breast cancers is supported by Level II evidence or Level III evidence. One test, Oncotype DX, is supported by Level II evidence. Current rules do not mandate approval by the U.S. Food and Drug Administration (FDA) for these tests if performed at a single, company-operated laboratory and, accordingly, the Oncotype DX assay is not specifically FDA approved. Oncotype DX assesses 16 cancer-related genes and 5 comparative reference genes, and is therefore sometimes known as the 21-gene assay, and has been endorsed by the American Society of Clinical Oncology. Clinical trial results suggest that not only does Oncotype stratify estrogen-receptor positive breast

cancer into different prognostic groups, but also suggest that cancers that have a particularly favorable Oncotype DX microarray result tend to derive minimal benefit from chemotherapy and so it may be appropriate to choose to avoid the associated treatment side effects. The results are reported as a Recurrence Score (RS), where a higher RS is associated with a worse prognosis, referring to the likelihood of recurrence without treatment, as well as a higher RS being associated with a higher probability of response to chemotherapy, termed a positive predictive factor. For example, a neoadjuvant clinical treatment program that included initial chemotherapy followed by surgery and subsequent additional chemotherapy, radiotherapy, and hormonal therapy found a strong correlation with higher RS with the likelihood of a complete response (CR) to the presurgical chemotherapy. Since high risk features may already be evident in many high risk cancers, for example hormone-receptor negativity or HER-2 positive disease, Oncotype may especially improve the risk assessment that is derived from routine clinical variables in intermediate risk disease. Although supported by Level III evidence, MammaPrint, sometimes also known as the Amsterdam or 70-gene profile, is approved by the FDA, as Agendia, the manufacturer of the test system, applied for FDA clearance even though it was not required to do so. The evidence for Oncotype was assessed favorably by the California Technology Assessment Forum (CTAF) in 2006, while the available evidence for Mammaprint had not yet fulfilled all CTAF criteria in 2010. Mammaprint requires fresh tissue, unlike Oncotype. Two other tests also have Level III evidence: Theros and MapQuant Dx. No tests have been verified by Level I evidence, if this is rigorously defined as being derived from a prospective, randomized controlled trial where patients who used the test had a better outcome than those who did not. Acquiring extensive Level I evidence would be clinically and ethically challenging. However, several validation approaches are being actively pursued. Firstly, in a looser definitional sense, since the validation of the Oncotype DX Breast Cancer Assay Recurrence Score used a designed study of archived tumor samples from a randomized clinical trial it might be considered Level of Evidence I, a position that Genomic Health has taken. Additionally, Oncotype DX is being evaluated in node negative, estrogen-receptor positive breast cancer in a prospective trial, the **Trial Assigning Individualized Options for Treatment (Rx) (TAILORx)**, launched 2006 May, that has enrolled 10,000 people with intermediate results on the test with an estimated completion date of 2014. Oncotype is also being evaluated in node positive, estrogen-receptor positive breast cancer in a Milan/European trial. Mammaprint is being evaluated in the **Microarray In Node negative Disease may Avoid ChemoTherapy** trial (MINDACT). One review characterized these genetic tests collectively as adding "modest prognostic information for patients with HER2-positive and triple-negative tumors, but when measures of clinical risk are equivocal (e.g., intermediate expression of ER and intermediate histologic grade), these assays could guide clinical decisions".

The choice of established chemotherapy medications, if chemotherapy is needed, may also be affected by DNA assays that predict relative resistance or sensitivity. Topoisomerase II (TOP2A) expression predicts whether doxorubicin is relatively useful. Expression of genes that regulate tubulin may help predict the activity of taxanes.

Various DNA results are being incorporated in the design of clinical trials of new medicines. Specific genes such as p53, NME1, BRCA and PIK3CA/Akt may be associated with responsiveness of the cancer cells to innovative research pharmaceuticals. BRCA1 and BRCA2 polymorphic variants can increase the risk of breast cancer, and these cancers tend to express a profile of genes, such as p53, in a pattern that has been called "BRCA-ness." Cancers arising from BRCA1 and BRCA2 mutations, as well as other cancers that share a similar "BRCA-ness" profile, including some basal-like receptor triple negative breast cancers, respond to treatment with PARP inhibitors such as olaparib. Combining these newer medicines with older agents such as 6-Thioguanine (6TG) may overcome the resistance that can arise in BRCA cancers to PARP inhibitors or platinum-based chemotherapy. mTOR inhibitors such as everolimus may show more effect in PIK3CA/Akt e9 mutants than in e20 mutants or wild types.

DNA methylation patterns can epigenetically affect gene expression in breast cancer and may contribute to some of the observed differences between genetic subtypes.

Clinical investigations have looked at whether testing for variant genotype polymorphic alleles of several genes can predict whether or not to prescribe tamoxifen, based on the rate of conversion of tamoxifen to the active metabolite, endoxifen. Although some studies had suggested a potential advantage from CYP2D6 testing, data from two large clinical trials found no benefit and testing for the CYP2C19*2 polymorphism gave counterintuitive results. The medical utility of potential biomarkers of tamoxifen responsiveness such as HOXB13, PAX2, and estrogen receptor (ER) alpha and beta isoforms interaction with SRC3 have all yet to be fully defined.

Chapter 3

Metastatic Breast Cancer

Metastatic breast cancer is a complex multi-step process involving the expansion of cancerous cells from the breast to other areas of the body. It is a serious complication of breast cancer, as metastatic disease in breast cancer is often fatal, with treatments mainly limited to palliation.

Breast cancer primarily metastasizes to the bone, lungs, regional lymph nodes, liver and to the brain, with the most common site being the bone. The typical environmental barriers in any metastatic event would include physical (basement membrane), chemical (Reactive oxygen species (ROS), hypoxia and low PH) and biological (immune surveillance, inhibitory cytokines and regulatory Extracellular Matrix (ECM) peptides) components. Organ-specific anatomic considerations can also influence metastasis; these include blood flow patterns from the primary tumor and the homing ability of cancer cells for certain tissues. The targeting by cancer cells of specific organs is likely regulated by chemoattractant factors and adhesion molecules, which are produced by the target organ along with the cell-surface receptors expressed by the tumor cells.

The main steps involved in the metastatic cascade of a cancer cell are:

- The cell division and growth within the primary tumor.
- Invasion of the primary tumor border (basement membrane, referred to as BM) and the local tissue surrounding the tumor by the cell.
- Intravasation of the circulatory system: the cell enters the bloodstream or lymph channels.
- The cell must survive the transit into the new environment until it ultimately arrests in the microvasculature of the secondary site.
- Extravasation to a distant site : The cell then invades into the BM of the target tissue.
- Proliferation of the cancer cell at the metastatic site.
- Formation of a micrometastasis inside the secondary site.
- Progressive colonization to form a life threatening metastasis.

The potential of a tumor cell to metastasize depends on its microenvironment, or the “niche” interactions with the local factors that promote tumor-cell growth, survival, angiogenesis, invasion and metastasis. This is explained by the theory called the "seed and soil hypothesis".

Symptoms

The symptoms produced by metastatic breast cancer vary by the location of the metastases. For instance:

- Metastatic disease to the bone causes severe, progressive pain, and, less commonly, pathological fracture, erythema over the affected bone, and swelling.
- Metastatic breast cancer to the brain causes the following symptoms: persistent, progressively worsening headache, visual changes, seizures, nausea or vomiting, vertigo, behavioral and personality changes, and increased intracranial pressure.
- Metastatic disease to the liver causes jaundice, elevated liver enzymes, abdominal pain, loss of appetite, nausea, and vomiting
- Metastatic breast cancer to the lung or pleura causes chronic cough, dyspnea, abnormal chest X-ray, and chest pain.
- Other nonspecific systemic symptoms of metastatic breast cancer include fatigue, malaise, weight loss, and poor appetite.

Seed and soil hypothesis

The **seed and soil** hypothesis states that specific organs harbor metastases from one type of cancer by stimulating their growth better than other types of cancer. This interaction is dynamic and reciprocal, since cancer cells modify the environment they encounter.

Extracellular matrix degradation in cancer

Cell-cell and cell-ECM matrix adhesion, motility, and localised proteolysis are mediated mainly by matrix metalloproteases (MMPs). Degradation of extracellular matrix is the starting process that facilitates metastasis. The cell develops structures called invadopodia, which are highly concentrated in several proteases and have a highly dynamic actin cytoskeleton.

Mechanisms of metalloprotease action in cell motility involve:

- Proteolytic cleavage of growth factors so that they are readily available to cells not in direct physical contact.
- Degradation of the ECM is facilitated by MMPs so that the cells can move across tissues into nearby stroma .
- Regulated receptor cleavage to modulate migratory signaling.

Most of these processes require a delicate balance between the functions of matrix metalloproteases (MMPs) or metalloprotease-disintegrins (ADAMs) and natural tissue inhibitors of metalloproteases (TIMPs). Regulated proteolysis is an important mechanism to maintain homeostasis. There is increased expression of protease systems in cancer cells to equip them with the tools necessary to degrade the extracellular matrix and release several growth factors or transmembrane receptors. MMP-2 is upregulated in the bone, increased levels of MMP-1 and MMP-19 are observed in the brain. This in turn,

upregulates the signaling pathways necessary to provide increased cell adhesion, cell motility, cell migration, invasion, cancer cell proliferation and survival.

Bone

Metastasis is the cause of about 90% of deaths due to breast cancer and roughly 70% of all patients dying of breast cancer have evidence of metastatic bone disease. The important extracellular matrix components and cell surface receptors which could help in metastasis are discussed here.

Integrin signalling

Integrin $\alpha v \beta 3$, a cell surface adhesion molecule is important for tumor attachment, cell-cell communication between the breast tumor cells and the environment in the bone, osteoclast bone resorption, and angiogenesis. Integrin-mediated adhesion between cancer cells and osteoclasts in bone metastases induces phosphorylation of extracellular signal-regulated kinases (ERK1/2) in osteoclasts, which in turn induces osteoclast differentiation and survival.

Cancer cell-blood platelet interaction

Metastatic breast cancer cells excrete lysophosphatidic acid (LPA) that binds to receptors on tumor cells, inducing cell proliferation and release of cytokines (IL-6 and IL-8, potent bone resorptive agents) and stimulating bone resorption.

After the breast cancer cells have traveled away from the primary tumor, they establish a tight interaction with the bone microenvironment and secrete osteolytic factors capable of osteoclast formation and bone resorption. Apart from the breast tumor cells, the resident stromal cells also contribute to tumor survival. Growth factors like epidermal growth factor (EGF), fibroblast growth factor (FGF), and transforming growth factor beta (TGF- β) are implicated in the development and progression of metastatic breast cancer.

Matrix metalloproteinases (MMPs)

MMP-2 is the main metalloprotease secreted by breast cancer cells or induced in the adjacent bone stroma ; it plays an important role in the degradation of extracellular matrix essential for cancer metastasis. Tumor cells use MMP-2 secreted by bone marrow fibroblasts (BMFs). MMP-2 is stored in an inactive conformation in association with the cell surface or extracellular matrix of BMFs.. Inactive MMP-2 present on the surface of BMFs is displaced by breast cancer cells. Cancer cells can then use the proteinase to facilitate tissue invasion, which requires the degradation of connective tissue associated with vascular basement membranes and interstitial connective tissue.

Brain

Brain metastasis is observed in 10% of breast cancer patients with metastatic properties. Many of the breast cancer therapies (like targeted antibodies) fail to penetrate the blood-brain barrier (BBB), hence allowing for tumor recurrence in the Central Nervous System. Brain is a special organ for metastasis as the breast tumor cells have to pass the BBB in order to form micrometastases in the brain.

CD44

CD44, a cell-surface transmembrane glycoprotein is a receptor for hyaluronic acid involved in cell adhesion by binding to specific extracellular matrix components. A proposed mechanism for the function of CD44 may be to regulate the adhesion of circulating cancer cells in the brain to endothelium at the secondary site with the help of hyaluronate matrix ligand or by its cytoplasmic attachments to actin-associated proteins of the merlin/ezrin/radixin/moesin family .

Sialyl transferase (glycosylation modifications of gangliosides)

Cell-surface sialylation has been implicated in cell–cell interactions and overexpression of a brain sialyltransferase in breast cancer cells is a mechanism that highlights the role of cell-surface glycosylation in organ-specific metastatic interactions. Breast cancer metastasis to the brain involves mediators of extravasation through non-fenestrated capillaries, complemented by specific enhancers of blood–brain barrier crossing and brain colonization .

ECM components in breast cancer metastasis

ECM-tumor cell interactions play a critical role in each of the events of the metastatic cascade. Interactions of the breast cancer cells with integrins, fibronectin, laminins, collagens, hyaluronan, proteoglycans which can contribute to the metastatic process. Some of these proteins are discussed here in relevance to breast cancer metastasis.

Fibrinogen - Integrin

Fibronectin is an extracellular glycoprotein that can bind to integrins and other ECM components like collagen, fibrin and Heparan Sulphate ProteoGlycans(HSPGs). Several different integrins bind to fibronectin. Fibronectin-integrin interactions are important in tumor cell migration, invasion, and metastasis and also cell proliferation by signaling through integrins. Integrin-mediated tumor cell adhesion to ECM proteins can trigger signal transduction and cause upregulation of gene expression, increased tyrosine phosphorylation of the focal adhesion kinase, activation and nuclear translocation of mitogen-activated protein (MAP) kinases.

Heparanase

Heparanase cleaves heparin sulfate chains of HSPGs which have an extensive network with several proteins on cell surface and ECM. The basic HSPG structure consists of a protein core to which several linear heparin sulfate (HS) chains are covalently O-linked and acts as an assembly of different ECM proteins, including fibronectin, laminins, and interstitial collagens, heparin-binding growth factors, chemokines, lipoproteins. HSPGs are prominent components of blood vessels.. Binding to HS stabilizes FGFs and Vascular Endothelial Growth Factors (VEGFs) and prevents them from inactivation. HS chains function as low affinity co-receptors that promote dimerization of FGFs, hence helps in the sequestration of the GFs and causes activation of the signaling tyrosine kinase receptors even under low circulating concentrations of the growth factors. Heparanase expressed by cancer cells participates in angiogenesis and neovascularization by degrading the polysaccharide scaffold of the endothelial BM, thereby releasing angiogenic growth factors from ECM.

Tenascin

The ECM protein tenascin C (TNC) is up-regulated in metastatic breast cancer. TNC is an adhesion-modulating extracellular matrix glycoprotein. It is highly expressed in tumor stroma and stimulates tumor cell proliferation. It is hypothesized that TNC stimulates invasion via up-regulation of MMP-1 expression through activation of MAPK pathway. MMP-1 (interstitial collagenase) cleaves collagen type I, II, III, VII and X. Hence, tenascin overexpression can significantly alter the collagen in the ECM and influence tumor cell migration in cartilaginous tissues.

Endoglin

Endoglin is a cell-surface disulfide-linked homodimeric glycoprotein which binds to the integrins and other RGD ligands and a coreceptor for TGF-beta. Brain metastatic breast tumor cells express endoglin in large amounts. Endoglin-overexpressing cells develop large numbers of invadopodia and endoglin is localized in these structures. Endoglin-expression in tumor cells contributes to metastasis by upregulating MMP-1 and MMP-19. MMP-19 cleaves components of the basal lamina, such as collagen type IV, laminin 5, nidogen (entactin) and other ECM proteins like tenascin, aggrecan, fibronectin. Hence endoglin-overexpression alters the proteolytic balance of the cells to higher matrix degradation and increased invasive properties of the breast cancer.

Therapies

Metastasis is a complex and interconnected multi-step process. Each step in the process is a potential target for therapies to prevent or reduce metastasis. Those steps which have a good clinical window period are the best targets for therapy. Each event in metastasis is highly regulated and requires a synergistic activation of different ECM proteins, growth factors, etc. Although the occasional patient with metastatic breast cancer benefits from surgical resection of an isolated metastasis, and most patients receive radiotherapy (often

for palliation alone), during the course of their disease, the treatment of metastatic breast carcinoma typically has to involve the use of systemic therapy.

Chemotherapy

Chemotherapy is one of the most important parts of therapy for metastatic breast cancer. The Taxenes are very active in metastatic breast cancer, and abraxane, a form of paclitaxel without solvents, is approved for patients with metastatic breast cancer who either relapsed within 6 months of adjuvant chemotherapy or failed to respond to combination chemotherapy, with a higher response rate than solvent-based paclitaxel (15% vs 8%) also, abraxane can deliver a 49% higher dose of medication than solvent based paclitaxel. However, side effects are severe. Also, severe sensory neuropathy can occur in patients treated with abraxane. Combination chemotherapy is often used in patients with metastatic breast cancer. Vinorelbine is also active in metastatic breast cancer.

Eribulin was approved by FDA in Nov 2010.

Tamoxifen and other anti-estrogens

For estrogen-receptor positive metastatic breast carcinoma, the first line of therapy is often Tamoxifen or another anti-estrogen drug, unless there are liver metastases, significant lung involvement, rapidly progressive disease, or severe symptoms requiring immediate palliation.

Radiotherapy

Radiotherapy is used in the treatment of metastatic breast cancer. The most common reasons for a patient with metastatic breast carcinoma to be treated with radiotherapy are:

- Spinal cord compression. Spinal cord compression is an oncological emergency, as untreated spinal cord compression can cause permanent paralysis or even death. In breast cancer, spinal cord compression occurs when either a bone metastasis or spinal metastasis began to push on the spinal cord, resulting in inflammation, and if untreated, spinal cord injury. Radiotherapy is an important part of therapy for cord compression secondary to metastatic breast cancer, along with corticosteroids and laminectomy.
- Liver metastases. Typically, pain from liver metastases responds to chemotherapy and pain medication. However, in cases when chemotherapy is contraindicated, or the liver metastases are refractory to chemotherapy, and pain medication fails to provide appropriate palliation of liver metastasis related pain, radiotherapy should be considered, as it can be effective in relieving pain and may shrink the metastases, and perhaps even extend survival in a subset of patients who have a good response to radiotherapy.
- Brain metastases. Brain metastases occur in up to 10–15% of breast cancer patients, and often, but not always, occur late in the disease. They require urgent

treatment, as brain metastases can progress rapidly, and can suddenly produce life-threatening complications such as increased intracranial pressure, herniation of the brain, and seizures. Radiotherapy is essential in the treatment of brain metastases from breast cancer, as it halts tumor progression quickly and can induce a response in the majority of patients.

- Bone metastases. The bones are a very common site of metastatic disease from breast cancer, and bone metastases can cause severe pain, hypercalcemia, and pathologic fracture. Radiotherapy is indicated to prevent pathologic fracture, as well as part of postoperative treatment following repair of a pathologic fracture. Strontium 89, a radiopharmaceutical that is injected into the bloodstream, is under investigation for the treatment of bone metastases from breast cancer. Currently, there is evidence that it can relieve pain for up to three months after its administration. It is not known whether or not it can prevent pathologic fracture, but it should be considered in patients who have three or more sites of painful bone metastases who cannot be treated with external beam radiotherapy. In some patients with estrogen receptor positive breast carcinoma metastatic to the bone only, external beam radiotherapy followed by tamoxifen or another anti-estrogen may be sufficient to control disease for at least a period of time. In most cases, however, the combination of radiotherapy and hormonal therapy is not enough to maintain disease control, and chemotherapy is needed.

Alternative therapies

Some patients with metastatic breast cancer opt to try alternative therapies, such as vitamin therapy, homeopathic treatments, macrobiotic diet, chiropractic, or acupuncture. There is no evidence that any of these therapies are effective, and they may be harmful, either because patients pass up effective conventional therapies such as chemotherapy or anti-estrogen therapy in favor of alternative treatments, or because the treatments themselves are harmful, as in the case of apricot pit therapy, which exposes the patient to cyanide, or in chiropractic, which can be dangerous to patients with cancer metastatic to the spinal bones or spinal cord. Also, the macrobiotic diet is neither effective nor safe, as it could hypothetically encourage weight loss, owing to the severe dietary restrictions. There is limited evidence acupuncture could relieve pain in cancer patients, but data so far is not sufficient to recommend its use outside of clinical trials. Also, there could be a risk of HIV, or hepatitis if needles are not sterilized.

Experimental therapies

Treatment of metastatic breast cancer is currently an active area of research. A very promising experimental therapy for breast cancer is Nexavar, a drug already approved for patients with metastatic renal cell carcinoma and hepatocellular carcinoma. In a study of more than 200 patients, those who received Nexavar and the chemotherapeutic agent Xeloda had longer time to progression than those who took Xeloda alone, the study said—with the median progression free survival time being 6.4 months in the Xeloda-and-Nexavar group compared to 4.1 months in the Xeloda-alone group.

Nanotherapies using nanoprobes

Recently, nanomedicine has become popular and there are several interesting developments involving the targeting of cancer cells using nanoprobes. Here are a few instances where nanoprobes are used to target specific tumor cells (based on the organ to which they have metastasized):

- Chlorotoxin, a chemical derived from the giant Israeli scorpion, binds to MMP-2 to cause endocytosis of the metalloprotease, thus reducing its activity. Chemically bonded iron oxide nanoparticles were coated with about 20 molecules of chlorotoxin and targeted to the brain metastatic cancer cells. It was found that nanoprobes reduced the brain metastatic tumors in mice by 98%.
- Nanotherapy using antibodies to herceptin coated on gold nanoparticles has showed results of slowing down the growth and invasion of aggressive breast tumors in mice. Such therapies targeted to specific cell types might be useful in the future to develop better treatments to prevent or treat metastasis in breast cancer.

Central nervous system metastases

Clinically symptomatic CNS metastases are reported to occur in 10-15% of patients with metastatic breast cancer, but in large autopsy studies, up to 40% of woman who died of metastatic breast cancer were reported to have at least one brain metastasis. CNS metastases are often viewed by patients and doctors alike as a late complication of metastatic breast cancer for which few effective treatments exist. In most cases, CNS involvement occurs after metastatic dissemination to the bones, liver, and/or lungs has already occurred, and for that reason, many patients already have refractory, terminal breast cancer by the time they are diagnosed with brain metastases. Diagnosis of brain metastases from breast cancer relies mainly on patient reported symptoms and neuroimaging. Symptoms of brain metastases from breast cancer are:

- new onset headache
- alterations in mental status, cognition, and behavior.
- ataxia
- cranial neuropathy, which can cause diplopia, and bells palsy
- vomiting and nausea
- deficits in sensation, motor function, and speech

Breast cancer involving the CNS is traditionally viewed as a late complication of progressive metastatic disease, for which few effective treatment options exist. For all brain metastatic patients, those with controlled extra-cranial tumor, age less than 65 years, and a favorable general performance (Karnofsky performance status ≥ 70) fare best whereas older patients with a Karnofsky performance status < 70 do poorly. However, effective treatments for brain metastases from breast cancer do exist, although symptomatic therapy alone may be chosen for those with poor performance status. Corticosteroids are crucial in the treatment of brain metastases from any origin-including

the breast, and are effective in reducing peri-tumoral edema and providing symptomatic relieve.

Chemotherapy has not been found to be effective in the treatment of brain metastases from breast cancer, due to the inability of most chemotherapeutic agents to penetrate the blood brain barrier. Whole brain radiation can provide a median survival of 4 to 5 months, which can be further extended by stereotactic radiosurgery months. Several nonrandomized studies have suggested that stereotactic radiosurgery may provide nearly equivalent outcomes compared to surgery followed by whole brain irradiation. Surgery tends to reduce symptoms quickly and prolong life significantly, with persistent increases in quality of life. Multiple metastases (up to three) can be removed surgically with a risk similar to that of a single lesion, providing similar benefits. At present, adjuvant radiotherapy follows surgical resection because this combined approach has been shown in general to prolong median survival significantly, to 12 months depending on the factors noted above. There is also a growing body of evidence that surgery may be useful in select patients with recurrent brain metastases. Mean survival from diagnosis of a brain metastasis varies between studies but ranges from 2 to 16 months, depending on involvement of the CNS, the extent of the extra-cranial metastatic disease, and the treatment applied. The mean 1-year survival is estimated at 20%. Improvements in the treatment of brain metastases are clearly needed.

Chapter 4

Male Breast Cancer

Male breast cancer

ICD-10	C50.
ICD-9	175,175.0,175.9,
OMIM	114480
MedlinePlus	000913
eMedicine	radio/115
MeSH	D001943

Male breast cancer is a relatively rare cancer in men that originates from the breast. As it presents a similar pathology as female breast cancer, assessment and treatment relies on experiences and guidelines that have been developed in female patients. The optimal treatment is currently not known.

Incidence

About one percent of breast cancer develops in males. It is estimated that about 1,910 new cases are diagnosed annually in the US and about 300 in the UK, and the number of annual deaths is about 440 in the US. In a study from India, eight out of 1,200 (0.7%) male cancer diagnoses in a pathology review represented breast cancer. The incidence of breast cancer in men has been increasing. The tumor can occur over a wide age range, but typically appears in men in their sixties and seventies. Known risk factors include radiation exposure, exposure to female hormones (estrogen), and genetic factors. High estrogen exposure may occur by medications, obesity, or liver disease, and genetic links include a high prevalence of female breast cancer in close relatives. Chronic alcoholism has been linked to male breast cancer. The highest risk for male breast cancer is carried by men with Klinefelter syndrome. Male BRCA mutation carriers are thought to be at higher risk for breast cancer.

Pathology

As in females, infiltrating ductal carcinoma is the most common type. While intraductal cancer, inflammatory carcinoma, and Paget's disease of the nipple have been described, lobular carcinoma in situ has not been seen in men. Breast cancer in men spreads via lymphatics and blood stream like female breast cancer. Accordingly, the TNM staging system for breast cancer is the same for men and women.

Size of the lesion and lymph node involvement determine prognosis; thus small lesions without lymph node involvement have the best prognosis. Estrogen receptor and progesterone receptor status and HER2/neu gene amplification need to be reported as they may affect treatment options. About 85% of all male breast cancers are estrogen receptor–positive, and 70% are progesterone receptor–positive.

Diagnosis

Typically self-examination leads to the detection of a lump in the breast which requires further investigation. Other less common symptoms include nipple discharge, nipple retraction, swelling of the breast, or a skin lesion such as an ulcer. Ultrasound and mammography may be used for its further definition. The lump can be examined either by a needle biopsy where a thin needle is placed into the lump to extract some tissue or by an excisional biopsy where under local anesthesia a small skin cut is made and the lump is removed. Not all palpable lesions in the male breast are cancerous, for instance a biopsy may reveal a benign fibroadenoma. In a larger study from Finland the average size of a male breast cancer lesion was 1.8 cm. Beside the histologic examination estrogen and progesterone receptor studies are performed. Further, the HER2 test is used to check for a growth factor protein. Its activity can be increased in active cancer cells and helps determine if monoclonal antibody therapy (i.e. Trastuzumab) may be useful.

Male breast cancer can recur locally after therapy, or can become metastatic.

Staging

In addition to TNM staging surgical staging for breast cancer is used; it is the same as in female breast cancer and facilitates treatment and analysis.

- Stage I refers to invasive breast cancer with the tumor not exceeding 2 cm and absence of lymph node involvement.
- Stage II describes to invasive breast cancer when the tumor is either 2 cm or less and the local armpit (axillary) lymph nodes are involved (Stage IIA), or the tumor is 2–5 cm in size with local lymph node involvement (Stage IIB), or greater than 5 cm without lymph node involvement (Stage IIB).
- Stage III is divided into three subcategories:
 - In IIIA there is breast cancer with axillary lymph nodes clumped together or attached to other structures.

- In IIIB the tumor has spread to the chestwall or skin, and may have involved lymph nodes of the axilla and/or breastbone.
- In IIIC the tumor has spread to the chest wall or skin and lymph nodes below or above the collar bone are affected.
- Stage IV is applied to metastatic breast cancer; typically lungs, liver, bone, or brain are involved.

Differences to female breast cancer

There are significant differences between male and female breast cancer. Lesions are easier to find in men due to the smaller breast size, however, lack of awareness may postpone seeking medical attention. The presence of gynecomastia may mask the condition. The diagnosis is made later in men—at age 67 on average—than in women with their average at 63. Lesions are less contained in men as they do not have to travel far to infiltrate skin, nipple, or muscle tissue. Thus, lesions in men tend to be more advanced. Indeed, almost half of male breast cancer patients are stage III or IV. In familial cases, male BRCA2 carriers are at risk, rather than BRCA1 carriers. With the relative infrequency of male breast cancer, randomized studies are lacking.

Treatment

Treatment largely follows patterns that have been set for the management of postmenopausal breast cancer. The initial treatment is surgical and consists of a modified radical mastectomy with axillary dissection or lumpectomy and radiation therapy with similar treatment results as in women. Also, mastectomy with sentinel lymph node biopsy is a treatment option. In men with node-negative tumors, adjuvant therapy is applied under the same considerations as in women with node-negative breast cancer. Similarly, with node-positive tumors, men increase survival using the same adjuvants as affected women, namely both chemotherapy plus tamoxifen and other hormonal therapy. There are no controlled studies in men comparing adjuvant options. In the vast majority of men with breast cancer hormone receptor studies are positive, and those situations are typically treated with hormonal therapy.

Locally recurrent disease is treated with surgical excision or radiation therapy combined with chemotherapy. Distant metastases are treated with hormonal therapy, chemotherapy, or a combination of both. Bones can be affected either by metastasis or weakened from hormonal therapy; bisphosphonates may be used to counterbalance this process and strengthen bones.

Chemotherapeutic and hormonal options in male breast cancer

Chemotherapeutic options include:

- cyclophosphamide plus methotrexate plus fluorouracil (CMF).
- cyclophosphamide plus doxorubicin plus fluorouracil (CAF).
- Trastuzumab (monoclonal antibody therapy).

Hormonal options include:

- Orchiectomy.
- Gonadotropin hormone releasing hormone agonist (GNRH agonist) with or without total androgen blockage (anti-androgen).
- Tamoxifen for estrogen receptor–positive patients.
- Progesterone.
- Aromatase inhibitors.

Prognosis

Adjusted for age and stage the prognosis for breast cancer in men is similar to that in women. Prognostically favorable are smaller tumor size and absence or paucity of local lymph node involvement. Hormonal treatment may be associated with hot flashes and impotence.

Chapter 5

Lung cancer

Lung Cancer



Cross section of a human lung. The white area in the upper lobe is cancer; the black areas are discoloration due to smoking.

ICD-10	C33.-C34.
ICD-9	162
DiseasesDB	7616
MedlinePlus	007194
eMedicine	med/1333 med/1336 emerg/335 radio/807 radio/405 radio/406
MeSH	D002283

Lung cancer is a disease which consists of uncontrolled cell growth in tissues of the lung. This growth may lead to metastasis, which is the invasion of adjacent tissue and infiltration beyond the lungs. The vast majority of primary lung cancers are carcinomas, derived from epithelial cells. Lung cancer, the most common cause of cancer-related death in men and women, is responsible for 1.3 million deaths worldwide annually, as of 2004. The most common symptoms are shortness of breath, coughing (including coughing up blood), and weight loss.

The main types of lung cancer are *small-cell lung carcinoma* and *non-small-cell lung carcinoma*. This distinction is important, because the treatment varies; non-small-cell lung carcinoma (NSCLC) is sometimes treated with surgery, while small-cell lung carcinoma (SCLC) usually responds better to chemotherapy and radiation. The most common cause of lung cancer is long-term exposure to tobacco smoke. The occurrence of lung cancer in nonsmokers, who account for as many as 15% of cases, is often attributed to a combination of genetic factors, radon gas, asbestos, and air pollution including secondhand smoke.

Lung cancer may be seen on chest radiograph and computed tomography (CT scan). The diagnosis is confirmed with a biopsy. This is usually performed by bronchoscopy or CT-guided biopsy. Treatment and prognosis depend upon the histological type of cancer, the stage (degree of spread), and the patient's performance status. Possible treatments include surgery, chemotherapy, and radiotherapy. Survival varies, depending on stage, overall health, and other factors, but the overall five-year survival rate for all persons diagnosed with lung cancer is 14%.

Signs and symptoms

Symptoms that suggest lung cancer include:

- dyspnea (shortness of breath)
- hemoptysis (coughing up blood)
- chronic coughing or change in regular coughing pattern
- wheezing
- chest pain or pain in the abdomen
- cachexia (weight loss), fatigue, and loss of appetite
- dysphonia (hoarse voice)
- clubbing of the fingernails (uncommon)
- dysphagia (difficulty swallowing).

If the cancer grows in the airway, it may obstruct airflow, causing breathing difficulties. The obstruction can lead to accumulation of secretions behind the blockage, and predispose to pneumonia. Many lung cancers have a rich blood supply. The surface of the cancer may be fragile, leading to bleeding from the cancer into the airway. This blood may subsequently be coughed up.

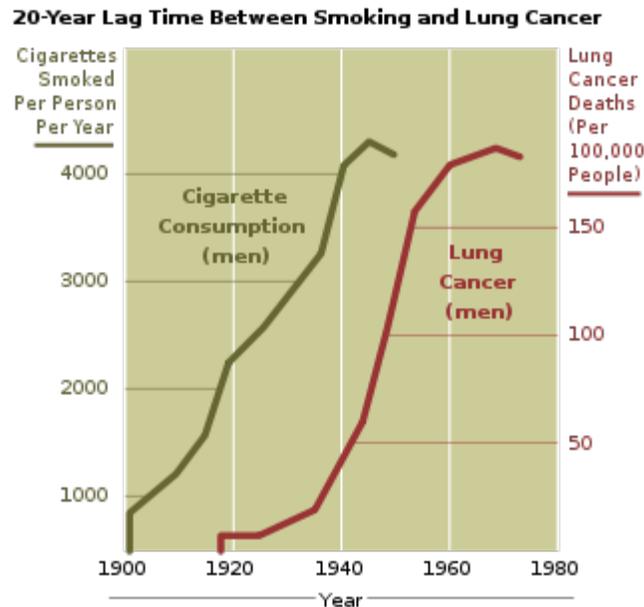
Depending on the type of tumor, so-called paraneoplastic phenomena may initially attract attention to the disease. In lung cancer, these phenomena may include Lambert-Eaton myasthenic syndrome (muscle weakness due to auto-antibodies), hypercalcemia, or syndrome of inappropriate antidiuretic hormone (SIADH). Tumors in the top (apex) of the lung, known as Pancoast tumors, may invade the local part of the sympathetic nervous system, leading to changed sweating patterns and eye muscle problems (a combination known as Horner's syndrome) as well as muscle weakness in the hands due to invasion of the brachial plexus.

Many of the symptoms of lung cancer (bone pain, fever, and weight loss) are nonspecific; in the elderly, these may be attributed to comorbid illness. In many patients, the cancer has already spread beyond the original site by the time they have symptoms and seek medical attention. Common sites of metastasis include the brain, bone, adrenal glands, contralateral (opposite) lung, liver, pericardium, and kidneys. About 10% of people with lung cancer do not have symptoms at diagnosis; these cancers are incidentally found on routine chest radiograph.

Causes

The main causes of any cancer include carcinogens (such as those in tobacco smoke), ionizing radiation, and viral infection. This exposure causes cumulative changes to the DNA in the tissue lining the bronchi of the lungs (the bronchial epithelium). As more tissue becomes damaged, eventually a cancer develops.

Smoking



NIH graph showing the correlation and time-lag between tobacco smoking and lung cancer rate in the U.S. male population.

Smoking, particularly of cigarettes, is by far the main contributor to lung cancer. Cigarette smoke contains over 60 known carcinogens, including radioisotopes from the radon decay sequence, nitrosamine, and benzopyrene. Additionally, nicotine appears to depress the immune response to malignant growths in exposed tissue. Across the developed world, almost 90% of lung cancer deaths are caused by smoking. In the United States, smoking is estimated to account for 87% of lung cancer cases (90% in men and 85% in women). Among male smokers, the lifetime risk of developing lung cancer is 17.2%; among female smokers, the risk is 11.6%. This risk is significantly lower in nonsmokers: 1.3% in men and 1.4% in women.

Women who smoke (former smokers and current smokers) and take hormone therapy are at a much higher risk of dying of lung cancer. In a study by Chlebowski *et al.* published in 2009, the women taking hormones were about 60% more likely to die of lung cancer than the women taking a placebo. Not surprisingly, the risk was highest for current smokers, followed by past smokers, and lowest for never smokers. Among the women who smoked (former or current smokers), 3.4% of those taking hormone therapy died of lung cancer compared to 2.3% for women taking the placebo.

The time a person smokes (as well as rate of smoking) increases the person's chance of developing lung cancer. If a person stops smoking, this chance steadily decreases as damage to the lungs is repaired and contaminant particles are gradually removed. In addition, there is evidence that lung cancer in never-smokers has a better prognosis than in smokers, and that patients who smoke at the time of diagnosis have shorter survival times than those who have quit.

Passive smoking—the inhalation of smoke from another's smoking—is a cause of lung cancer in nonsmokers. A passive smoker can be classified as someone living or working with a smoker. Studies from the U.S., Europe, the UK, and Australia have consistently shown a significant increase in relative risk among those exposed to passive smoke. Recent investigation of sidestream smoke suggests that it is more dangerous than direct smoke inhalation.

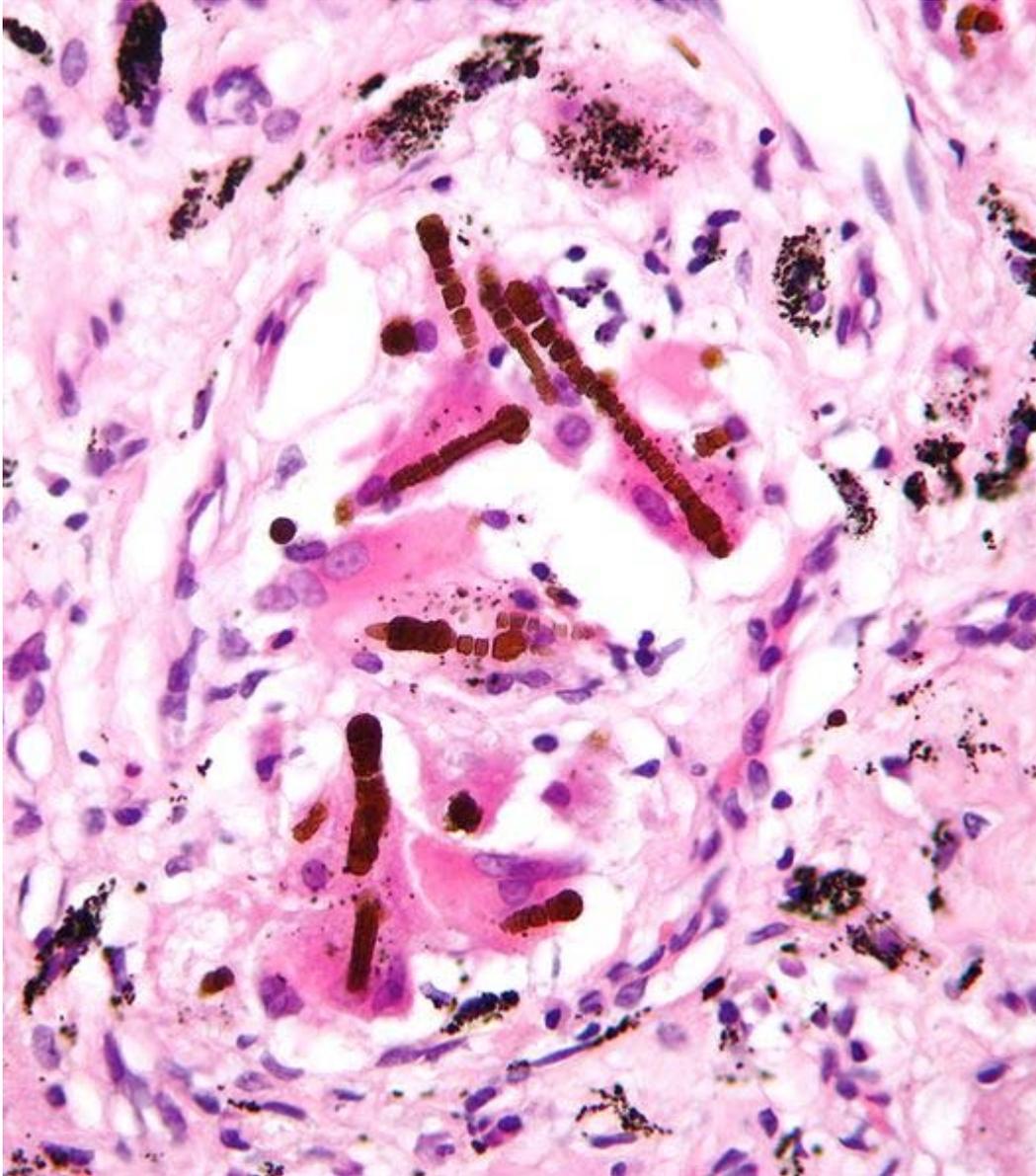
10–15% of lung cancer patients have never smoked. That means between 20,000 to 30,000 never-smokers are diagnosed with lung cancer in the United States each year. Because of the five-year survival rate, each year in the U.S. more never-smokers die of lung cancer than do patients of leukemia, ovarian cancer, or AIDS.

Radon gas

Radon is a colorless and odorless gas generated by the breakdown of radioactive radium, which in turn is the decay product of uranium, found in the Earth's crust. The radiation decay products ionize genetic material, causing mutations that sometimes turn cancerous. Radon exposure is the second major cause of lung cancer in the general population, after smoking with the risk increasing by 8% to 16% for every 100 Bq/m³ increase in the radon concentration. Radon gas levels vary by locality and the composition of the underlying soil and rocks. For example, in areas such as Cornwall in the UK (which has

granite as substrata), radon gas is a major problem, and buildings have to be force-ventilated with fans to lower radon gas concentrations. The United States Environmental Protection Agency (EPA) estimates that one in 15 homes in the U.S. has radon levels above the recommended guideline of 4 picocuries per liter (pCi/L) (148 Bq/m³). Iowa has the highest average radon concentration in the United States; studies performed there have demonstrated a 50% increased lung cancer risk, with prolonged radon exposure above the EPA's action level of 4 pCi/L.

Asbestos



Ferruginous bodies the histopathologic finding associated with asbestosis

Asbestos can cause a variety of lung diseases, including lung cancer. There is a synergistic effect between tobacco smoking and asbestos in the formation of lung cancer. In the UK, asbestos accounts for 2–3% of male lung cancer deaths. Asbestos can also cause cancer of the pleura, called mesothelioma (which is different from lung cancer).

Viruses

Viruses are known to cause lung cancer in animals, and recent evidence suggests similar potential in humans. Implicated viruses include human papillomavirus, JC virus, simian virus 40 (SV40), BK virus, and cytomegalovirus. These viruses may affect the cell cycle and inhibit apoptosis, allowing uncontrolled cell division.

Particulate matter

Studies of the American Cancer Society cohort directly link the exposure to particulate matter with lung cancer. For example, if the concentration of particles in the air increases by only 1%, the risk of developing a lung cancer increases by 14%. Further, it has been established that particle size matters, as ultrafine particles penetrate further into the lungs.

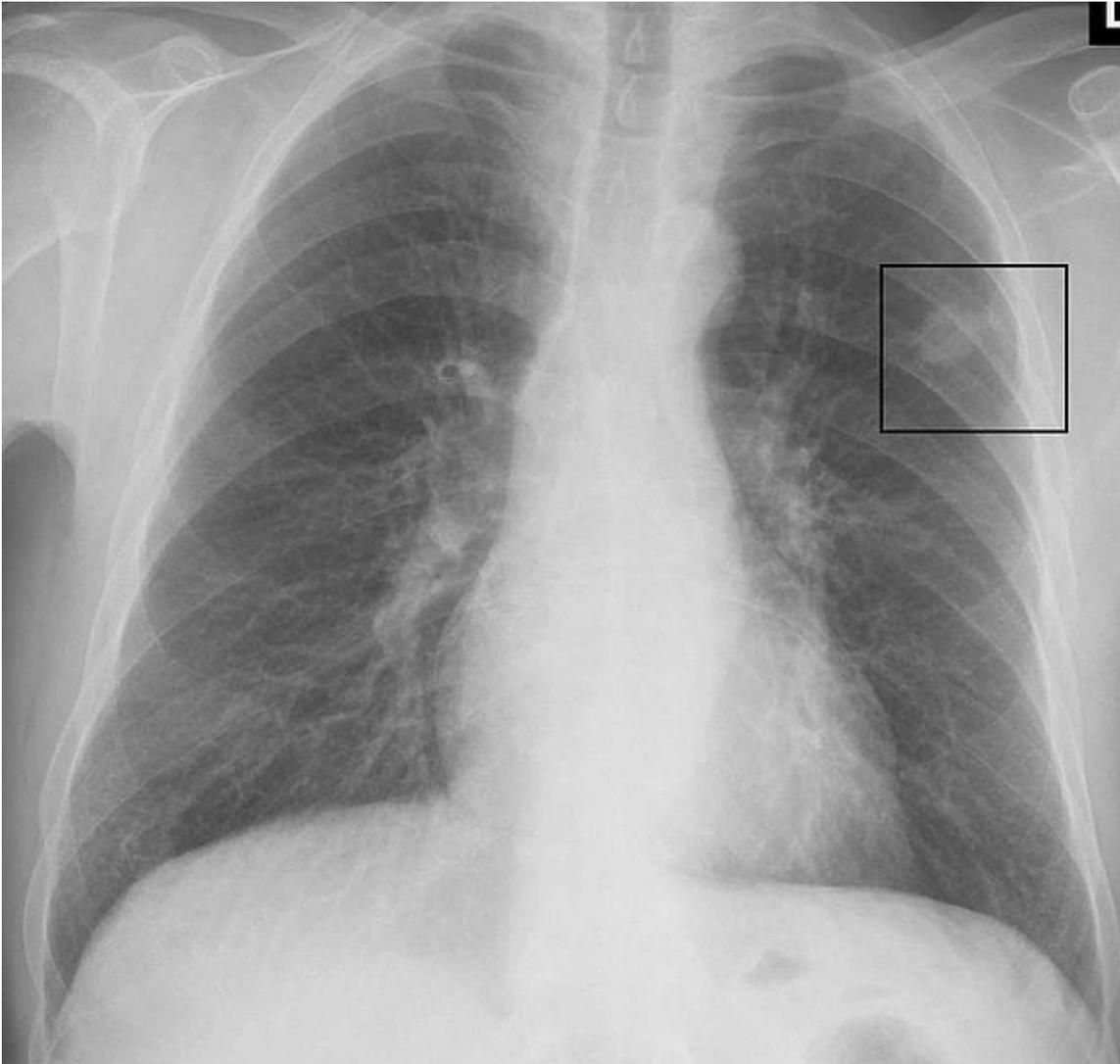
Pathogenesis

Similar to many other cancers, lung cancer is initiated by activation of oncogenes or inactivation of tumor suppressor genes. Oncogenes are genes that are believed to make people more susceptible to cancer. Proto-oncogenes are believed to turn into oncogenes when exposed to particular carcinogens. Mutations in the *K-ras* proto-oncogene are responsible for 10–30% of lung adenocarcinomas. The epidermal growth factor receptor (EGFR) regulates cell proliferation, apoptosis, angiogenesis, and tumor invasion. Mutations and amplification of EGFR are common in non-small-cell lung cancer and provide the basis for treatment with EGFR-inhibitors. Her2/neu is affected less frequently. Chromosomal damage can lead to loss of heterozygosity. This can cause inactivation of tumor suppressor genes. Damage to chromosomes 3p, 5q, 13q, and 17p are particularly common in small-cell lung carcinoma. The *p53* tumor suppressor gene, located on chromosome 17p, is affected in 60-75% of cases. Other genes that are often mutated or amplified are *c-MET*, *NKX2-1*, *LKB1*, *PIK3CA*, and *BRAF*.

Several genetic polymorphisms are associated with lung cancer. These include polymorphisms in genes coding for interleukin-1, cytochrome P450, apoptosis promoters such as caspase-8, and DNA repair molecules such as XRCC1. People with these polymorphisms are more likely to develop lung cancer after exposure to carcinogens.

A recent study suggested that the MDM2 309G allele is a low-penetrant risk factor for developing lung cancer in Asians.

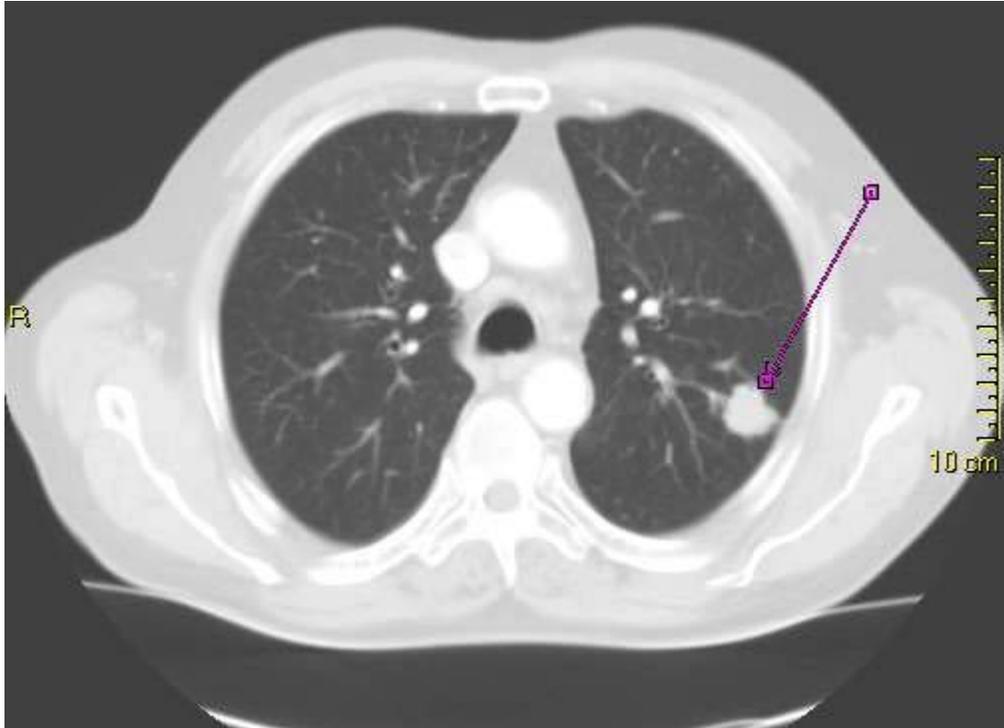
Diagnosis



Chest radiograph showing a cancerous tumor in the left lung

Performing a chest radiograph is the first step if a patient reports symptoms that may suggest lung cancer. This may reveal an obvious mass, widening of the mediastinum (suggestive of spread to lymph nodes there), atelectasis (collapse), consolidation (pneumonia), or pleural effusion. If there are no radiographic findings but the suspicion is high (such as a heavy smoker with blood-stained sputum), bronchoscopy and/or a CT scan may provide the necessary information. Bronchoscopy or CT-guided biopsy is often used to identify the tumor type.

Abnormal findings in cells ("atypia") in sputum are associated with an increased risk of lung cancer. Sputum cytologic examination combined with other screening examinations may have a role in the early detection of lung cancer.



CT scan showing a cancerous tumor in the left lung

The differential diagnosis for patients who present with abnormalities on chest radiograph includes lung cancer as well as nonmalignant diseases. These include infectious causes such as tuberculosis or pneumonia, or inflammatory conditions such as sarcoidosis. These diseases can result in mediastinal lymphadenopathy or lung nodules, and sometimes mimic lung cancers. Lung cancer can also be an incidental finding: a solitary pulmonary nodule (also called a coin lesion) on a chest radiograph or CT scan taken for an unrelated reason. The definitive diagnosis of lung cancer and its classification (described above) is based on examination of the suspicious tissue under the microscope.

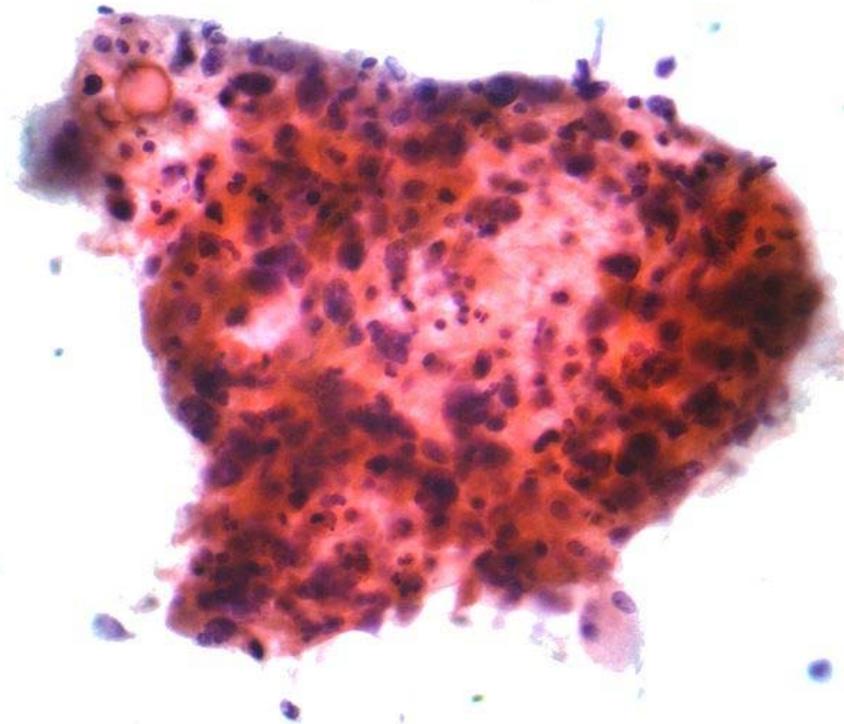
Classification

Lung cancers are classified according to histological type. This classification has important implications for clinical management and prognosis of the disease. The vast majority of lung cancers are carcinomas—malignancies that arise from epithelial cells. The two most prevalent histological types of lung carcinoma, categorized by the size and appearance of the malignant cells seen by a histopathologist under a microscope: *non-small-cell* and *small-cell* lung carcinoma. The non-small-cell type is the most prevalent by far.

Frequency of histological types of lung cancer	
Histological type	Frequency (%)
Non-small-cell lung carcinoma	80.4
Small-cell lung carcinoma	16.8
Carcinoid	0.8
Sarcoma	0.1
Unspecified lung cancer	1.9

Cancer found outside of the lung may be determined to have arisen within the lung, as lung cancers that metastasize, i.e. spread, often retain a cell marker profile that allow a pathologist to say, with a good deal of certainty, that the tumor arose from the lung, i.e. is a *primary lung cancer*. Primary lung cancers of adenocarcinoma histology typically have nuclear immunostaining with TTF-1.

Non-small-cell lung carcinoma



Micrograph of squamous carcinoma, a type of non-small-cell carcinoma. FNA specimen. Pap stain.

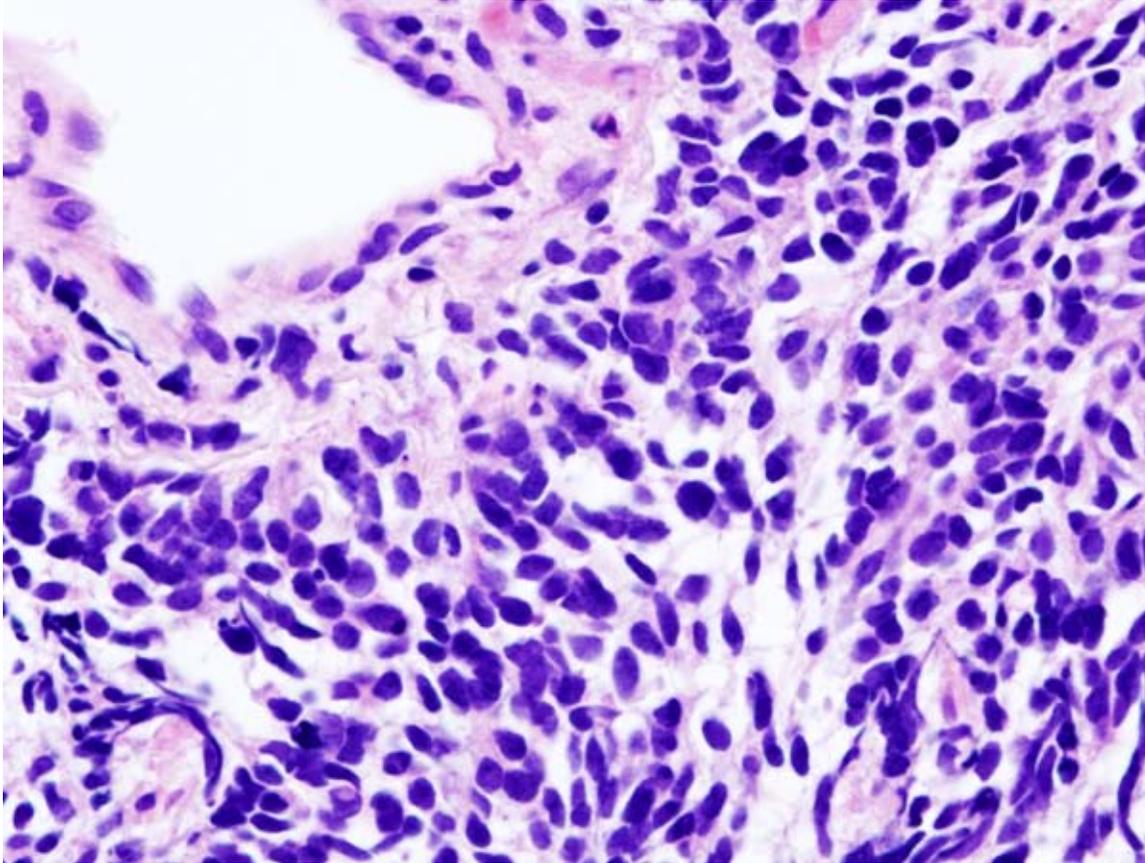
The non-small-cell lung carcinomas (NSCLC) are grouped together because their prognosis and management are similar. There are three main sub-types: squamous cell lung carcinoma, adenocarcinoma, and large-cell lung carcinoma.

Sub-types of non-small-cell lung cancer in smokers and never-smokers		
Histological sub-type	Frequency of non-small-cell lung cancers (%)	
	Smokers	Never-smokers
Squamous cell lung carcinoma	42	33
Adenocarcinoma (not otherwise specified)	39	35
Adenocarcinoma Bronchioloalveolar carcinoma	4	10
Carcinoid	7	16
Other	8	6

Accounting for 25% of lung cancers, squamous cell lung carcinoma usually starts near a central bronchus. A hollow cavity and associated necrosis are commonly found at the center of the tumor. Well-differentiated squamous cell lung cancers often grow more slowly than other cancer types.

Adenocarcinoma accounts for 40% of non-small-cell lung cancers. It usually originates in peripheral lung tissue. Most cases of adenocarcinoma are associated with smoking; however, among people who have never smoked ("never-smokers"), adenocarcinoma is the most common form of lung cancer. A subtype of adenocarcinoma, the bronchioloalveolar carcinoma, is more common in female never-smokers, and may have different responses to treatment.

Small-cell lung carcinoma



Small-cell lung carcinoma (microscopic view of a core needle biopsy)

Small-cell lung carcinoma (SCLC) is less common. It was formerly referred to as "oat-cell" carcinoma. Most cases arise in the larger airways (primary and secondary bronchi) and grow rapidly, becoming quite large. The small cells contain dense neurosecretory granules (vesicles containing neuroendocrine hormones), which give this tumor an endocrine/paraneoplastic syndrome association. While initially more sensitive to chemotherapy and radiation, it is often metastatic at presentation, and ultimately carries a worse prognosis. Small-cell lung cancers have long been dichotomously staged into limited and extensive stage disease. This type of lung cancer is strongly associated with smoking.

Others

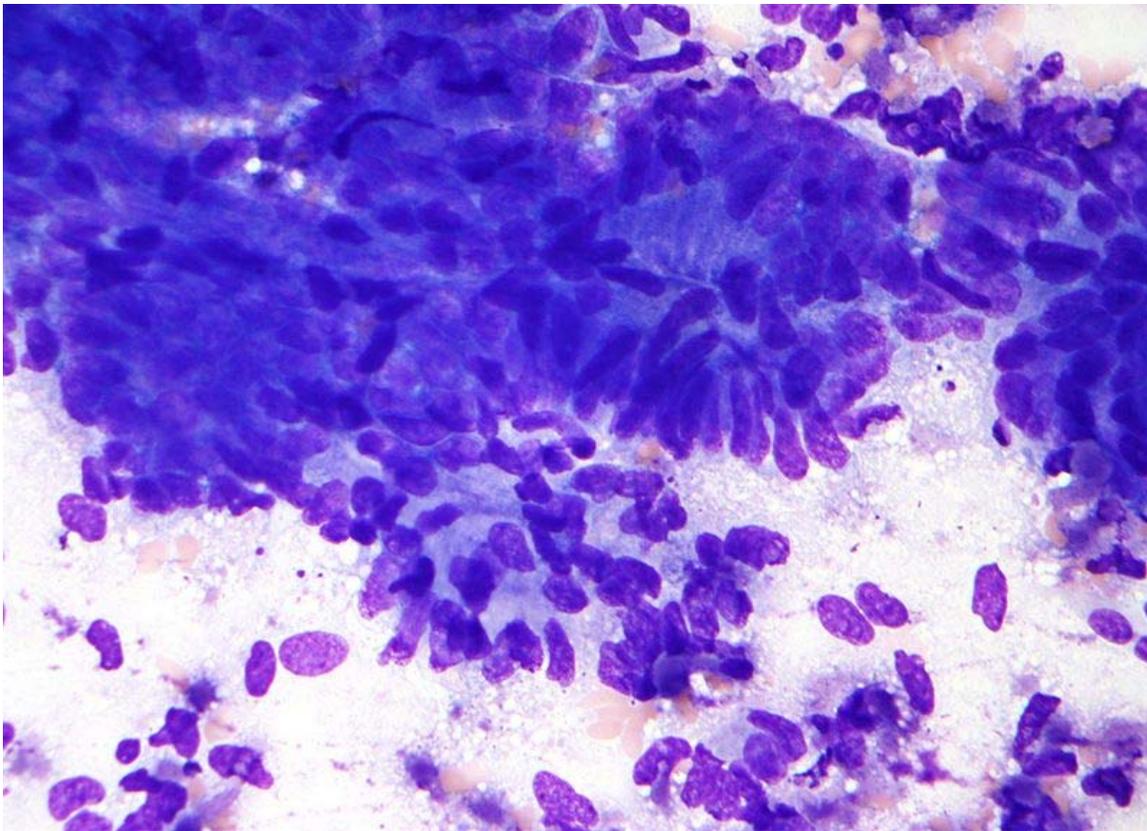
Lung cancers are highly heterogeneous malignancies, with tumors containing more than one subtype being very common.

Currently, the most widely recognized and utilized lung cancer classification system is the 4th revision of the Histological Typing of Lung and Pleural Tumours, published in 2004 as a cooperative effort by the World Health Organization and the International

Association for the Study of Lung Cancer. It recognizes numerous other distinct histopathological entities of non-small-cell lung carcinoma, organized into several additional subtypes, including sarcomatoid carcinoma, salivary gland tumors, carcinoid tumor, and adenosquamous carcinoma. The latter subtype includes tumors containing at least 10% each of adenocarcinoma and squamous cell carcinoma. When a tumor is found to contain a mixture of both small-cell carcinoma and non-small-cell carcinoma, it is classified as a variant of small-cell carcinoma and called a combined small-cell carcinoma. Combined small-cell carcinoma is the only currently recognized variant of small-cell carcinoma.

In infants and children, the most common primary lung cancers are pleuropulmonary blastoma and carcinoid tumor.

Metastasis



Micrograph of a lung lymph node biopsy showing metastatic colorectal adenocarcinoma. Field stain.

The lung is a common place for metastasis of tumors from other parts of the body. Secondary cancers are classified by the site of origin; e.g., breast cancer that has spread to the lung is called *breast cancer*. Metastases often have a characteristic round appearance on chest radiograph. Solitary round lung nodules are not infrequently of an uncertain etiology and may prompt a lung biopsy.

In children, the majority of lung cancers are secondary.

Primary lung cancers themselves most commonly metastasize to the adrenal glands, liver, brain, and bone.

Staging

Lung cancer staging is an assessment of the degree of spread of the cancer from its original source. It is an important factor affecting the prognosis and potential treatment of lung cancer. Non-small-cell lung carcinoma is staged from IA ("one A"; best prognosis) to IV ("four"; worst prognosis). Small-cell lung carcinoma is classified as *limited stage* if it is confined to one half of the chest and within the scope of a single radiotherapy field; otherwise, it is *extensive stage*.

Prevention

Prevention is the most cost-effective means of fighting lung cancer. While in most countries industrial and domestic carcinogens have been identified and banned, tobacco smoking is still widespread. Eliminating tobacco smoking is a primary goal in the prevention of lung cancer, and smoking cessation is an important preventive tool in this process. Of utmost importance are prevention programs that target the young. In 1998 the Master Settlement Agreement entitled 46 states in the USA to an annual payout from the tobacco companies. Between the settlement money and tobacco taxes, each state's public health department funds their prevention programs, although none of the states are living up to the Center for Disease Control's recommended amount by spending 15 percent of tobacco taxes and settlement revenues on these prevention efforts.

Policy interventions to decrease passive smoking in public areas such as restaurants and workplaces have become more common in many Western countries, with California taking a lead in banning smoking in public establishments in 1998. Ireland played a similar role in Europe in 2004, followed by Italy and Norway in 2005, Scotland as well as several others in 2006, England in 2007, France in 2008 and Turkey in 2009. New Zealand has banned smoking in public places as of 2004. The state of Bhutan has had a complete smoking ban since 2005. In many countries, pressure groups are campaigning for similar bans. In 2007, Chandigarh became the first city in India to become smoke-free. India introduced a total ban on smoking at public places on Oct 2 2008.

Arguments cited against such bans are criminalisation of smoking, increased risk of smuggling, and the risk that such a ban cannot be enforced.

The long-term use of supplemental multivitamins—such as vitamin C, vitamin E, and folate—does not reduce the risk of lung cancer. Indeed long-term intake of high doses of vitamin E supplements may even increase the risk of lung cancer.

The World Health Organization has called for governments to institute a total ban on tobacco advertising to prevent young people from taking up smoking. They assess that such bans have reduced tobacco consumption by 16% where already instituted.

Screening

Screening refers to the use of medical tests to detect disease in asymptomatic people. Possible screening tests for lung cancer include chest radiograph or computed tomography (CT). As of December 2009, screening programs for lung cancer have not demonstrated any benefit.

Treatment

Treatment for lung cancer depends on the cancer's specific cell type, how far it has spread, and the patient's performance status. Common treatments include palliative care, surgery, chemotherapy, and radiation therapy.

Surgery



Pneumonectomy specimen containing a squamous cell carcinoma, seen as a white area near the bronchi.

If investigations confirm lung cancer, CT scan and often positron emission tomography (PET) are used to determine whether the disease is localized and amenable to surgery or whether it has spread to the point where it cannot be cured surgically.

Blood tests and spirometry (lung function testing) are also necessary to assess whether the patient is well enough to be operated on. If spirometry reveals poor respiratory reserve (often due to chronic obstructive pulmonary disease), surgery may be contraindicated.

Surgery for lung cancer has an operative death rate of about 4.4%, depending on the patient's lung function and other risk factors. In non-small-cell lung carcinoma, surgery is usually only an option if the cancer is limited to one lung, up to stage IIIA. This is assessed with medical imaging (computed tomography, positron emission tomography). A sufficient preoperative respiratory reserve must be present to allow adequate lung function after the tissue is removed.

Procedures include wedge resection (removal of part of a lobe), segmentectomy (removal of an anatomic division of a particular lobe of the lung), lobectomy (one lobe), bilobectomy (two lobes), or pneumonectomy (whole lung). In patients with adequate respiratory reserve, lobectomy is the preferred option, as this minimizes the chance of local recurrence. If the patient does not have enough functional lung for this, wedge resection may be performed. Radioactive iodine brachytherapy at the margins of wedge excision may reduce recurrence to that of lobectomy.

Video-assisted thoracoscopic surgery and VATS lobectomy have allowed for minimally invasive approaches to lung cancer surgery that may have the advantages of quicker recovery, shorter hospital stay and diminished hospital costs.

Early studies suggested that small-cell lung carcinoma (SCLC) fared better when treated with chemotherapy and/or radiation than when treated surgically. While this approach to treating SCLC remains the current standard of care, the role of surgery in SCLC is being reconsidered, recent reviews indicating that surgery might improve outcomes when added to chemotherapy and radiation in early stage SCLC and combined forms of SCLC and NSCLC.

Radiotherapy

Radiotherapy is often given together with chemotherapy, and may be used with curative intent in patients with non-small-cell lung carcinoma who are not eligible for surgery. This form of high intensity radiotherapy is called *radical radiotherapy*. A refinement of this technique is continuous hyperfractionated accelerated radiotherapy (CHART), in which a high dose of radiotherapy is given in a short time period. For small-cell lung carcinoma cases that are potentially curable, chest radiation is often recommended in addition to chemotherapy. The use of adjuvant thoracic radiotherapy following curative intent surgery for non-small-cell lung carcinoma is not well established and is

controversial. Benefits, if any, may only be limited to those in whom the tumor has spread to the mediastinal lymph nodes.

For both non-small-cell lung carcinoma and small-cell lung carcinoma patients, smaller doses of radiation to the chest may be used for symptom control (palliative radiotherapy). Unlike other treatments, it is possible to deliver palliative radiotherapy without confirming the histological diagnosis of lung cancer.

Brachytherapy (localized radiotherapy) may be given directly inside the airway when cancer affects a short section of bronchus. It is used when inoperable lung cancer causes blockage of a large airway.

Patients with limited-stage small-cell lung carcinoma are usually given prophylactic cranial irradiation (PCI). This is a type of radiotherapy to the brain, used to reduce the risk of metastasis. More recently, PCI has also been shown to be beneficial in those with extensive small-cell lung cancer. In patients whose cancer has improved following a course of chemotherapy, PCI has been shown to reduce the cumulative risk of brain metastases within one year from 40.4% to 14.6%.

Recent improvements in targeting and imaging have led to the development of extracranial stereotactic radiation in the treatment of early-stage lung cancer. In this form of radiation therapy, very high doses are delivered in a small number of sessions using stereotactic targeting techniques. Its use is primarily in patients who are not surgical candidates due to medical comorbidities.

Chemotherapy

The chemotherapy regimen depends on the tumor type.

Small-cell lung carcinoma

Even if relatively early stage, small-cell lung carcinoma is treated primarily with chemotherapy and radiation. In small-cell lung carcinoma, cisplatin and etoposide are most commonly used. Combinations with carboplatin, gemcitabine, paclitaxel, vinorelbine, topotecan, and irinotecan are also used. Celecoxib showed a potential signal of response in a small study.

Non-small-cell lung carcinoma

Primary chemotherapy is also given in advanced and metastatic non-small-cell lung carcinoma.

Testing for the molecular genetic subtype of non-small-cell lung cancer may be of assistance in selecting the most appropriate initial therapy. For example, mutation of the epidermal growth factor receptor gene may predict whether initial treatment with a specific inhibitor or with chemotherapy is more advantageous.

Advanced non-small-cell lung carcinoma is often treated with cisplatin or carboplatin, in combination with gemcitabine, paclitaxel, docetaxel, etoposide, or vinorelbine. Bevacizumab improves results in non-squamous cancers treated with paclitaxel and carboplatin in patients less than 70 years old who have reasonable general performance status.

Pemetrexed has been studied extensively in non-small-cell lung cancer, with numerous studies since 1995. For adenocarcinoma and large-cell lung cancer, cisplatin with pemetrexed was more beneficial than cisplatin and gemcitabine; squamous cancer had the opposite results. As a consequence, subtyping of non-small lung cancer histology has become more important.

Bronchoalveolar carcinoma is a subtype of non-small-cell lung carcinoma that may respond to gefitinib and erlotinib.

Maintenance therapy

In advanced non-small-cell lung cancer there are several approaches for continuing treatment after an initial response to therapy. Switch maintenance changes to different medications than the initial therapy and can use pemetrexed, erlotinib, and docetaxel, although pemetrexed is only used in non-squamous NSCLC.

Adjuvant chemotherapy

Adjuvant chemotherapy refers to the use of chemotherapy after apparently curative surgery to improve the outcome. In non-small-cell lung cancer, samples are taken during surgery of nearby lymph nodes. If these samples contain cancer, the patient has stage II or III disease. In this situation, adjuvant chemotherapy may improve survival by up to 15%. Standard practice has often been to offer platinum-based chemotherapy (including either cisplatin or carboplatin). However, the benefit of platinum-based adjuvant chemotherapy was confined to patients who had tumors with low ERCC1 (excision repair cross-complementing 1) activity.

Adjuvant chemotherapy for patients with stage IB cancer is controversial, as clinical trials have not clearly demonstrated a survival benefit. Trials of preoperative chemotherapy (neoadjuvant chemotherapy) in resectable non-small-cell lung carcinoma have been inconclusive.

Interventional radiology

Radiofrequency ablation should currently be considered an investigational technique in the treatment of bronchogenic carcinoma. It is done by inserting a small heat probe into the tumor to kill the tumor cells.

Palliative care

In metastatic non–small-cell lung cancer the addition of palliative care to standard treatments improved the quality of life, lessened depression, lengthened life by 3 months, and decreased the use of aggressive care at the end of life.

Other studies in advanced cancer also found benefit from palliative care, or found hospice involvement to be beneficial. These approaches allow additional discussion of treatment options and provide opportunities to arrive at well-considered decisions and may avoid unhelpful but expensive care at the end of life.

However, palliative care may often be more appropriate in conjunction with chemotherapy at some point in the treatment of the cancer, rather than on its own. Over the past 20 years, the opposite question has also been asked: does chemotherapy add to supportive care? Superior survival has been repeatedly found in advanced non-small-cell lung cancer when study eligible recipients receive appropriate chemotherapy rather than supportive care alone. For example, 1994 recommendations based on reports that combined the results of several available studies found an increase in average survival from 3.9 months for best supportive care alone to 6.7 months with the addition of chemotherapy, as well as an improved quality of life. A systematic review from Sweden in 2001 looked at numerous chemotherapy reports over many years in lung cancer with adequate physical fitness. Compared to supportive care alone there was a 1.5 to 3 months prolongation of survival with chemotherapy in general, with better results seen with what were then newer agents. Symptomatic relief and an improvement in quality of life were also evident. A contemporaneous independent British review was consistent with this conclusion.

Despite a change in population demographics, this continues to hold up. A 2008 update by the NSCLC Meta-Analyses Collaborative Group looked at individual patient data from clinical trials subsequent to 1995, and recommended that chemotherapy should be considered in advanced non-small-cell lung cancer provided the recipient wanted treatment and was adequately fit to be able to tolerate it. This analysis was the basis of a 2010 Cochrane Review reporting that chemotherapy improves overall survival in advanced non-small-cell lung cancer, and finding a benefit in different subtypes of the cancer.

Palliative care is an essential and routine component of evidence-based, high-quality care for the management of advanced lung cancer but it is also clear that the best way to deliver palliative care is unknown. By way of emphasis, an analysis of almost 400 randomized controlled trials of palliative care concluded that the evidence for specialized palliative care as a specific intervention is limited, due to methodological shortcomings of the data. That review found that the most consistent benefit of palliative care was a increased perception by family members of good quality care. Which specific components of palliative care are of benefit is unknown, warranting further clinical assessment of different palliative approaches.

Prognosis

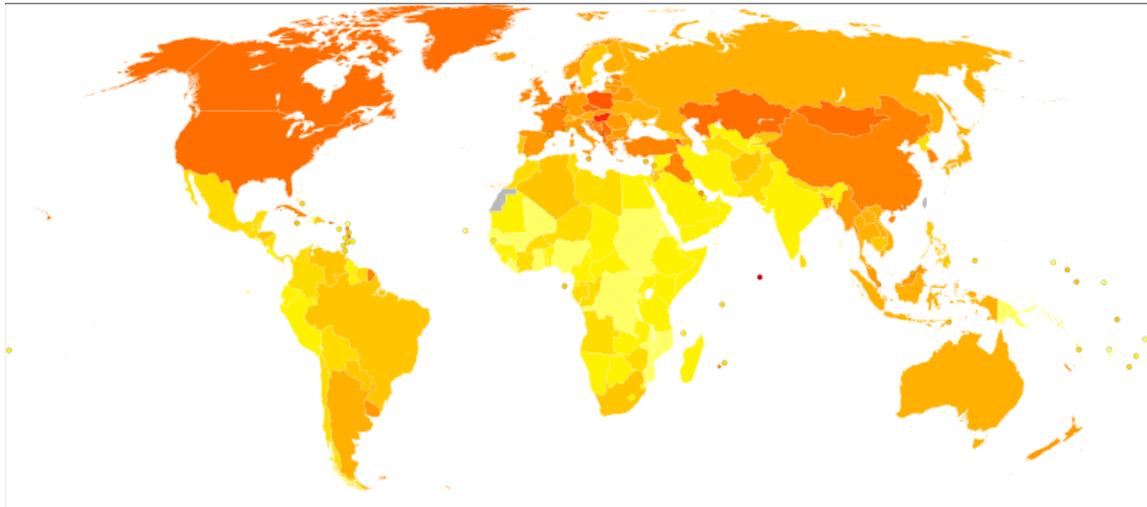
Prognostic factors in non-small-cell lung cancer include presence or absence of pulmonary symptoms, tumor size, cell type (histology), degree of spread (stage) and metastases to multiple lymph nodes, and vascular invasion. For patients with inoperable disease, prognosis is adversely affected by poor performance status and weight loss of more than 10%. Prognostic factors in small-cell lung cancer include performance status, gender, stage of disease, and involvement of the central nervous system or liver at the time of diagnosis.

For non-small-cell lung carcinoma (NSCLC), prognosis is generally poor. Following complete surgical resection of stage IA disease, five-year survival is 67%. With stage IB disease, five-year survival is 57%. The five-year survival rate of patients with stage IV NSCLC is about 1%.

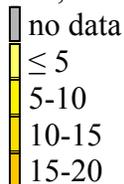
For small-cell lung carcinoma, prognosis is also generally poor. The overall five-year survival for patients with SCLC is about 5%. Patients with extensive-stage SCLC have an average five-year survival rate of less than 1%. The median survival time for limited-stage disease is 20 months, with a five-year survival rate of 20%.

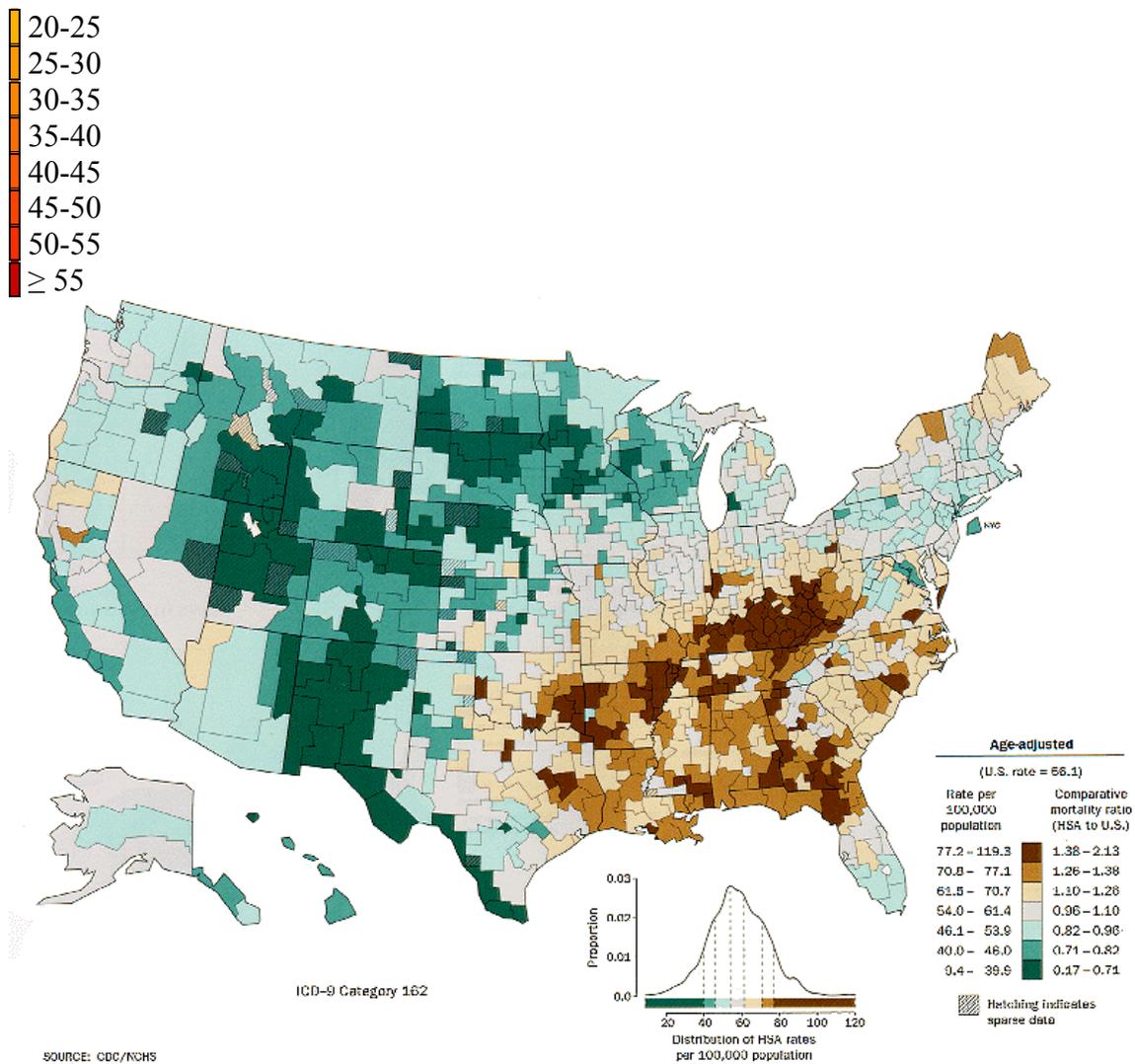
According to data provided by the National Cancer Institute, the median age at diagnosis of lung cancer in the United States is 70 years, and the median age at death is 72 years.

Epidemiology



Age-standardized death from tracheal, bronchial, and lung cancers per 100,000 inhabitants in 2004.





Lung cancer distribution in the United States

Worldwide, lung cancer is the most common cancer in terms of both incidence and mortality (1.1 million new cases per year and 0.95 million deaths in males and 0.51 million new cases per year and 0.43 million deaths in females). The highest rates are in Europe and North America. The population segment most likely to develop lung cancer is over-fifties who have a history of smoking. Lung cancer is the second most commonly occurring form of cancer in most Western countries, and it is the leading cancer-related cause of death. In contrast to the mortality rate in men, which began declining more than 20 years ago, women's lung cancer mortality rates have been rising for over the last decades, and are just recently beginning to stabilize. The evolution of "Big Tobacco" plays a significant role in the smoking culture. Tobacco companies have focused their efforts since the 1970s at marketing their product toward women and girls, especially with "light" and "low-tar" cigarettes. Among lifetime nonsmokers, men have higher age-standardized lung cancer death rates than women.

Not all cases of lung cancer are due to smoking, but the role of passive smoking is increasingly being recognized as a risk factor for lung cancer—leading to policy interventions to decrease undesired exposure of nonsmokers to others' tobacco smoke. Emissions from automobiles, factories, and power plants also pose potential risks.

Eastern Europe has the highest lung cancer mortality among men, while northern Europe and the U.S. have the highest mortality among women. In the United States, black men and women have a higher incidence. Lung cancer incidence is currently less common in developing countries. With increased smoking in developing countries, the incidence is expected to increase in the next few years, notably in China and India.

Lung cancer incidence (by country) has an inverse correlation with sunlight and UVB exposure. One possible explanation is a preventive effect of vitamin D (which is produced in the skin on exposure to sunlight).

From the 1950s, the incidence of lung adenocarcinoma started to rise relative to other types of lung cancer. This is partly due to the introduction of filter cigarettes. The use of filters removes larger particles from tobacco smoke, thus reducing deposition in larger airways. However the smoker has to inhale more deeply to receive the same amount of nicotine, increasing particle deposition in small airways where adenocarcinoma tends to arise. The incidence of lung adenocarcinoma in the U.S. has fallen since 1999. This may be due to reduction in environmental air pollution. However, in some developing countries like India, there has been little change in the epidemiology with squamous cell carcinoma continuing to be the predominant histological type. An absence of change in the type of tobacco smoking or the pattern of tobacco consumption in the population could be one of the possible reasons.

History

Lung cancer was uncommon before the advent of cigarette smoking; it was not even recognized as a distinct disease until 1761. Different aspects of lung cancer were described further in 1810. Malignant lung tumors made up only 1% of all cancers seen at autopsy in 1878, but had risen to 10–15% by the early 1900s. Case reports in the medical literature numbered only 374 worldwide in 1912, but a review of autopsies showed that the incidence of lung cancer had increased from 0.3% in 1852 to 5.66% in 1952. In Germany in 1929, physician Fritz Lickint recognized the link between smoking and lung cancer, which led to an aggressive antismoking campaign. The British Doctors Study, published in the 1950s, was the first solid epidemiological evidence of the link between lung cancer and smoking. As a result, in 1964 the Surgeon General of the United States recommended that smokers should stop smoking.

The connection with radon gas was first recognized among miners in the Ore Mountains near Schneeberg, Saxony. Silver has been mined there since 1470, and these mines are rich in uranium, with its accompanying radium and radon gas. Miners developed a disproportionate amount of lung disease, eventually recognized as lung cancer in the

1870s. An estimated 75% of former miners died from lung cancer. Despite this discovery, mining continued into the 1950s, due to the USSR's demand for uranium.

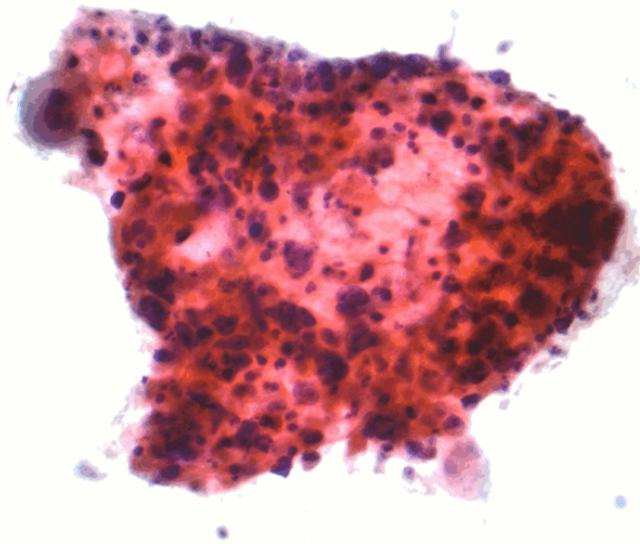
The first successful pneumonectomy for lung cancer was performed in 1933. Palliative radiotherapy has been used since the 1940s. Radical radiotherapy, initially used in the 1950s, was an attempt to use larger radiation doses in patients with relatively early stage lung cancer but who were otherwise unfit for surgery. In 1997, continuous hyperfractionated accelerated radiotherapy (CHART) was seen as an improvement over conventional radical radiotherapy.

With small-cell lung carcinoma, initial attempts in the 1960s at surgical resection and radical radiotherapy were unsuccessful. In the 1970s, successful chemotherapy regimens were developed.

Chapter 6

Non-Small-Cell Lung Carcinoma

Non-small-cell lung carcinoma



Micrograph of a squamous carcinoma, a type of non-small-cell lung carcinoma. FNA specimen. Pap stain.

MedlinePlus 007194

eMedicine med/1333

MeSH D002289

Non-small-cell lung carcinoma (NSCLC) is any type of epithelial lung cancer other than small-cell lung carcinoma (SCLC). As a class, NSCLCs are relatively insensitive to chemotherapy, compared to small-cell carcinoma. When possible, they are primarily treated by surgical resection with curative intent, although chemotherapy is increasingly being used both pre-operatively (so-called "neoadjuvant chemotherapy") and post-operatively ("adjuvant chemotherapy").

Types

The most common types of NSCLC are squamous-cell carcinoma, large-cell carcinoma, and adenocarcinoma, but there are several other types that occur less frequently, and all types can occur in unusual histologic variants and as multiphasic combinations.

Sometimes the phrase **non-small-cell lung cancer [Not Otherwise Specified, or NOS]** is used generically, usually when a more specific diagnosis cannot be made. This is most often the case when a pathologist examines a small amount of malignant cells or tissue in a cytology or biopsy specimen.

Lung cancer in never smokers is almost universally NSCLC, with a sizeable majority being adenocarcinoma.

On relatively rare occasions, malignant lung tumors are found to contain components of both SCLC and NSCLC. In these cases, the tumors are sometimes classified as Combined small-cell lung carcinoma (c-SCLC), and (usually) treated like "pure" SCLC.

Squamous-cell lung carcinoma



Photograph of a squamous-cell carcinoma. Tumour is on the left, obstructing the bronchus (lung). Beyond the tumour, the bronchus is inflamed and contains mucus.

Squamous-cell carcinoma of the lung is more common in men than in women. It is closely correlated with a history of tobacco smoking, more so than most other types of lung carcinoma. It most often arises centrally in larger bronchi, and while it often metastasizes to locoregional lymph nodes (particularly the hilar nodes) early in its course, it generally disseminates outside the thorax somewhat later than other major types. Large tumors may undergo central necrosis, resulting in cavitation. A squamous-cell carcinoma is often preceded for years by squamous-cell metaplasia or dysplasia in the respiratory epithelium of the bronchi, which later transforms to carcinoma in situ. In carcinoma in situ, atypical cells may be identified by cytologic smear test of sputum, bronchoalveolar lavage or samples from endobronchial brushings. However, squamous-cell carcinoma in situ is asymptomatic and undetectable on X-ray radiographs. Eventually, it becomes symptomatic, usually when the tumor mass begins to obstruct the lumen of a major bronchus, often producing distal atelectasis and infection. Simultaneously, the lesion invades into the surrounding pulmonary substance. On histopathology, these tumors range from well-differentiated, showing keratin pearls and cell junctions, to anaplastic with only minimal residual squamous-cell features.

Currently, four variants (papillary, small cell, clear cell, and basaloid) of squamous-cell carcinoma of the lung are recognized. Of these variants, there is some evidence that the basaloid and small-cell variants may have worse prognoses than "conventional" squamous-cell carcinomas. The papillary variant occurs more frequently as a primarily superficial, endobronchial lesion, with a modestly better prognosis. Very little data is currently available on the clear-cell variant of squamous-cell carcinoma, and no consensus has been reached on the prognostic implications of clear-cell changes in lung cancers

Recently, four mRNA expression subtypes (Primitive, Basal, Secretory, and Classical) were identified and validated within squamous-cell carcinoma. The Primitive subtype correlates with worse patient survival. These subtypes defined by intrinsic expression differences provide a foundation for improved patient prognosis and research into individualized therapies.

Lung adenocarcinoma

Adenocarcinoma of the lung is currently the most common type of lung cancer in "never smokers" (lifelong non-smokers). Adenocarcinomas account for approximately 40% of lung cancers. This cancer is more often seen peripherally in the lungs than are small-cell lung cancer and squamous-cell lung cancer, both of which tend to be more often centrally located. Interestingly, however, recent studies suggest that the "ratio of centrally-to-peripherally occurring" lesions may be converging toward unity for both adenocarcinoma and squamous-cell carcinoma.

Staging

Staging is an important part of the assessment of patients with non-small-cell lung carcinoma. These patients undergo staging as part of the process of considering prognosis

and treatment. The American Joint Committee on Cancer (AJCC) recommends TNM staging followed by further grouping.

As of January 2010 the new TNM staging system for lung cancer has included several radical changes which are applicable to NSCLC, SCLC and broncho-pulmonary carcinoid tumors. Revisions to the TNM were determined by differences in the overall survival of 81,015 patients; after meticulous validation the proposals for changes were accepted by the American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) and published in the new 7th edition of the “TNM Classification of Malignant Tumors”.

TNM staging

The first part of the staging classification is the TNM system.

Primary tumor (T)

- TX: The primary tumor cannot be assessed, or there are malignant cells in the sputum or bronchoalveolar lavage but not seen on imaging or bronchoscopy.
- Tis: Carcinoma in situ.
- T0: No evidence of primary tumor.
- T1: Tumor less than 3 cm in its greatest dimension, surrounded by lung or visceral pleura and without bronchoscopic invasion into the main bronchus.
- T2: A tumor with any of: -
 - More than 3 cm in greatest dimension.
 - Extending into the main bronchus, but more than 2 cm distal to the carina.
 - Obstructive pneumonitis, but not involving the entire lung.
- T3: A tumor with any of: -
 - Invasion of the chest wall, diaphragm, mediastinal pleura, or parietal pericardium.
 - Extending into the main bronchus, within 2 cm of the carina, but not involving the carina.
 - Obstructive pneumonitis of the entire lung.
- T4: A tumor with any of: -
 - Invasion of the mediastinum, heart, great vessels, trachea, oesophagus, vertebra, or carina.
 - Separate tumor nodules in the same lobe.
 - Malignant pleural effusion.

Lymph nodes (N)

- NX: Lymph nodes cannot be assessed.
- N0: No lymph nodes involved.
- N1: Metastasis to ipsilateral peribronchial or ipsilateral hilar lymph nodes.
- N2: Metastasis to ipsilateral mediastinal or subcarinal lymph nodes.
- N3: Metastasis to any of: -

- Ipsilateral supraclavicular lymph nodes.
- Ipsilateral scalene lymph nodes.
- Contralateral lymph nodes.

Distant metastasis (M)

- MX: Distant metastasis cannot be assessed.
- M0: No distant metastasis.
- M1: Distant metastasis is present.

Mountain classification

Clifton Mountain, a surgeon in Texas, assigned further categories of staging on the basis of similarities in treatment and prognosis.

Non-small-cell lung carcinoma staging	
Grouping	TNM staging
Occult carcinoma	TX N0 M0
Stage 0	Tis N0 M0
Stage IA	T1 N0 M0
Stage IB	T2 N0 M0
Stage IIA	T1 N1 M0
Stage IIB	T2 N1 M0
	T3 N0 M0
Stage IIIA	T1 N2 M0
	T2 N2 M0
	T3 N1 M0
	T3 N2 M0
Stage IIIB	Any T N3 M0
	T4 Any N M0
Stage IV	Any T Any N M1

A recent study proposed changes for the new stage grouping were to upstage T2bN0M0 from stage IB to stage IIA, and to downstage T2aN1M0 from stage IIB to stage IIA and T4N0-N1M0 from stage IIIB to stage IIIA.

Prognosis

Non-small-cell lung carcinoma survival by stage(1997)					
Grouping	Survival rate (percents)				
	One year	Two years	Three years	Four years	Five years
IA	82%	79%	71%	67%	61%
IB	72%	54%	46%	41%	38%
IIA	79%	49%	38%	34%	34%
IIB	59%	41%	33%	26%	24%
IIIA	50%	25%	18%	14%	13%
IIIB	34%	13%	7%	6%	5%
IV	19%	6%	2%	2%	1%

Treatment

More than one kind of treatment is often used, depending on the stage of the cancer, the individual's overall health, age, response to chemotherapy, and other factors such as the likely side effects of the treatment.

Early/non-metastatic NSCLC

NSCLCs are usually *not* very sensitive to chemotherapy and/or radiation, so surgery is the treatment of choice if diagnosed at an early stage, often with adjuvant (ancillary) chemotherapy involving cisplatin. Other treatment choices are chemotherapy, radiation therapy (radiotherapy), including radiosurgery (SRS), or targeted therapy.

New methods of giving radiation treatment allow doctors to be more accurate in treating lung cancers. This means less radiation affects nearby healthy tissues. New methods being tried are Gamma knife, Cyberknife and Stereotactic linear accelerators. Other new treatments being used are Radiofrequency ablation and Chemoembolization.

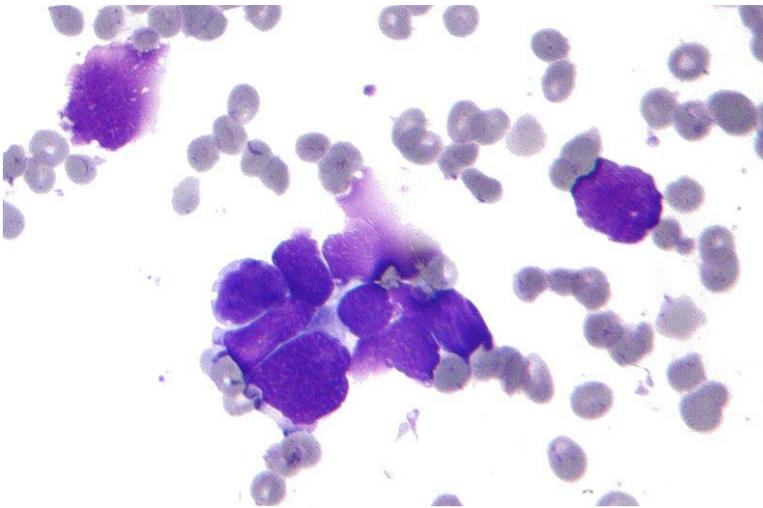
Advanced/metastatic NSCLC

A wide variety of chemotherapies are used in advanced (metastatic) NSCLC. Some patients with particular mutations in the *EGFR* gene respond to EGFR tyrosine kinase inhibitors such as gefitinib.

Chapter 7

Small-Cell Carcinoma

Small-cell carcinoma



Micrograph of a **small-cell carcinoma** of the lung showing cells with nuclear moulding, minimal amount of cytoplasm and stippled chromatin. FNA specimen. Field stain.

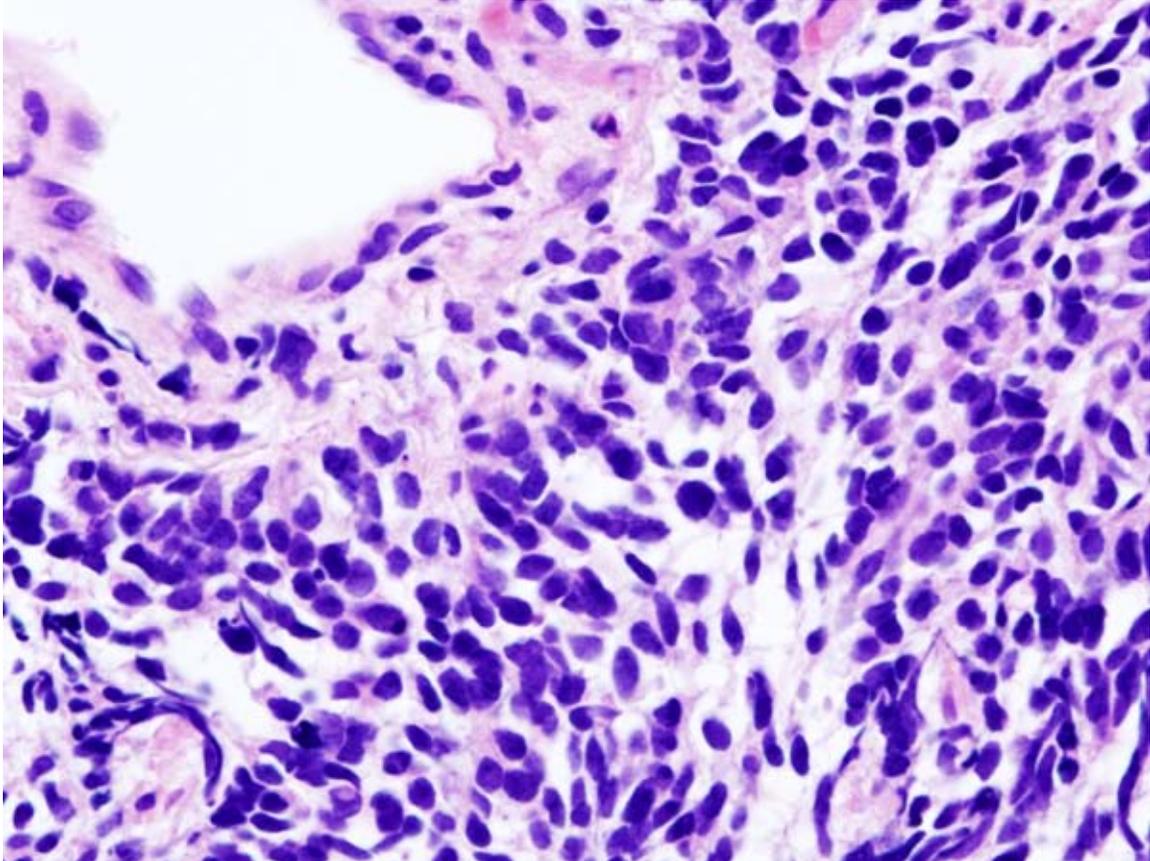
ICD-O:	M8041/3
MedlinePlus	000122
eMedicine	med/1336
MeSH	D018288

Small-cell carcinoma is a type of highly malignant carcinoma usually associated with the lung, though it can be associated with other topographies, such as in cervical cancer or prostate cancer.

Types

Paraneoplastic Syndromes: Small-cell carcinomas produce ACTH and ADH, which can lead to SIADH.

Lung



Histopathologic image of small-cell carcinoma of the lung. CT-guided core needle biopsy. H&E stain.

When associated with the lung, it is sometimes called "oat-cell carcinoma" due to the flat cell shape and scanty cytoplasm.

It is thought to originate from neuroendocrine cells (APUD cells) in the bronchus called Feyrter cells (named for Friedrich Feyrter). Hence, they express a variety of neuroendocrine markers, and may lead to ectopic production of hormones like ADH and ACTH that may result in paraneoplastic syndromes and Cushing's syndrome.

It is more metastatic than non-small-cell lung carcinoma (and hence staged differently) and is sometimes seen in combination with squamous-cell carcinomas. There is usually early involvement of the hilar and mediastinal lymph nodes.

Smoking is a significant etiological factor.

Symptoms and signs are as for other lung cancers. In addition, because of their neuroendocrine cell origin, small-cell carcinomas will often secrete substances that result in paraneoplastic syndromes such as Lambert-Eaton myasthenic syndrome.

On histopathology, small-cell lung carcinoma generally appears as a pale gray mass located centrally (near the hilum). It generally extends into the lung parenchyma. It is composed of tumor cells with a round to fusiform shape, scant cytoplasm, and finely granular chromatin. Mitoses are frequently seen. Cell necrosis is always present and may be extensive, and the tumor cells often form "rosette" patterns around these areas of necrosis. The tumor cells often show cell fragmentation. There is also *nuclear molding* (the shape of one nucleus conforms around the shape of an adjacent nucleus) resulting from tumor cells with scant cytoplasm lying close to each other.

Prostate

In the prostate, small-cell carcinoma (SCCP) is a rare form of cancer (approx 1% of PC). Due to the fact that there is little variation in prostate specific antigen levels, this form of cancer is normally diagnosed at an advanced stage, after metastasis.

It can metastasize to the brain.

Treatment for small-cell lung carcinoma

For the purpose of treatment, small-cell lung cancer is pragmatically divided into two stages: Limited Stage and Extensive Stage depending on the presence of metastases and, for disease limited to the thorax, whether it can feasibly be encompassed in a radiotherapy portal. In cases of limited-stage small-cell lung carcinoma, combination chemotherapy (often consisting of a cyclophosphamide, cisplatin, doxorubicin, etoposide, vincristine and/or paclitaxel) is administered together with concurrent chest radiotherapy. Thoracic irradiation improves survival in limited stage small-cell lung carcinoma. In this setting, initial response rates are exceptionally high with chemotherapy alone, but relapse is quite common, though up to 40-50% of patients with limited stage disease may survive two years, according to one study. Overall, between 60-90% of patients with limited stage small-cell lung carcinoma respond to chemotherapy, and 45-75% of patients have a complete response, but median survival is only 18–24 months. As small-cell lung carcinoma spreads rapidly and is highly responsive to chemotherapy, there is little role for surgery in the treatment of limited stage small-cell lung carcinoma, however, some have hypothesized that in cases of asymptomatic, node negative small-cell lung cancer, surgical excision may improve survival when used prior to chemotherapy. In extensive disease, combination chemotherapy is the standard of care, with radiotherapy added only to palliate symptoms such as dyspnea, pain from liver or bone metastases, or for the treatment of brain metastases, which, in small-cell lung carcinoma, typically have a rapid, if temporary, response to whole brain radiotherapy. Combination chemotherapy consists of a wide variety of agents, including cisplatin,

cyclophosphamide, vincristine and carboplatin. Response rates are high even in extensive disease, with up 15-30% of patients with extensive stage small-cell lung carcinoma having a complete response to combination chemotherapy and the vast majority of patients having at least some response to combination chemotherapy. However, responses are often of short duration. If in either limited or extensive disease, complete response to chemotherapy occurs, then prophylactic cranial irradiation will often be considered to prevent brain metastases. Although this treatment is likely effective to prevent brain metastases from small-cell lung carcinoma, it can cause hair loss, and fatigue. Prospective randomised trials with almost two years follow-up have not shown neurocognitive ill-effects. Meta-analyses of randomised trials confirm that prophylactic cranial irradiation provides significant survival benefit. All in all small-cell carcinoma is very responsive to chemotherapy and radiotherapy in particular the platinum based agents. However, most people with the disease relapse and median survival remains low in both limited and extensive stage disease.

Prognosis

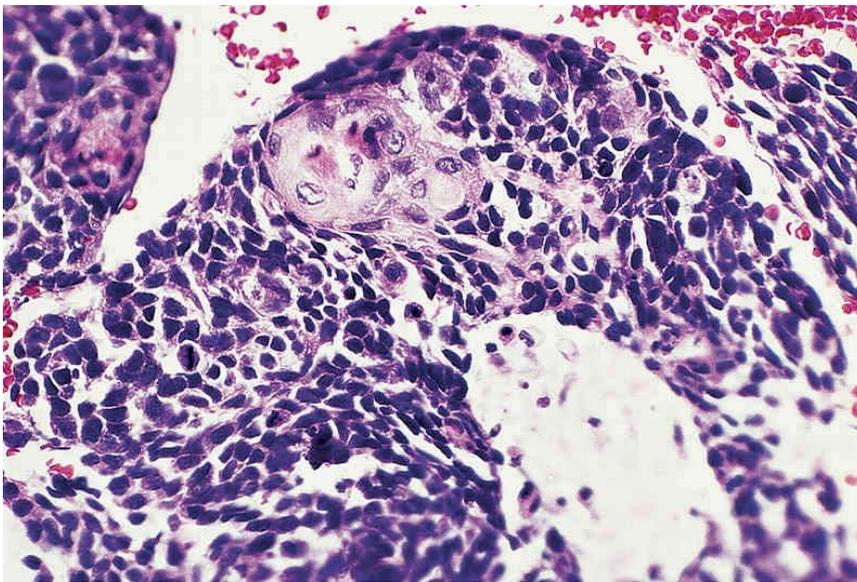
In *limited stage* disease, median survival with treatment is 14–20 months, and about 20% of patients with limited stage small-cell lung carcinoma live 5 years or longer.

The prognosis is far worse in *extensive stage* small-cell lung carcinoma, with treatment, median survival is just 8–13 months, and only 1-5% of patients with extensive stage small-cell lung carcinoma treated with chemotherapy live 5 years or longer.

Chapter 8

Combined Small-Cell Lung Carcinoma

Combined Small-Cell Lung Carcinoma



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Combined small-cell lung carcinoma containing a component of squamous-cell carcinoma

ICD-10	C33.-C34.
ICD-9	162
ICD-O:	8045/3
DiseasesDB	7616
MedlinePlus	007194
eMedicine	med/
MeSH	D018288

Combined small-cell lung carcinoma (c-SCLC) is a form of multiphasic lung cancer that is diagnosed when a malignant tumor arising from lung tissue contains a component of small-cell lung carcinoma (SCLC) admixed with one (or more) components of non-small-cell lung carcinoma (NSCLC).

Classification

Lung cancer is a large and exceptionally heterogeneous family of malignancies. Over 50 different histological variants are explicitly recognized within the 2004 revision of the World Health Organization (WHO) typing system ("WHO-2004"), currently the most widely used lung cancer classification scheme. Many of these entities are rare, recently described, and poorly understood. However, since different forms of malignant tumors generally exhibit diverse genetic, biological, and clinical properties, including response to treatment, accurate classification of lung cancer cases are critical to assuring that patients with lung cancer receive optimum management.

Approximately 98% of lung cancers are carcinoma, a term for malignant neoplasms derived from cells of epithelial lineage, and/or that exhibit cytological or tissue architectural features characteristically found in epithelial cells. Under WHO-2004, lung carcinomas are divided into 8 major taxa:

- Squamous-cell carcinoma
- Small-cell carcinoma
- Adenocarcinoma
- Large-cell carcinoma
- Adenosquamous carcinoma
- Sarcomatoid carcinoma
- Carcinoid tumor
- Salivary gland-like carcinoma

SCLC is generally considered to be the most aggressive form of lung cancer, with the worst long term prognosis and survival rates. Therefore, all tumor(s) containing SCLC cells are classified as c-SCLC, and not as combined forms of any other component(s) present, regardless of their relative proportions. The only exception occurs in cases where anaplastic large cell lung carcinoma (LCLC) is the second component. In these instances, a minimum of 10% of the malignant cells must be identified as LCLC before the tumor is considered a c-SCLC. Under WHO-2004, c-SCLC is the only recognized variant of SCLC.

Incidence

Reliable comprehensive incidence statistics for c-SCLC are unavailable. In the literature, the frequency with which the c-SCLC variant is diagnosed largely depends on the size of tumor samples, tending to be higher in series where large surgical resection specimens are examined, and lower when diagnoses are based on small cytology and/or biopsy samples. Tatematsu *et al.* reported 15 cases of c-SCLC (12%) in their series of 122

consecutive SCLC patients, but only 20 resection specimens were examined. In contrast, Nicholson *et al.* found 28 c-SCLC (28%) in a series of 100 consecutive resected SCLC cases. It appears likely, then, that the c-SCLC variant comprises 25% to 30% of all SCLC cases.

As the incidence of SCLC has declined somewhat in the U.S. in recent decades, it is likely that c-SCLC has also decreased in incidence. Nevertheless, small-cell carcinomas (including the c-SCLC variant) still comprise 15%–20% of all lung cancers, with c-SCLC probably accounting for 4%–6%. With 220,000 cases of newly diagnosed lung cancer in the U.S. each year, it can be estimated that between 8,800 and 13,200 of these are c-SCLC.

In a study of 408 consecutive patients with SCLC, Quoix and colleagues found that presentation as a solitary pulmonary nodule (SPN) is particularly indicative of a c-SCLC - about 2/3 of their SPN's were pathologically confirmed to be c-SCLC's containing a large cell carcinoma component.

Significance

In terms of case numbers, the estimated 8,800 to 13,200 c-SCLC cases occurring annually in the U.S. makes this disease roughly comparable in incidence to Hodgkin's Disease (8,500), testicular cancer (8,400), cervical cancer (11,300), and cancers of the larynx (12,300). However, these four "better-known" cancers all have exceptionally high (85%-95%) cure rates. In contrast, less than 10% of c-SCLC patients will be cured, and thus the number of annual cases of c-SCLC is a reasonable approximation of the annual number of deaths. Therefore, given the significant incidence and mortality attributable to this malignancy, it is arguably critical to better understand these aggressive lesions so specific strategies for their management can be rationally designed.

However, as patients with tumors containing mixtures of histological subtypes are usually excluded from clinical trials, the properties of multiphasic tumors like c-SCLC are much less well understood than those of monophasic tumors. C-SCLC contains both SCLC and NSCLC by definition, and since patients with SCLC and NSCLC are usually treated differently, the lack of good data on c-SCLC means there is little evidence available with which to form consensus about whether c-SCLC should be treated like SCLC, NSCLC, or uniquely.

Histogenesis

In most cases, lung cancers probably result from the malignant transformation of a single multipotent cell. This newly formed cancer stem cell then begins to divide uncontrollably, giving rise to new daughter cancer cells in an exponential (or near exponential) fashion. Unless this runaway cell division process is checked, a clinically apparent tumor will eventually form.

Approximately 98% of lung cancers are carcinoma, a term which implies that the tumor derives from transformed epithelial cells, or consists of cells that have acquired epithelial characteristics as a result of cell differentiation. In most cases of c-SCLC, genomic and immunohistochemical studies suggest that the morphological divergence of the separate components in a c-SCLC occurs when a SCLC-like cell is transformed into a cell with the potential to develop NSCLC variant characteristics, and not *vice versa*. Daughter cells of this transdifferentiated SCLC-like cell then repeatedly divide and, under both intrinsic genomic and extrinsic environmental influences, acquire additional mutations, a process known as tumor progression. The end result is that the tumor acquires specific cytologic and architectural features suggesting a mixture of SCLC and NSCLC.

Other molecular studies, however, suggest that - in at least a minority of cases - independent development of the components in c-SCLC occurs via mutation and transformation in two different cells in close spatial proximity to each other, due to field cancerization. In these cases, repeated division and mutational progression in both cancer stem cells generate a biclonal collision tumor.

Regardless of which of these mechanisms give rise to the tumor, recent studies suggest that, in the later stages of c-SCLC oncogenesis, continued mutational progression within each tumor component results in the cells of the combined tumor developing molecular profiles that more closely resemble each other than they do cells of the "pure" forms of the individual morphological variants. This molecular oncogenetic convergence likely has important implications for treatment of these lesions, given the differences between standard therapeutic regimens for SCLC and NSCLC.

C-SCLC also occurs quite commonly after treatment of "pure" SCLC with chemotherapy and/or radiation, probably as a result of a combination of tumor genome-specific "progressional" mutations, stochastic genomic phenomena, and additional mutations induced by the cytotoxic therapy.

The most common forms of NSCLC identified as components within c-SCLC are large cell carcinoma, adenocarcinoma, and squamous cell carcinoma. Rarer variants of NSCLC are seen less commonly, such as combinations with carcinoids, spindle cell carcinoma, and giant cell carcinoma. Giant cell carcinoma components are seen much more commonly in patients who have undergone radiation. With the approval and use of newer "molecularly targeted" agents revealing differential efficacies in specific subtypes and variants of NSCLC, it is becoming more important for pathologists to correctly subclassify NSCLC's as distinct tumor entities, or as components of c-SCLC's.

Staging

Staging of c-SCLC patients is usually performed in an analogous fashion to patients with "pure" small-cell lung carcinoma.

For several decades, SCLC has been staged according to a dichotomous distinction of "limited disease" (LD) vs. "extensive disease" (ED) tumor burdens. Nearly all clinical

trials have been conducted on SCLC patients staged dichotomously in this fashion. LD is roughly defined as a locoregional tumor burden confined to one hemithorax that can be encompassed within a single, tolerable radiation field, and without detectable distant metastases beyond the chest or supraclavicular lymph nodes. A patient is assigned an ED stage when the tumor burden is greater than that defined under LD criteria - either far advanced locoregional disease, malignant effusions from the pleura or pericardium, or distant metastases.

However, more recent data reviewing outcomes in very large numbers of SCLC patients suggests that the TNM staging system used for NSCLC is also reliable and valid when applied to SCLC patients, and that more current versions may allow better treatment decisionmaking and prognostication in SCLC than with the old dichotomous staging protocol.

Treatment

A very large number of clinical trials have been conducted in "pure" SCLC over the past several decades. As a result, evidence-based sets of guidelines for treating monophasic SCLC are available. While the current set of SCLC treatment guidelines recommend that c-SCLC be treated in the same manner as "pure" SCLC, they also note that the evidence supporting their recommendation is quite weak. It is likely, then, that the optimum treatment for patients with c-SCLC remains unknown.

The current generally accepted standard of care for all forms of SCLC is concurrent chemotherapy (CT) and thoracic radiation therapy (TRT) in LD, and CT only in ED. For complete responders (patients in whom all evidence of disease disappears), prophylactic cranial irradiation (PCI) is also given. TRT serves to increase the probability of total eradication of residual locoregional disease, while PCI aims to eliminate any micrometastases to the brain.

Surgery is not often considered as a treatment option in SCLC (including c-SCLC) due to the high probability of distant metastases at the time of diagnosis. This paradigm was driven by early studies showing that the administration of systemic therapies resulted in improved survival as compared to patients undergoing surgical resection. Recent studies, however, have suggested that surgery for highly selected, very early-stage c-SCLC patients may indeed improve outcomes. Other experts recommend resection for residual masses of NSCLC components after complete local tumor response to chemotherapy and/or radiotherapy in c-SCLC.

Although other combinations of drugs have occasionally been shown to be noninferior at various endpoints and in some subgroups of patients, the combination of cisplatin or carboplatin plus etoposide or irinotecan are considered comparable first-line regimens for SCLC. For patients who do not respond to first line therapy, or who relapse after complete remission, topotecan is the only agent which has been definitively shown to offer increased survival over best supportive care (BSC), although in Japan amirubicin is considered effective as salvage therapy.

Importantly, c-SCLC is usually much more resistant to CT and RT than "pure" SCLC. While the mechanisms for this increased resistance of c-SCLC to conventional cytotoxic treatments highly active in "pure" SCLC remain mostly unknown, recent studies suggest that the earlier in its biological history that a c-SCLC is treated, the more likely it is to resemble "pure" SCLC in its response to CT and RT.

Targeted agents

In recent years, several new types of "molecularly targeted" agents have been developed and used to treat lung cancer. While a very large number of agents targeting various molecular pathways are being developed and tested, the main classes and agents that are now being used in lung cancer treatment include:

- Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI's):
 - Erlotinib (Tarceva)
 - Gefitinib (Iressa)
 - Cetuximab (Erbix)
- Inhibitors of vascular endothelial growth factor (VEGF)
 - Bevacizumab (Avastin)
- Inhibitors of folate metabolism
 - Pemetrexed (Alimta)

To date, most clinical trials of targeted agents, alone and in combination with previously tested treatment regimens, have either been ineffective in SCLC or no more effective than standard platinum-based doublets. While there have been no randomized clinical trials of targeted agents in c-SCLC, some small case series suggest that some may be useful in c-SCLC. Many targeted agents appear more active in certain NSCLC variants. Given that c-SCLC contains components of NSCLC, and that the chemoradioresistance of NSCLC components impact the effectiveness of c-SCLC treatment, these agents may permit the design of more rational treatment regimens for c-SCLC.

EGFR-TKI's have been found to be active against variants exhibiting certain mutations in the EGFR gene. While EGFR mutations are very rare (<5%) in "pure" SCLC, they are considerably more common (about 15%-20%) in c-SCLC, particularly in non-smoking females whose c-SCLC tumors contain an adenocarcinoma component. These patients are much more likely to have classical EGFR mutations in the small-cell component of their tumors as well, and their tumors seem to be more likely to respond to treatment with EGFR-TKI's. EGFR-targeted agents appear particularly effective in papillary adenocarcinoma, non-mucinous bronchioloalveolar carcinoma, and adenocarcinoma with mixed subtypes.

The role of VEGF inhibition and bevacizumab in treating SCLC remains unknown. Some studies suggest it may, when combined with other agents, improve some measures of survival in SCLC patients and in some non-squamous cell variants of NSCLC.

Pemetrexed has been shown to improve survival in non-squamous cell NSCLC, and is the first drug to reveal differential survival benefit in large cell lung carcinoma.

Interestingly, c-SCLC appear to express female hormone (i.e. estrogen and/or progesterone) receptors in a high (50%-67%) proportion of cases, similar to breast carcinomas. However, it is at present unknown whether blockade of these receptors affects the growth of c-SCLC.

Prognosis and survival

Current consensus is that the long-term prognosis of c-SCLC patients is determined by the SCLC component of their tumor, given that "pure" SCLC seems to have the worst long-term prognosis of all forms of lung cancer. Although data on c-SCLC is very sparse, some studies suggest that survival rates in c-SCLC may be even worse than that of pure SCLC, likely due to the lower rate of complete response to chemoradiation in c-SCLC, although not all studies have shown a significant difference in survival.

Untreated "pure" SCLC patients have a median survival time of between 4 weeks and 4 months, depending on stage and performance status at the time of diagnosis.

Given proper multimodality treatment, SCLC patients with limited disease have median survival rates of between 16 and 24 months, and about 20% will be cured. In patients with extensive disease SCLC, although 60% to 70% will have good-to-complete responses to treatment, very few will be cured, with a median survival of only 6 to 10 months.

Some evidence suggests that c-SCLC patients who continue to smoke may have much worse outcomes after treatment than those who quit.

Chapter 9

Chest Pain and Dyspnea (Symptoms of Lung Cancer)

Chest pain

Chest pain

ICD-10 R07.

ICD-9 786.5

Chest pain may be a symptom of a number of serious conditions and is generally considered a medical emergency. Even though it may be determined that the pain is **non-cardiac** in origin, this is often a diagnosis of exclusion made after ruling out more serious causes of the pain.

Differential diagnosis

The causes of chest pain range from non-serious to life threatening. DiagnosisPro lists more than 440 causes.

Cardiovascular

- Acute coronary syndrome
 - Unstable Angina Pectoris - requiring emergency medical treatment but not primary intervention as in a myocardial infarction.
 - Myocardial infarction ("heart attack")
- Aortic dissection
- Pericarditis and cardiac tamponade
- Arrhythmia - atrial fibrillation and a number of other arrhythmias can cause chest pain.
- Stable angina pectoris - this can be treated medically and although it warrants investigation, it is not an emergency in its strictest sense

Pulmonary

- Pulmonary embolism
- Pneumonia
- Hemothorax
- Pneumothorax and Tension pneumothorax
- Pleurisy - an inflammation which can cause painful respiration

GI

- Gastroesophageal reflux disease (GERD) and other causes of heartburn
- Hiatus hernia
- Achalasia, nutcracker esophagus and other neuromuscular disorders of the esophagus
- Functional dyspepsia

Chest wall

- Costochondritis or Tietze's syndrome - a benign and harmless form of osteochondritis often mistaken for heart disease
- Spinal nerve problem
- Fibromyalgia
- Chest wall problems
- Radiculopathy
- Precordial catch syndrome
- Breast conditions
- Herpes zoster commonly known as shingles
- Tuberculosis

Psychological

- Panic attack
- Anxiety
- Clinical depression
- Somatization disorder
- Hypochondria

Others

- Hyperventilation syndrome often presents with chest pain and a tingling sensation of the fingertips and around the mouth
- Da Costa's syndrome
- Bornholm disease - a viral disease that can mimic many other conditions
- Precordial catch syndrome - another benign and harmless form of a sharp, localised chest pain often mistaken for heart disease
- Carbon monoxide poisoning

- Sarcoidosis
- Lead poisoning
- High abdominal pain may also mimic chest pain

Diagnostic approach

In the emergency department the typical approach to chest pain involves ruling out the most dangerous causes: heart attack, pulmonary embolism, thoracic aortic dissection, esophageal rupture, tension pneumothorax and cardiac tamponade. By elimination or confirmation the most serious causes, a diagnosis of the origin of the pain maybe made. Often, no definite cause will be found and reassurance is then provided.

If acute coronary syndrome ("unstable angina") is suspected, many people are admitted briefly for observation, sequential ECGs, and determination of cardiac enzymes over time. On occasion, further tests on follow up may determine the cause. TIMI score performed at time of admission may help stratify risk.

As in all medicine, a careful medical history and physical examination is essential in separating dangerous from trivial causes of disease, and the management of chest pain may be done on specialised units (termed *medical assessment units*) to concentrate the investigations. A rapid diagnosis can be life-saving and often has to be made without the help of X-rays or blood tests (e.g. aortic dissection). Occasionally, invisible medical signs will direct the diagnosis towards particular causes, such as Levine's sign in cardiac ischemia. Generally, however, additional tests are required to establish the diagnosis.

A focus on recent health changes, family history (premature atherosclerosis, cholesterol disorders), tobacco smoking, diabetes and other risk factors is useful.

Features of the pain suggest of cardiac ischaemia are describing the pain as heaviness; radiation of the pain to neck, jaw or left arm; sweating; nausea; palpitations; the pain coming upon exertion; dizziness; shortness of breath and a "sense of impending doom."

On the basis of the above, a number of tests may be ordered:

- X-rays of the chest and/or abdomen (CT scanning may be better but is often not available). Routine X-rays and CT may however not be needed.
- An electrocardiogram (ECG)
- V/Q scintigraphy or CT pulmonary angiogram(when a pulmonary embolism is suspected)
- Blood tests:
 - Complete blood count
 - Electrolytes and renal function (creatinine)
 - Liver enzymes
 - Creatine kinase (and *CK-MB* fraction in many hospitals)
 - Troponin I or T (to indicate myocardial damage)
 - D-dimer (when suspicion for pulmonary embolism is present but low)

- serum amylase to exclude acute pancreatitis

Management

In people with chest pain supplemental oxygen is not needed unless the oxygen saturations are less than 94% or there are signs of respiratory distress.

Epidemiology

Chest pain is the presenting symptom in about 12% of emergency department visits in the United States and has a one year mortality of about 5%.

Dyspnea

Dyspnea

ICD-10	R06.0
ICD-9	786.05
DiseasesDB	15892
MedlinePlus	003075
MeSH	D004417

Dyspnea (also spelled **dyspnoea**) or (**shortness of breath (SOB)**, **air hunger**), is the subjective symptom of *breathlessness*. It is a normal symptom of heavy exertion but becomes pathological if it occurs in unexpected situations. In 85% of cases it is due to either asthma, pneumonia, cardiac ischemia, interstitial lung disease, congestive heart failure, chronic obstructive pulmonary disease, or psychogenic causes. Treatment typically depends on the underlying cause.

Definition

Dyspnea does not have a well defined or universally accepted definition. It is defined by the American Thoracic Society as the "subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioral responses." Other definitions of dyspnea include "difficulty in breathing", "disordered or inadequate breathing", "uncomfortable awareness of breathing", or simple "breathlessness".

Acute breathlessness is defined as severe shortness of breath that develops over minutes to hours. Chronic breathlessness on the other hand comes on over weeks or months.

Differential diagnosis

While shortness of breath is generally caused by disorders of the cardiac or respiratory system other system such as musculoskeletal, endocrine, hematologic, and psychiatric may be the cause. DiagnosisPro, an online medical expert system, listed 497 distinct causes in October of 2010. The most common cardiovascular causes are acute myocardial infarction and congestive heart failure while common pulmonary causes include chronic obstructive pulmonary disease, asthma, pneumothorax, and pneumonia.

Acute coronary syndrome

Acute coronary syndrome frequently presents with retrosternal chest discomfort and difficulty catching the breath. It however may atypically present with shortness of breath alone. Risk factors include old age, smoking, hypertension, hyperlipidemia, and diabetes. An electrocardiogram and cardiac enzymes are important both for diagnosis and directing treatment. Treatment involves measures to decrease the oxygen requirement of the heart and efforts to increase blood flow.

Congestive heart failure

Congestive heart failure frequently presents with SOB with exertion, orthopnea, and paroxysmal nocturnal dyspnea. It affects between 1-2% of the general United States population and occurs in 10% of those over 65 years old. Risk factors for acute decompensation include high dietary salt intake, medication noncompliance, cardiac ischemia, dysrhythmias, renal failure, pulmonary emboli, hypertension, and infections. Treatment efforts are directed towards decreasing lung congestion.

Chronic obstructive pulmonary disease

People with chronic obstructive pulmonary disease (COPD), most commonly emphysema or chronic bronchitis, frequently have chronic shortness of breath and a chronic productive cough. An acute exacerbation presents with increased shortness of breath and sputum production. COPD is a risk factor for pneumothorax thus this condition should be ruled out. In an acute exacerbation treatment is with a combination of anticholinergics, beta₂-adrenoceptor agonists, steroids and possibly positive pressure ventilation.

Asthma

Asthma is the most common reason for presenting to the emergency with shortness of breath. It is the most common lung disease in both developing and developed countries affecting about 5% of the population. Other symptoms include wheezing, tightness in the chest, and a non productive cough. Inhaled beta₂-adrenergic agonist (salbutamol) are first line therapy and usually lead to prompt improvement.

Pneumothorax

Pneumothorax presents typically with pleuritic chest pain of acute onset and shortness of breath not improved with oxygen. Physical findings may include absent breath sounds on one side of the chest, jugular venous distension, and tracheal deviation.

Pneumonia

The symptoms of pneumonia are fever, productive cough, shortness of breath, and pleuritic chest pain. Inspiratory crackles may be heard on exam. A chest x-ray can be useful to differentiate pneumonia from congestive heart failure. As the cause is usually a bacterial infection, antibiotics are typically used for treatment.

Pulmonary embolism

Pulmonary embolism classically presents with an acute onset of shortness of breath. Other presenting symptoms include pleuritic chest pain, cough, hemoptysis, and fever. Risk factors include deep vein thrombosis, recent surgery, cancer, and previous thromboembolism. It must always be considered in those with acute onset of shortness of breath due to its high risk of mortality. Diagnosis however may be difficult. Treatment is typically with anticoagulants.

Other

Other important or common causes of shortness of breath include cardiac tamponade, anemia, anaphylaxis, interstitial lung disease and panic attacks. Cardiac tamponade presents with dyspnea, tachycardia, elevated jugular venous pressure, and pulsus paradoxus. The gold standard for diagnosis is ultrasound. Anemia, that develops gradually, usually presents with exertional dyspnea, fatigue, weakness, and tachycardia. It may lead to heart failure. Anaphylaxis typically begins over a few minutes in a person with a previous history of the same. Other symptoms include urticaria, throat swelling, and gastrointestinal upset. The primary treatment is epinephrine. Interstitial lung disease presents with gradual onset of shortness of breath typically with a history of a predisposing environmental exposure. Shortness of breath is often the only symptom in those with tachydysrhythmias. Panic attacks typically present with hyperventilation, sweating, and numbness. They are however a diagnosis of exclusion. Around 2/3 of women experience shortness of breath as a part of a normal pregnancy.

Pathophysiology

A number of different physiological pathways may lead to shortness of breath including via chemoreceptors, mechanoreceptors, and lung receptors.

It is currently thought that there are three main components that contribute to dyspnea: afferent signals, efferent signals, and central information processing. It is believed that the central processing in the brain compares the afferent and efferent signals, and that a

"mismatch" results in the sensation of dyspnea. In other words, dyspnea may result when the need for ventilation (afferent signaling) is not being met by the physical breathing that is occurring (efferent signaling). Afferent signals are sensory neuronal signals that ascend to the brain. Afferent neurons significant in dyspnea arise from a large number of sources including the carotid bodies, medulla, lungs, and chest wall. Chemoreceptors in the carotid bodies and medulla supply information regarding the blood gas levels of O₂, CO₂ and H⁺. In the lungs, juxtacapillary (J) receptors are sensitive to pulmonary interstitial edema, while stretch receptors signal bronchoconstriction. Muscle spindles in the chest wall signal the stretch and tension of the respiratory muscles. Thus, poor ventilation leading to hypercapnia, left heart failure leading to interstitial edema (impairing gas exchange), asthma causing bronchoconstriction (limiting airflow) and muscle fatigue leading to ineffective respiratory muscle action could all contribute to a feeling of dyspnea.

Efferent signals are the motor neuronal signals descending to the respiratory muscles. The most important respiratory muscle is the diaphragm. Other respiratory muscles include the external and internal intercostal muscles, the abdominal muscles and the accessory breathing muscles.

As the brain receives its plentiful supply of afferent information relating to ventilation, it is able to compare it to the current level of respiration as determined by the efferent signals. If the level of respiration is inappropriate for the body's status then dyspnea might occur. It is worth noting that there is a psychological component of dyspnea as well, as some people may become aware of their breathing in such circumstances but not experience the distress typical of dyspnea.

Evaluation

MRC Breathlessness Scale	
Grade	Degree of dyspnea
0	no dyspnea except with strenuous exercise
1	dyspnea when walking up an incline or hurrying on the level
2	walks slower than most on the level, or stops after 15 minutes of walking on the level
3	stops after a few minutes of walking on the level
4	with minimal activity such as getting dressed, too dyspneic to leave the house

The initial approach to evaluation begins by assessment of the airway, breathing, and circulation followed by a medical history and physical examination. Signs that represent significant severity include hypotension, hypoxemia, tracheal deviation, altered mental status, unstable dysrhythmia, stridor, intercostal indrawing, cyanosis, and absent breath sounds.

A number of scales may be used to quantify the degree of shortness of breath. It may be subjectively rated on a scale from 1 to 10 with descriptors associated with the number (The Modified Borg Scale). Alternatively a scale such as the MRC Breathlessness Scale might be used - it suggests five different grades of dyspnea based on the circumstances in which it arises.

Blood tests

A number of labs maybe helpful in determining the cause of shortness of breath. D-dimer while useful to rule out a pulmonary embolism in those who are at low risk is not of much value if it is positive as it may be positive in a number of conditions that lead to shortness of breath. A low level of brain natriuretic peptide is useful in ruling out congestive heart failure however a high level while supportive of the diagnosis could also be due to advanced age, renal failure, acute coronary syndrome, or a large pulmonary embolism.

Imaging

A chest x-ray is useful to confirm or rule out a pneumothorax, pulmonary edema, or pneumonia. Spiral computed tomography with intravenousradiocontrast is the imaging study of choice to evaluate for pulmonary embolism.

Treatment

In those who are none palliative the primary treatment of shortness of breath is directed at its underlying cause. Extra oxygen is effective in those with hypoxia however has no effect in those with normal blood oxygen saturations even in those with who are palliative.

Palliative

Along with the measure above systemic immediate release opioids are beneficial in reducing the symptom of shortness of breath due to both cancer and non cancer causes. There is a lack of evidence to recommend midazolam, nebulised opioids, the use of gas mixtures, or cognitive-behavioral therapy.

Epidemiology

Shortness of breath is the primary reason 3.5% of people present to the emergency department in the United States. Of these approximately 51% are admitted to hospital and 13% are dead within a year. Some studies have suggested that up to 27% of people suffer from dyspnea, while in dying patients 75% will experience it. Acute shortness of breath is the most common reason people who are palliative visit an emergency department.

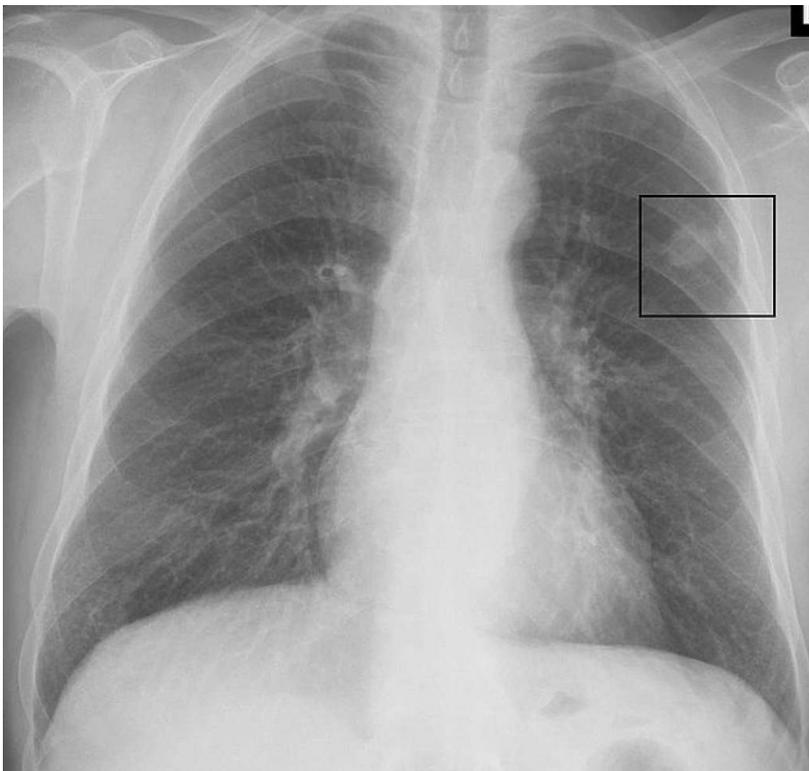
Etymology

Dyspnea, (from Latin *dyspnoea*, from Greek *dyspnoia* from *dyspnoos*) literally means disordered breathing.

Chapter 10

Solitary Pulmonary Nodule

Solitary pulmonary nodule



Chest X-ray showing a **solitary pulmonary nodule** (indicated by a black box) in the left upper lobe.

ICD-9	518.89
DiseasesDB	29456
MedlinePlus	000071
eMedicine	RADIO/782
MeSH	D003074

In radiology, a **solitary pulmonary nodule (SPN)** or **coin lesion** is a mass in the lung smaller than 3 centimeters in diameter. It can be an incidental finding found in up to 0.2% of chest X-rays and around 1% of CT scans.

The nodule most commonly represents a benign tumor such as a granuloma or hamartoma, but in around 20% of cases it represents a malignant cancer, especially in older adults and smokers. Conversely, 10 to 20% of patients with lung cancer are diagnosed in this way. Thus, the possibility of cancer needs to be excluded through further radiological studies and interventions, possibly including surgical resection. The prognosis depends on the underlying condition.

Definition

A solitary pulmonary nodule needs to be separated from larger lung tumors, smaller infiltrates or masses with other accompanying characteristics. An often used formal radiological definition is the following: a single lesion in the lung completely surrounded by lung parenchyma (functional tissue) with a diameter less than 3 cm and without associated pneumonia, atelectasis (lung collapse) or lymphadenopathies (swollen lymph nodes).

Causes

Not every round spot on a radiological image is a coin lesion: it should not be confused with the projection of a structure of the chest wall or skin, such as a nipple, a healing rib fracture or electrocardiographic monitoring.

The most important cause to exclude is a form of lung cancer, including rare forms such as primary pulmonary lymphoma, carcinoid tumor and a solitary metastasis to the lung (common unrecognised primary tumor sites are melanomas, sarcomas or testicular cancer). Benign tumors in the lung include hamartomas and chondromas.

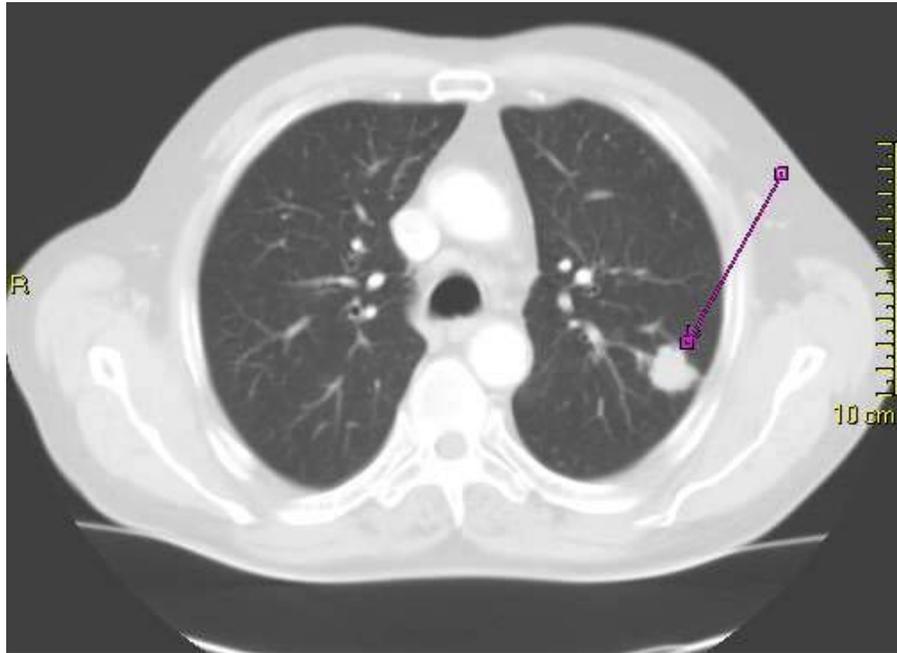
The most common benign coin lesion is a granuloma (inflammatory nodule), for example due to tuberculosis or a fungal infection. Other infectious causes include a pulmonary abscess, pneumonia (including *Pneumocystis carinii* pneumonia) or rarely nocardial infection or worm infection (such as dirofilariasis or dog heartworm infestation). Lung nodules can also occur in immune disorders such as rheumatoid arthritis or Wegener's granulomatosis.

An SPN can be found to be an arteriovenous malformation, a hematoma or an infarction zone. It may also be caused by bronchial atresia, sequestration, an inhaled foreign body or pleural plaque.

Initial evaluation

The medical history, physical examination and imaging results form the basis of the initial risk assessment and determine the further course of action. Most patients will have a CT scan.

Radiological features



A solitary pulmonary nodule (*indicated by the purple arrow*) on a CT scan of the chest

Several features help to distinguish benign conditions from possible lung cancer. The first parameter is the size of the lesion: the smaller, the less risk for malignant cancer. Benign causes tend to have a well defined border, whereas lobulated lesions or those with an irregular margin extending into the neighbouring tissue tend to be malignant.

If there is a central cavity, then a thin wall points to a benign cause whereas a thick wall is associated with malignancy (especially 4mm or less versus 16mm or more). In lung cancer, cavitation can represent central tumor necrosis (tissue death) or secondary abscess formation. If the walls of an airway are visible (air bronchogram), bronchioloalveolar carcinoma is a possibility.

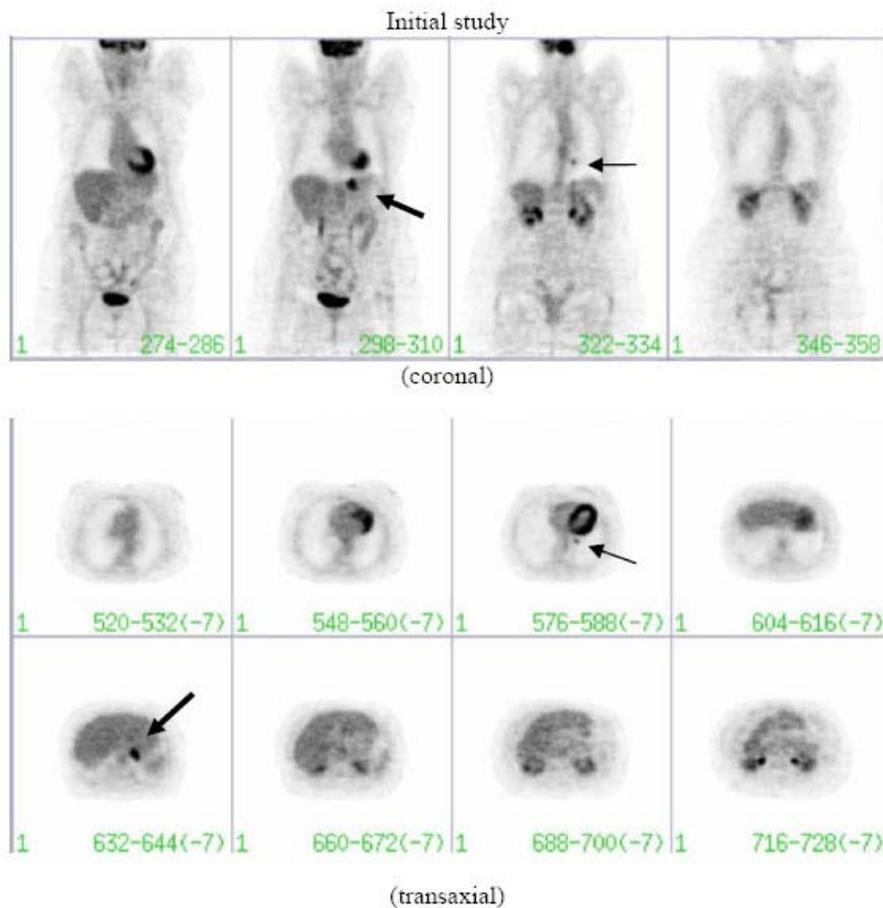
An SPN often contains calcifications. Certain patterns of calcification are reassuring, such as the popcorn-like appearance of hamartoma. An SPN with a density below 15 Hounsfield units on computed tomography tends to be benign, whereas malignant tumors often measure more than 20 Hounsfield units. Fatty tissue inside hamartomas will have a strongly negative value on the Hounsfield scale.

The growth velocity of a lesion is also informative: very fast or very slow growing tumors are rarely malignant, in contrary to inflammatory or congenital conditions. It is therefore important to retrieve previous imaging studies to see if a lesion was presented and how fast its volume is increasing. This is more difficult for nodules smaller than 1 centimeter. Moreover, the predictive value of stable lesion over a period of 2 years has been found to be rather low and unreliable.

Patient features

Several patient factors may influence the likelihood of a benign versus a malignant condition: these include previous exposure to smoke or other carcinogens such as asbestos, and previously diagnosed cancer or respiratory infections. A patient with airway symptoms, especially coughing up blood (hemoptysis), is more likely to have cancer compared to a patient with no respiratory symptoms.

Work-up



FDG-PET study of a 71-year-old woman with a solitary pulmonary nodule (*thin arrow*) in the left lower lobe near the heart. The scan also revealed abnormal increased activity at the gastro-esophageal junction (*thick arrow*). The final diagnosis was non-Hodgkin lymphoma at both sites.

The work-up in patients with a solitary pulmonary nodule is based on an initial risk assessment. If the risk of malignancy is thought to be low, follow-up imaging (usually serial CT scans) can be planned at a later time. The frequency of further scans can be determined by the patient's risk for cancer and the size of the nodule. If the initial impression is that there is a high likelihood of cancer, than a surgical intervention is appropriate (provided that the patient is fit for surgery).

If there is an intermediate risk of malignancy, further imaging with positron emission tomography (PET scan) is appropriate (if available). Around 95% of patients with a malignant nodule will have an abnormal PET scan, while around 78% of patients with a benign nodule will look normal on PET (this is the test sensitivity and specificity). Thus, an abnormal PET scan will reliably pick up cancer, but several other types of nodules (inflammatory or infectious, for example) will also show up on a PET scan. If the nodule has a diameter below 1 centimeter, PET scans are often avoided because there is an increased risk of falsely normal results. Cancerous lesions usually have a high metabolism on PET, as demonstrated by their high uptake of FDG (a radioactive sugar). If the lesion is found on further imaging to be suspicious, it should be surgically excised (via thoracotomy or video-assisted thoracic surgery) to confirm the diagnosis by microscopical examination.

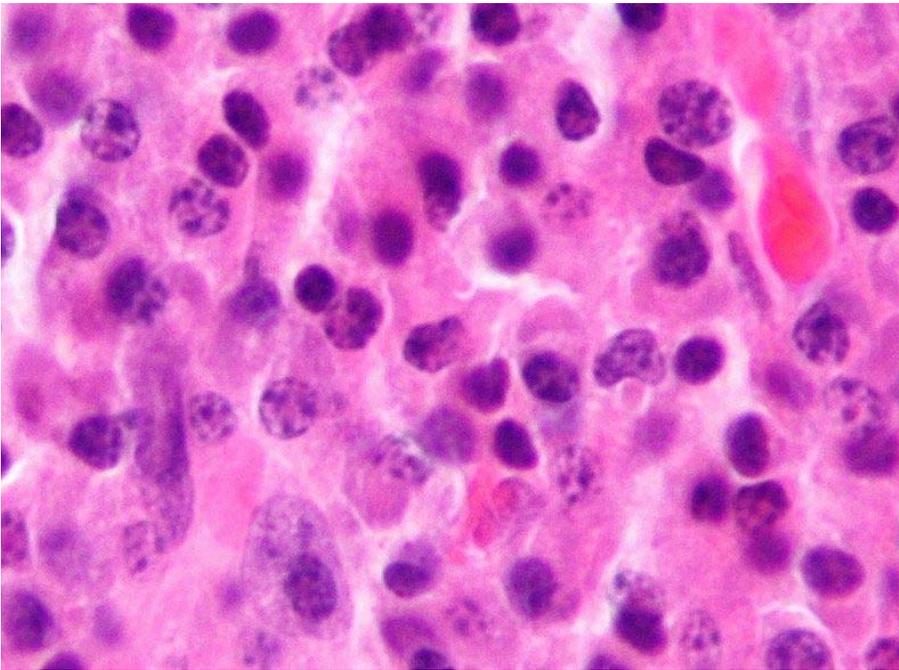
In selected cases, nodules can also be sampled through the airways using bronchoscopy or through the chest wall using needle aspiration (which can be done under CT guidance). Needle aspiration can only retrieve groups of cells for cytology and not a tissue cylinder or biopsy, precluding evaluation of the tissue architecture. Theoretically, this makes the diagnosis of benign conditions more difficult, although rates higher than 90% have been reported. Complications of the latter technique include hemorrhage into the lung and air leak in the pleural space between the lung and the chest wall (pneumothorax). However, not all these cases of pneumothorax need treatment with a chest tube.

Other imaging techniques include PET-CT (simultaneous PET scan and CT scan with superposition of the images), magnetic resonance imaging (MRI) or single photon emission computed tomography (SPECT).

Chapter 11

Hematological Malignancy

Hematological malignancy



Micrograph of a plasmacytoma, a **hematological malignancy**.

ICD-10 C81.-C96.

ICD-9 200-208

ICD-O: 9590-9999

MeSH D019337

Hematological malignancies are the types of cancer that affect blood, bone marrow, and lymph nodes. As the three are intimately connected through the immune system, a disease affecting one of the three will often affect the others as well: although lymphoma is technically a disease of the lymph nodes, it often spreads to the bone marrow, affecting the blood and occasionally producing a paraprotein.

While uncommon in solid tumors, chromosomal translocations are a common cause of these diseases. This commonly leads to a different approach in diagnosis and treatment of hematological malignancies.

Hematological malignancies are malignant neoplasms ("cancer"), and they are generally treated by specialists in hematology and/or oncology. "Hematology/oncology" is a single subspecialty of internal medicine (there are also surgical and radiation oncologists). Not all hematological disorders are malignant ("cancerous"); these other blood conditions may also be managed by a hematologist.

Hematological malignancies may derive from either of the two major blood cell lineages: myeloid and lymphoid cell lines. The myeloid cell line normally produces granulocytes, erythrocytes, thrombocytes, macrophages and mast cells; the lymphoid cell line produces B, T, NK and plasma cells. Lymphomas, lymphocytic leukemias, and myeloma are from the lymphoid line, while acute and chronic myelogenous leukemia, myelodysplastic syndromes and myeloproliferative diseases are myeloid in origin.

Classification and incidence

Taken together, hematological malignancies account for 9.5% of new cancer diagnoses in the United States. Within this category, lymphomas are more common than leukemias.

Historically, hematological malignancies have been most commonly divided by whether the malignancy is mainly located in the blood (leukemia) or in lymph nodes (lymphomas).

However, the influential WHO Classification (published in 2001) emphasized a greater emphasis on cell lineage.

Classic classification

Relative proportions of hematological malignancies in the United States:

Type of hematological malignancy	Percentage	Total
Leukemias	—	30.4%
Acute lymphoblastic leukemia (ALL)	4.0%	
Acute myelogenous leukemia (AML)	8.7%	
Chronic lymphocytic leukemia (CLL) sorted under lymphomas according to current WHO classification; called small lymphocytic lymphoma (SLL) when leukemic cells are absent.	10.2%	
Chronic myelogenous leukemia (CML)	3.7%	
Acute monocytic leukemia (AMOL)	0.7%	
Other leukemias	3.1%	

	Lymphomas	—	55.6%
Hodgkin's lymphomas (all four subtypes)		7.0%	
Non-Hodgkin's lymphomas (all subtypes)		48.6%	
	Myelomas		14.0%
Total			100%

By cell lineage

By cell lineage, hematological malignancies are classified according to their lineage in hematopoiesis:

- Lymphoid
 - Lymphoid leukemia
 - Lymphoma
- Myeloid leukemia

Diagnosis

For the analysis of a suspected *hematological malignancy*, a complete blood count and blood film are essential, as malignant cells can show in characteristic ways on light microscopy. When there is lymphadenopathy, a biopsy from a lymph node is generally undertaken surgically. In general, a bone marrow biopsy is part of the "work up" for the analysis of these diseases. All specimens are examined microscopically to determine the nature of the malignancy. A number of these diseases can now be classified by cytogenetics (AML, CML) or immunophenotyping (lymphoma, myeloma, CLL) of the malignant cells.

Treatment

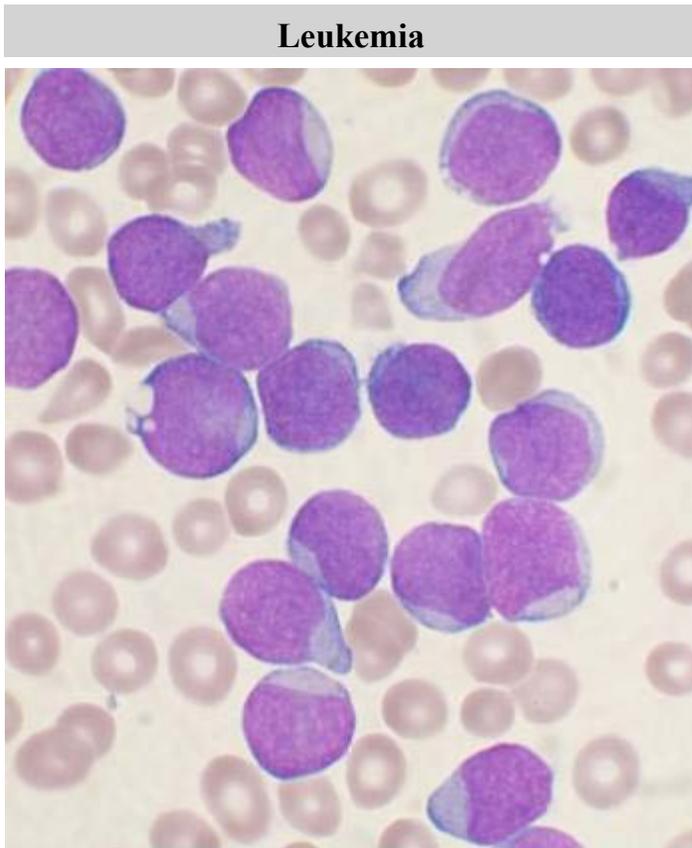
Treatment can occasionally consist of "watchful waiting" (e.g. in CLL) or symptomatic treatment (e.g. blood transfusions in MDS). The more aggressive forms of disease require treatment with chemotherapy, radiotherapy, immunotherapy and - in some cases - a bone marrow transplant.

Follow-up

If treatment has been successful ("complete" or "partial remission"), a patient is generally followed up at regular intervals to detect recurrence and monitor for "secondary malignancy" (an uncommon side-effect of some chemotherapy and radiotherapy regimens - the appearance of another form of cancer). In the follow-up, which should be done at pre-determined regular intervals, general anamnesis is combined with complete blood count and determination of lactate dehydrogenase or thymidine kinase in serum.

Chapter 12

Leukemia



A Wright's stained bone marrow aspirate smear of patient with precursor B-cell acute lymphoblastic leukemia.

ICD-10	C91.-C95.
ICD-9	208.9
ICD-O:	9800-9940
DiseasesDB	7431
MeSH	D007938

Leukemia (American English) or **leukaemia** (British English) is a type of cancer of the blood or bone marrow characterized by an abnormal increase of white blood cells. Leukemia is a broad term covering a spectrum of diseases. In turn, it is part of the even broader group of diseases called hematological neoplasms.

In 2000, approximately 256,000 children and adults around the world developed some form of leukemia, and 209,000 died from it. About 90% of all leukemias are diagnosed in adults.

Classification

Four major kinds of leukemia

Cell type	Acute	Chronic
Lymphocytic leukemia (or "lymphoblastic")	Acute lymphoblastic leukemia (ALL)	Chronic lymphocytic leukemia (CLL)
Myelogenous leukemia (also "myeloid" or "nonlymphocytic")	Acute myelogenous leukemia (AML)	Chronic myelogenous leukemia (CML)

Clinically and pathologically, leukemia is subdivided into a variety of large groups. The first division is between its *acute* and *chronic* forms:

- **Acute leukemia** is characterized by a rapid increase in the numbers of immature blood cells. Crowding due to such cells makes the bone marrow unable to produce healthy blood cells. Immediate treatment is required in acute leukemia due to the rapid progression and accumulation of the malignant cells, which then spill over into the bloodstream and spread to other organs of the body. Acute forms of leukemia are the most common forms of leukemia in children.
- **Chronic leukemia** is characterized by the excessive build up of relatively mature, but still abnormal, white blood cells. Typically taking months or years to progress, the cells are produced at a much higher rate than normal cells, resulting in many abnormal white blood cells in the blood. Whereas acute leukemia must be treated immediately, chronic forms are sometimes monitored for some time before treatment to ensure maximum effectiveness of therapy. Chronic leukemia mostly occurs in older people, but can theoretically occur in any age group.

Additionally, the diseases are subdivided according to which kind of blood cell is affected. This split divides leukemias into lymphoblastic or *lymphocytic leukemias* and myeloid or *myelogenous leukemias*:

- In lymphoblastic or **lymphocytic leukemias**, the cancerous change takes place in a type of marrow cell that normally goes on to form lymphocytes, which are infection-fighting immune system cells. Most lymphocytic leukemias involve a specific subtype of lymphocyte, the B cell.

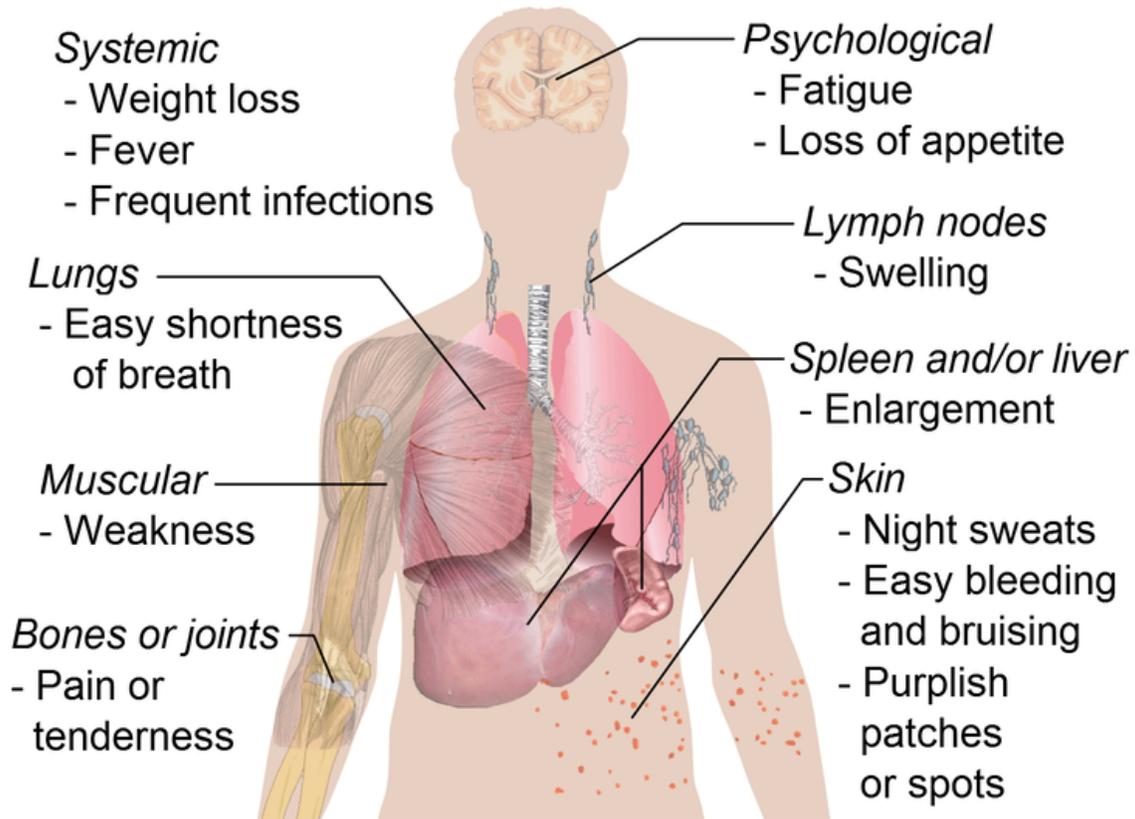
- In myeloid or **myelogenous leukemias**, the cancerous change takes place in a type of marrow cell that normally goes on to form red blood cells, some other types of white cells, and platelets.

Combining these two classifications provides a total of four main categories. Within these main categories, there are typically several subcategories. Finally, some rarer types are usually considered to be outside of this classification scheme.

- **Acute lymphoblastic leukemia (ALL)** is the most common type of leukemia in young children. This disease also affects adults, especially those age 65 and older. Standard treatments involve chemotherapy and radiation. The survival rates vary by age: 85% in children and 50% in adults. Subtypes include precursor B acute lymphoblastic leukemia, precursor T acute lymphoblastic leukemia, Burkitt's leukemia, and acute biphenotypic leukemia.
- **Chronic lymphocytic leukemia (CLL)** most often affects adults over the age of 55. It sometimes occurs in younger adults, but it almost never affects children. Two-thirds of affected people are men. The five-year survival rate is 75%. It is incurable, but there are many effective treatments. One subtype is B-cell prolymphocytic leukemia, a more aggressive disease.
- **Acute myelogenous leukemia (AML)** occurs more commonly in adults than in children, and more commonly in men than women. AML is treated with chemotherapy. The five-year survival rate is 40%. Subtypes of AML include acute promyelocytic leukemia, acute myeloblastic leukemia, and acute megakaryoblastic leukemia.
- **Chronic myelogenous leukemia (CML)** occurs mainly in adults. A very small number of children also develop this disease. Treatment is with imatinib (Gleevec) or other drugs. The five-year survival rate is 90%. One subtype is chronic monocytic leukemia.
- **Hairy cell leukemia (HCL)** is sometimes considered a subset of CLL, but does not fit neatly into this pattern. About 80% of affected people are adult men. There are no reported cases in young children. HCL is incurable, but easily treatable. Survival is 96% to 100% at ten years.
- **T-cell prolymphocytic leukemia (T-PLL)** is a very rare and aggressive leukemia affecting adults; somewhat more men than women are diagnosed with this disease. Despite its overall rarity, it is also the most common type of mature T cell leukemia; nearly all other leukemias involve B cells. It is difficult to treat, and the median survival is measured in months.
- **Large granular lymphocytic leukemia** may involve either T-cells or NK cells; like hairy cell leukemia, which involves solely B cells, it is a rare and indolent (not aggressive) leukemia.
- **Adult T-cell leukemia** is caused by human T-lymphotropic virus (HTLV), a virus similar to HIV. Like HIV, HTLV infects CD4+ T-cells and replicates within them; however, unlike HIV, it does not destroy them. Instead, HTLV "immortalizes" the infected T-cells, giving them the ability to proliferate abnormally.

Signs and symptoms

Common symptoms of **Leukemia**



Common symptoms of chronic or acute leukemia

Damage to the bone marrow, by way of displacing the normal bone marrow cells with higher numbers of immature white blood cells, results in a lack of blood platelets, which are important in the blood clotting process. This means people with leukemia may easily become bruised, bleed excessively, or develop pinprick bleeds (petechiae).

White blood cells, which are involved in fighting pathogens, may be suppressed or dysfunctional. This could cause the patient's immune system to be unable to fight off a simple infection or to start attacking other body cells. Because leukemia prevents the immune system from working normally, some patients experience frequent infection, ranging from infected tonsils, sores in the mouth, or diarrhea to life-threatening pneumonia or opportunistic infections.

Finally, the red blood cell deficiency leads to anemia, which may cause dyspnea and pallor.

Some patients experience other symptoms. These symptoms might include feeling sick, such as having fevers, chills, night sweats and other flu-like symptoms, or feeling

fatigued. Some patients experience nausea or a feeling of fullness due to an enlarged liver and spleen; this can result in unintentional weight loss. If the leukemic cells invade the central nervous system, then neurological symptoms (notably headaches) can occur.

All symptoms associated with leukemia can be attributed to other diseases. Consequently, leukemia is always diagnosed through medical tests.

The word *leukemia*, which means 'white blood', is derived from the disease's namesake high white blood cell counts that most leukemia patients have before treatment. The high number of white blood cells are apparent when a blood sample is viewed under a microscope. Frequently, these extra white blood cells are immature or dysfunctional. The excessive number of cells can also interfere with the level of other cells, causing a harmful imbalance in the blood count.

Some leukemia patients do not have high white blood cell counts visible during a regular blood count. This less-common condition is called *aleukemia*. The bone marrow still contains cancerous white blood cells which disrupt the normal production of blood cells, but they remain in the marrow instead of entering the bloodstream, where they would be visible in a blood test. For an aleukemic patient, the white blood cell counts in the bloodstream can be normal or low. Aleukemia can occur in any of the four major types of leukemia, and is particularly common in hairy cell leukemia.

Causes

No single known cause for all of the different types of leukemia exists. The known causes, which are not generally factors within the control of the average person, account for relatively few cases. The different leukemias likely have different causes.

Leukemia, like other cancers, results from somatic mutations in the DNA. Certain mutations produce leukemia by activating oncogenes or deactivating tumor suppressor genes, and thereby disrupting the regulation of cell death, differentiation or division. These mutations may occur spontaneously or as a result of exposure to radiation or carcinogenic substances, and are likely to be influenced by genetic factors.

Among adults, the known causes are natural and artificial ionizing radiation, a few viruses such as Human T-lymphotropic virus, and some chemicals, notably benzene and alkylating chemotherapy agents for previous malignancies. Use of tobacco is associated with a small increase in the risk of developing acute myeloid leukemia in adults. Cohort and case-control studies have linked exposure to some petrochemicals and hair dyes to the development of some forms of leukemia. A few cases of maternal-fetal transmission have been reported. Diet has very limited or no effect, although eating more vegetables may confer a small protective benefit.

Viruses have also been linked to some forms of leukemia. Experiments on mice and other mammals have demonstrated the relevance of retroviruses in leukemia, and human

retroviruses have also been identified. The first human retrovirus identified was Human T-lymphotropic virus, or HTLV-1, is known to cause adult T-cell leukemia.

Some people have a genetic predisposition towards developing leukemia. This predisposition is demonstrated by family histories and twin studies. The affected people may have a single gene or multiple genes in common. In some cases, families tend to develop the same kind of leukemia as other members; in other families, affected people may develop different forms of leukemia or related blood cancers.

In addition to these genetic issues, people with chromosomal abnormalities or certain other genetic conditions have a greater risk of leukemia. For example, people with Down syndrome have a significantly increased risk of developing forms of acute leukemia, and Fanconi anemia is a risk factor for developing acute myeloid leukemia.

Whether non-ionizing radiation causes leukemia has been studied for several decades. The International Agency for Research on Cancer expert working group undertook a detailed review of all data on static and extremely low frequency electromagnetic energy, which occurs naturally and in association with the generation, transmission, and use of electrical power. They concluded that there is limited evidence that high levels of ELF magnetic (but not electric) fields might cause childhood leukemia. Exposure to significant ELF magnetic fields might result in twofold excess risk for leukemia for children exposed to these high levels of magnetic fields. However, the report also says that methodological weaknesses and biases in these studies have likely caused the risk to be overstated. No evidence for a relationship to leukemia or another form of malignancy in adults has been demonstrated. Since exposure to such levels of ELF is relatively uncommon, the World Health Organization concludes that ELF exposure, if later proven to be causative, would account for just 100 to 2400 cases worldwide each year, representing 0.2 to 4.9% of the total incidence of childhood leukemia for that year (about 0.03 to 0.9% of all leukemias).

Diagnosis

Diagnosis is usually based on repeated complete blood counts and a bone marrow examination following observations of the symptoms, however, in rare cases blood tests may not show if a patient has leukemia, usually this is because the leukemia is in the early stages or has entered remission. A lymph node biopsy can be performed as well in order to diagnose certain types of leukemia in certain situations.

Following diagnosis, blood chemistry tests can be used to determine the degree of liver and kidney damage or the effects of chemotherapy on the patient. When concerns arise about visible damage due to leukemia, doctors may use an X-ray, MRI, or ultrasound. These can potentially view leukemia's effects on such body parts as bones (X-ray), the brain (MRI), or the kidneys, spleen, and liver (ultrasound). Finally, CT scans are rarely used to check lymph nodes in the chest.

Despite the use of these methods to diagnose whether or not a patient has leukemia, many people have not been diagnosed because many of the symptoms are vague, unspecific, and can refer to other diseases. For this reason, the American Cancer Society predicts that at least one-fifth of the people with leukemia have not yet been diagnosed.

Treatment

Most forms of leukemia are treated with pharmaceutical medications, typically combined into a multi-drug chemotherapy regimen. Some are also treated with radiation therapy. In some cases, a bone marrow transplant is useful.

Acute lymphoblastic

Management of ALL focuses on control of bone marrow and systemic (whole-body) disease. Additionally, treatment must prevent leukemic cells from spreading to other sites, particularly the central nervous system (CNS) e.g. monthly lumbar punctures. In general, ALL treatment is divided into several phases:

- *Induction chemotherapy* to bring about bone marrow remission. For adults, standard induction plans include prednisone, vincristine, and an anthracycline drug; other drug plans may include L-asparaginase or cyclophosphamide. For children with low-risk ALL, standard therapy usually consists of three drugs (prednisone, L-asparaginase, and vincristine) for the first month of treatment.
- *Consolidation therapy* or *intensification therapy* to eliminate any remaining leukemia cells. There are many different approaches to consolidation, but it is typically a high-dose, multi-drug treatment that is undertaken for a few months. Patients with low- to average-risk ALL receive therapy with antimetabolite drugs such as methotrexate and 6-mercaptopurine (6-MP). High-risk patients receive higher drug doses of these drugs, plus additional drugs.
- *CNS prophylaxis* (preventive therapy) to stop the cancer from spreading to the brain and nervous system in high-risk patients. Standard prophylaxis may include radiation of the head and/or drugs delivered directly into the spine.
- *Maintenance treatments* with chemotherapeutic drugs to prevent disease recurrence once remission has been achieved. Maintenance therapy usually involves lower drug doses, and may continue for up to three years.
- Alternatively, *allogeneic bone marrow transplantation* may be appropriate for high-risk or relapsed patients.

Chronic lymphocytic

Decision to treat

Hematologists base CLL treatment on both the stage and symptoms of the individual patient. A large group of CLL patients have low-grade disease, which does not benefit from treatment. Individuals with CLL-related complications or more advanced disease often benefit from treatment. In general, the indications for treatment are:

- Falling hemoglobin or platelet count
- Progression to a later stage of disease
- Painful, disease-related overgrowth of lymph nodes or spleen
- An increase in the rate of lymphocyte production

Typical treatment approach

CLL is probably incurable by present treatments. The primary chemotherapeutic plan is combination chemotherapy with chlorambucil or cyclophosphamide, plus a corticosteroid such as prednisone or prednisolone. The use of a corticosteroid has the additional benefit of suppressing some related autoimmune diseases, such as immunohemolytic anemia or immune-mediated thrombocytopenia. In resistant cases, single-agent treatments with nucleoside drugs such as fludarabine, pentostatin, or cladribine may be successful. Younger patients may consider allogeneic or autologous bone marrow transplantation.

Acute myelogenous

Many different anti-cancer drugs are effective for the treatment of AML. Treatments vary somewhat according to the age of the patient and according to the specific subtype of AML. Overall, the strategy is to control bone marrow and systemic (whole-body) disease, while offering specific treatment for the central nervous system (CNS), if involved.

In general, most oncologists rely on combinations of drugs for the initial, *induction phase* of chemotherapy. Such combination chemotherapy usually offers the benefits of early remission and a lower risk of disease resistance. *Consolidation* and *maintenance* treatments are intended to prevent disease recurrence. Consolidation treatment often entails a repetition of induction chemotherapy or the intensification chemotherapy with additional drugs. By contrast, maintenance treatment involves drug doses that are lower than those administered during the induction phase.

Chronic myelogenous

There are many possible treatments for CML, but the standard of care for newly diagnosed patients is imatinib (Gleevec) therapy. Compared to most anti-cancer drugs, it has relatively few side effects and can be taken orally at home. With this drug, more than 90% of patients will be able to keep the disease in check for at least five years, so that CML becomes a chronic, manageable condition.

In a more advanced, uncontrolled state, when the patient cannot tolerate imatinib, or if the patient wishes to attempt a permanent cure, then an allogeneic bone marrow transplantation may be performed. This procedure involves high-dose chemotherapy and radiation followed by infusion of bone marrow from a compatible donor. Approximately 30% of patients die from this procedure.

Hairy cell

Decision to treat

Patients with hairy cell leukemia who are symptom-free typically do not receive immediate treatment. Treatment is generally considered necessary when the patient shows signs and symptoms such as low blood cell counts (e.g., infection-fighting neutrophil count below 1.0 K/ μ L), frequent infections, unexplained bruises, anemia, or fatigue that is significant enough to disrupt the patient's everyday life.

Typical treatment approach

Patients who need treatment usually receive either one week of cladribine, given daily by intravenous infusion or a simple injection under the skin, or six months of pentostatin, given every four weeks by intravenous infusion. In most cases, one round of treatment will produce a prolonged remission.

Other treatments include rituximab infusion or self-injection with Interferon-alpha. In limited cases, the patient may benefit from *splenectomy* (removal of the spleen). These treatments are not typically given as the first treatment because their success rates are lower than cladribine or pentostatin.

T-cell prolymphocytic

Most patients with T-cell prolymphocytic leukemia, a rare and aggressive leukemia with a median survival of less than one year, require immediate treatment.

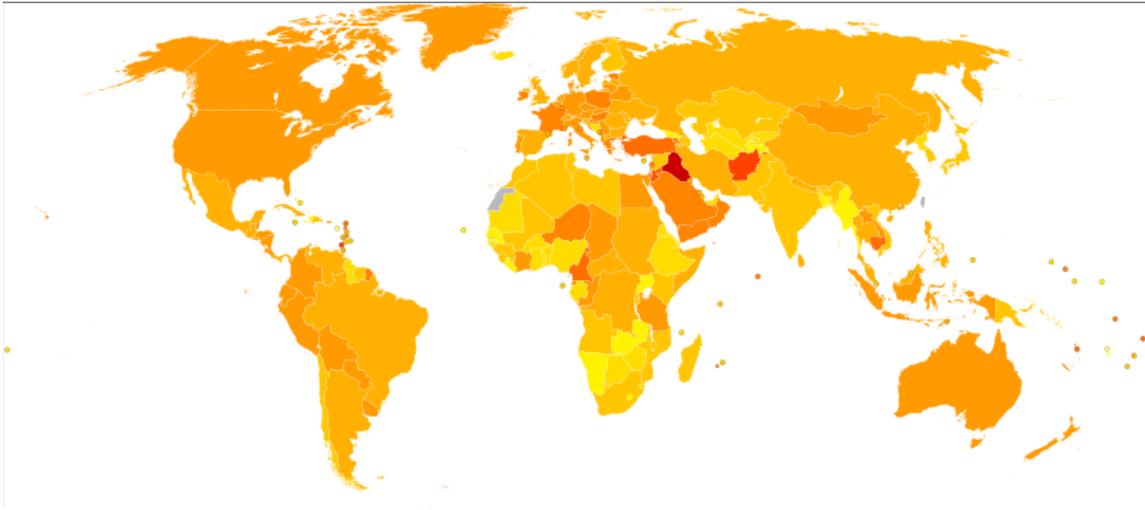
T-cell prolymphocytic leukemia is difficult to treat, and it does not respond to most available chemotherapeutic drugs. Many different treatments have been attempted, with limited success in certain patients: purine analogues (pentostatin, fludarabine, cladribine), chlorambucil, and various forms of combination chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone CHOP, cyclophosphamide, vincristine, prednisone [COP], vincristine, doxorubicin, prednisone, etoposide, cyclophosphamide, bleomycin VAPEC-B). Alemtuzumab (Campath), a monoclonal antibody that attacks white blood cells, has been used in treatment with greater success than previous options.

Some patients who successfully respond to treatment also undergo stem cell transplantation to consolidate the response.

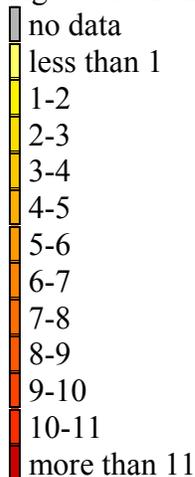
Juvenile myelomonocytic

Treatment for juvenile myelomonocytic leukemia can include splenectomy, chemotherapy, and bone marrow transplantation.

Epidemiology



Age-standardized death from leukemia per 100,000 inhabitants in 2004.



In 2000, approximately 256,000 children and adults around the world developed a form of leukemia, and 209,000 died from it. This represents about 3% of the almost seven million deaths due to cancer that year, and about 0.35% of all deaths from any cause. Of the sixteen separate sites the body compared, leukemia was the 12th most common class of neoplastic disease, and the 11th most common cause of cancer-related death.

About 245,000 people in the United States are affected with some form of leukemia, including those that have achieved remission or cure. Approximately 44,270 new cases of leukemia were diagnosed in the year of 2008 in the US. This represents 2.9% of all cancers (excluding simple basal cell and squamous cell skin cancers) in the United States, and 30.4% of all blood cancers.

Among children with some form of cancer, about a third have a type of leukemia, most commonly acute lymphoblastic leukemia. A type of leukemia is the second most common form of cancer in infants (under the age of 12 months) and the most common

form of cancer in older children. Boys are somewhat more likely to develop leukemia than girls, and white American children are almost twice as likely to develop leukemia than black American children. Only about 3% cancer diagnoses among adults are for leukemias, but because cancer is much more common among adults, more than 90% of all leukemias are diagnosed in adults.

History

Leukemia was first observed by pathologists Rudolf Virchow and John Hughes Bennett in 1845. Observing an abnormally large number of white blood cells in a blood sample from a patient, Virchow called the condition *Leukämie* in German, which he formed from the two Greek words *leukos* (λευκός), meaning "white", and *aima* (αίμα), meaning "blood". Around ten years after Virchow and Bennett's findings, pathologist Franz Ernst Christian Neumann found that one deceased leukemia patient's bone marrow was colored "dirty green-yellow" as opposed to the normal red. This finding allowed Neumann to conclude that a bone marrow problem was responsible for the abnormal blood of leukemia patients.

By 1900 leukemia was viewed as a family of diseases as opposed to a single disease. By 1947 Boston pathologist Sydney Farber believed from past experiments that aminopterin, a folic acid mimic, could potentially cure leukemia in children. The majority of the children with ALL who were tested showed signs of improvement in their bone marrow, but none of them actually were cured. This, however, led to further experiments.

In 1962, researchers Emil J. Freireich Jr. and Emil Frei III used combination chemotherapy to attempt to cure leukemia. The tests were successful with some patients surviving long after the tests.

Research

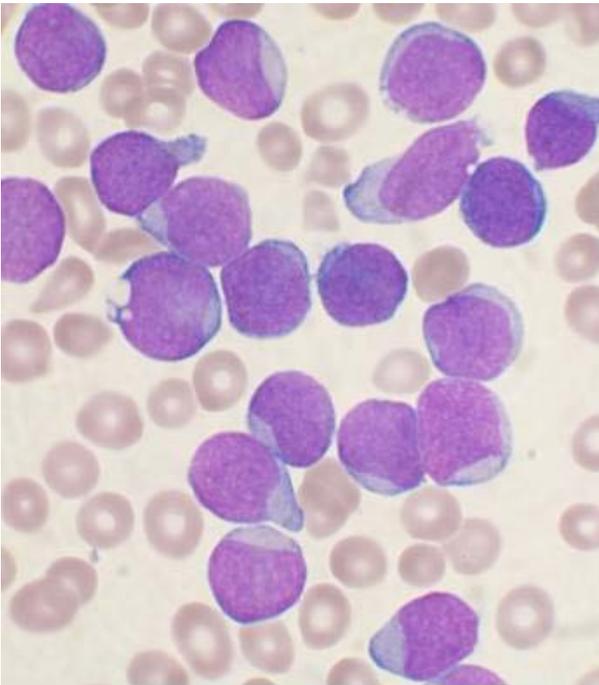
Significant research into the causes, prevalence, diagnosis, treatment, and prognosis of leukemia is being performed. Hundreds of clinical trials are being planned or conducted at any given time. Studies may focus on effective means of treatment, better ways of treating the disease, improving the quality of life for patients, or appropriate care in remission or after cures.

In general, there are two types of leukemia research: clinical/translational research and basic science research. Clinical/translational research focuses on studying the disease in a defined and generally immediately patient-applicable way, whereas basic science research studies the disease process at a distance and the results from such studies are generally less immediately useful to patients with the disease.

Chapter 13

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL)



ICD-10	C91.0
ICD-9	204.0
ICD-O:	M9835/3
DiseasesDB	195
eMedicine	med/3146 ped/2587
MeSH	D054198

Acute lymphoblastic leukemia (ALL), is a form of leukemia, or cancer of the white blood cells characterized by excess lymphoblasts.

Malignant, immature white blood cells continuously multiply and are overproduced in the bone marrow. ALL causes damage and death by crowding out normal cells in the bone marrow, and by spreading (infiltrating) to other organs. ALL is most common in childhood with a peak incidence at 2–5 years of age, and another peak in old age. The overall cure rate in children is about 80%, and about 45%-60% of adults have long-term disease-free survival.

Acute refers to the relatively short time course of the disease (being fatal in as little as a few weeks if left untreated) to differentiate it from the very different disease of Chronic Lymphocytic Leukemia which has a potential time course of many years. It is interchangeably referred to as Lymphocytic or Lymphoblastic. This refers to the cells that are involved, which if they were normal would be referred to as lymphocytes but are seen in this disease in a relatively immature (also termed 'blast') state.

Symptoms The signs and symptoms of ALL are variable but follow from bone marrow replacement and/or organ infiltration.

- Generalized weakness and Fatigue
- Anemia
- Frequent or unexplained [fever] and [infection]
- Weight loss and/or loss of appetite
- Excessive and unexplained bruising
- Bone pain, joint pain (caused by the spread of "blast" cells to the surface of the bone or into the joint from the marrow cavity)
- Breathlessness
- Enlarged lymph nodes, liver and/or spleen
- Pitting edema (swelling) in the lower limbs and/or abdomen
- Petechia, which are tiny red spots or lines in the skin due to low platelet levels

The signs and symptoms of ALL result from the lack of normal and healthy blood cells because they are crowded out by malignant and immature leukocytes (white blood cells). Therefore, people with ALL experience symptoms from malfunctioning of their erythrocytes (red blood cells), leukocytes, and platelets. Laboratory tests which might show abnormalities include blood count tests, renal function tests, electrolyte tests and liver enzyme tests.

Diagnosis

Diagnosing ALL begins with a medical history, physical examination, complete blood count, and blood smears. Because the symptoms are so general, many other diseases with similar symptoms must be excluded. Typically, the higher the white blood cell count, the worse the prognosis. Blast cells are seen on blood smear in majority of cases (blast cells are precursors (stem cells) to all immune cell lines). A bone marrow biopsy is conclusive proof of ALL. A lumbar puncture (also known as a spinal tap) will tell if the spinal column and brain has been invaded.

Pathological examination, cytogenetics (particularly the presence of Philadelphia chromosome) and immunophenotyping, establish whether the Myeloblastic (neutrophils, eosinophils or basophils) or Lymphoblastic (B lymphocytes or T lymphocytes) cells are the problem. RNA testing can establish how aggressive the disease is; different mutations have been associated with shorter or longer survival. Immunohistochemical testing may reveal TdT or CALLA antigens on the surface of leukemic cells. TdT is a protein expressed early in the development of pre-T and pre-B cells while CALLA is an antigen found in 80% of ALL cases and also in the "blast crisis" of CML.

Medical imaging (such as ultrasound or CT scanning) can find invasion of other organs commonly the lung, liver, spleen, lymph nodes, brain, kidneys and reproductive organs.

Pathophysiology

In general, cancer is caused by damage to DNA that leads to uncontrolled cellular growth and spread throughout the body, either by increasing chemical signals that cause growth, or interrupting chemical signals that control growth. Damage can be caused through the formation of fusion genes, as well as the dysregulation of a proto-oncogene via juxtaposition of it to the promotor of another gene, e.g. the T-cell receptor gene. This damage may be caused by environmental factors such as chemicals, drugs or radiation.

ALL is associated with exposure to radiation and chemicals in animals and humans. The association of radiation and leukemia in humans has been clearly established in studies of victims of the Chernobyl nuclear reactor and atom bombs in Hiroshima and Nagasaki. In animals, exposure to benzene and other chemicals can cause leukemia. Epidemiological studies have associated leukemia with workplace exposure to chemicals, but these studies are not as conclusive. Some evidence suggests that secondary leukemia can develop in individuals who are treated for other cancers with radiation and chemotherapy as a result of that treatment.

Cytogenetics

Cytogenetic translocations associated with specific molecular genetic abnormalities in ALL

Cytogenetic translocation	Molecular genetic abnormality	%
cryptic t(12;21)	TEL-AML1 fusion	25.4%
t(1;19)(q23;p13)	E2A-PBX (PBX1) fusion	4.8%
t(9;22)(q34;q11)	BCR-ABL fusion(P185)	1.6%
t(4;11)(q21;q23)	MLL-AF4 fusion	1.6%
t(8;14)(q24;q32)	IGH-MYC fusion	
t(11;14)(p13;q11)	TCR-RBTN2 fusion	

12:21 is the most common translocation and portends a good prognosis. 4:11 is the most common in children under 12 months and portends a poor prognosis.

Prognosis

The survival rate has improved from zero four decades ago, to 20-75 percent currently, largely due to clinical trials on new chemotherapeutic agents and improvements in stem cell transplantation (SCT) technology.

Five-year survival rates evaluate older, not current, treatments. New drugs, and matching treatment to the genetic characteristics of the blast cells, may improve those rates. The prognosis for ALL differs between individuals depending on a variety of factors:

- Sex: females tend to fare better than males.
- Ethnicity: Caucasians are more likely to develop acute leukemia than African-Americans, Asians and Hispanics and tend to have a better prognosis than non-Caucasians.
- Age at diagnosis: children between 1–10 years of age are most likely to develop ALL and to be cured of it. Cases in older patients are more likely to result from chromosomal abnormalities (e.g. the Philadelphia chromosome) that make treatment more difficult and prognoses poorer.
- White blood cell count at diagnosis of less than 50,000/ μ l
- Cancer spread into the Central nervous system (brain or spinal cord) has worse outcomes.
- Morphological, immunological, and genetic subtypes
- Patient's response to initial treatment
- Genetic disorders such as Down's Syndrome

Cytogenetics, the study of characteristic large changes in the chromosomes of cancer cells, is an important predictor of outcome.

Some cytogenetic subtypes have a worse prognosis than others. These include:

- A translocation between chromosomes 9 and 22, known as the Philadelphia chromosome, occurs in about 20% of adult and 5% in pediatric cases of ALL.
- A translocation between chromosomes 4 and 11 occurs in about 4% of cases and is most common in infants under 12 months.
- Not all translocations of chromosomes carry a poorer prognosis. Some translocations are relatively favorable. For example, Hyperdiploidy (>50 chromosomes) is a good prognostic factor.
- Genome-wide copy number changes can be assessed by conventional cytogenetics or virtual karyotyping. SNP array virtual karyotyping can detect copy number changes and LOH status, while arrayCGH can detect only copy number changes. Copy neutral LOH (acquired uniparental disomy) has been reported at key loci in ALL, such as CDKN2A gene, which have prognostic significance. SNP array virtual karyotyping can readily detect copy neutral LOH.

Array CGH, FISH, and conventional cytogenetics cannot detect copy neutral LOH.

Cytogenetic change	Risk category
Philadelphia chromosome	Poor prognosis
t(4;11)(q21;q23)	Poor prognosis
t(8;14)(q24.1;q32)	Poor prognosis
Complex karyotype (more than four abnormalities)	Poor prognosis
Low hypodiploidy or near triploidy	Poor prognosis
High hyperdiploidy (specifically, trisomy 4, 10, 17)	Good prognosis
del(9p)	Good prognosis

Correlation of prognosis with bone marrow cytogenetic finding in acute lymphoblastic leukemia

Prognosis	Cytogenetic findings
Favorable	Hyperdiploidy > 50 ; t (12;21)
Intermediate	Hyperdiploidy 47 -50; Normal(diploidy); del (6q); Rearrangements of 8q24
Unfavorable	Hypodiploidy-near haploidy; Near tetraploidy; del (17p); t (9;22); t (11q23)

Unclassified ALL is considered to have an intermediate prognosis.

Classification

As ALL is not a solid tumour, the TNM notation as used in solid cancers is of little use.

The FAB classification

Subtyping of the various forms of ALL used to be done according to the French-American-British (FAB) classification, which was used for all acute leukemias (including acute myelogenous leukemia, AML).

- ALL-L1: small uniform cells
- ALL-L2: large varied cells
- ALL-L3: large varied cells with vacuoles (bubble-like features)

Each subtype is then further classified by determining the surface markers of the abnormal lymphocytes, called immunophenotyping. There are 2 main immunologic types: pre-B cell and pre-T cell. The mature B-cell ALL (L3) is now classified as Burkitt's lymphoma/leukemia. Subtyping helps determine the prognosis and most appropriate treatment in treating ALL.

WHO proposed classification of acute lymphoblastic leukemia

The recent WHO International panel on ALL recommends that the FAB classification be abandoned, since the morphological classification has no clinical or prognostic relevance. It instead advocates the use of the immunophenotypic classification mentioned below.

1- Acute lymphoblastic leukemia/lymphoma Synonyms:Former Fab L1/L2

- i. Precursor B acute lymphoblastic leukemia/lymphoma. Cytogenetic subtypes:
 - t(12;21)(p12,q22) TEL/AML-1
 - t(1;19)(q23;p13) PBX/E2A
 - t(9;22)(q34;q11) ABL/BCR
 - T(V,11)(V;q23) V/MLL
- ii. Precursor T acute lymphoblastic leukemia/lymphoma

2- Burkitt's leukemia/lymphoma Synonyms:Former FAB L3

3- Biphenotypic acute leukemia

Variant Features of ALL

- 1- Acute lymphoblastic leukemia with cytoplasmic granules
- 2- Aplastic presentation of ALL
- 3- Acute lymphoblastic leukemia with eosinophilia
- 4- Relapse of lymphoblastic leukemia
- 5- Secondary ALL

Immunophenotyping in the diagnosis and classification of ALL

The use of a TdT assay and a panel of monoclonal antibodies (MoAbs) to T cell and B cell associated antigens will identify almost all cases of ALL.

Immunophenotypic categories of acute lymphoblastic leukemia (ALL)

Types	FAB Class	Tdt	T cell associate antigen	B cell associate antigen	c Ig	s Ig
Precursor B	L1,L2	+	-	+	-/+	-
Precursor T	L1,L2	+	+	-	-	-
B-cell	L3	-	-	+	-	+

Treatment

The earlier acute lymphocytic leukemia is detected, the more effective the treatment. The aim is to induce a lasting remission, defined as the absence of detectable cancer cells in the body (usually less than 5% blast cells on the bone marrow).

Treatment for acute leukemia can include chemotherapy, steroids, radiation therapy, intensive combined treatments (including bone marrow or stem cell transplants), and growth factors.

Chemotherapy

Chemotherapy is the initial treatment of choice. Most ALL patients will receive a combination of different treatments. There are no surgical options, due to the body-wide distribution of the malignant cells. In general, cytotoxic chemotherapy for ALL combines multiple antileukemic drugs in various combinations. Chemotherapy for ALL consists of three phases: remission induction, intensification, and maintenance therapy.

Phase	Description	Agents
Remission induction	The aim of remission induction is to rapidly kill most tumor cells and get the patient into remission. This is defined as the presence of less than 5% leukemic blasts in the bone marrow, normal blood cells and absence of tumor cells from blood, and absence of other signs and symptoms of the disease. CNS prophylaxis should begin during this phase of treatment and continue during the consolidation/intensification period. The rationale is based on the presence of CNS involvement in 10%-40% of adult patients at diagnosis.	Combination of Prednisolone or dexamethasone, vincristine, asparaginase (better tolerance in pediatric patients), and daunorubicin (used in Adult ALL) is used to induce remission.

Consolidation/Intensification	<p>Intensification uses high doses of intravenous multidrug chemotherapy to further reduce tumor burden. Since ALL cells sometimes penetrate the Central Nervous System (CNS), most protocols include delivery of chemotherapy into the CNS fluid (termed intrathecal chemotherapy). Some centers deliver the drug through Ommaya reservoir (a device surgically placed under the scalp and used to deliver drugs to the CNS fluid and to extract CNS fluid for various tests). Other centers would perform multiple lumbar punctures as needed for testing and treatment delivery.</p>	<p>Typical intensification protocols use vincristine, cyclophosphamide, cytarabine, daunorubicin, etoposide, thioguanine or mercaptopurine given as blocks in different combinations. For CNS protection, intrathecal methotrexate or cytarabine is usually used combined with or without cranio-spinal irradiation (the use of radiation therapy to the head and spine). Central nervous system relapse is treated with intrathecal administration of hydrocortisone, methotrexate, and cytarabine. For this purpose, daily oral mercaptopurine, once weekly oral methotrexate, once monthly 5-day course of intravenous vincristine and oral corticosteroids are usually used. The length of maintenance therapy is 3 years for boys, 2 years for girls and adults.</p>
Maintenance therapy	<p>The aim of maintenance therapy is to kill any residual cell that was not killed by remission induction, and intensification regimens. Although such cells are few, they will cause relapse if not eradicated.</p>	

As the chemotherapy regimens can be intensive and protracted (often about 2 years in case of the GMALL UKALL, HyperCVAD or CALGB protocols; for ALL about 3 years, 2 months for males on COG protocols; 2 years, 2 months for females- longer for males as testicles are a potential reservoir), many patients have an intravenous catheter inserted into a large vein (termed a central venous catheter or a Hickman line), or a Portacath, a cone-shaped port with a silicone nose that is surgically planted under the skin, usually near the collar bone, and the most effective product available, due to low infection risks and the long-term viability of a portacath.

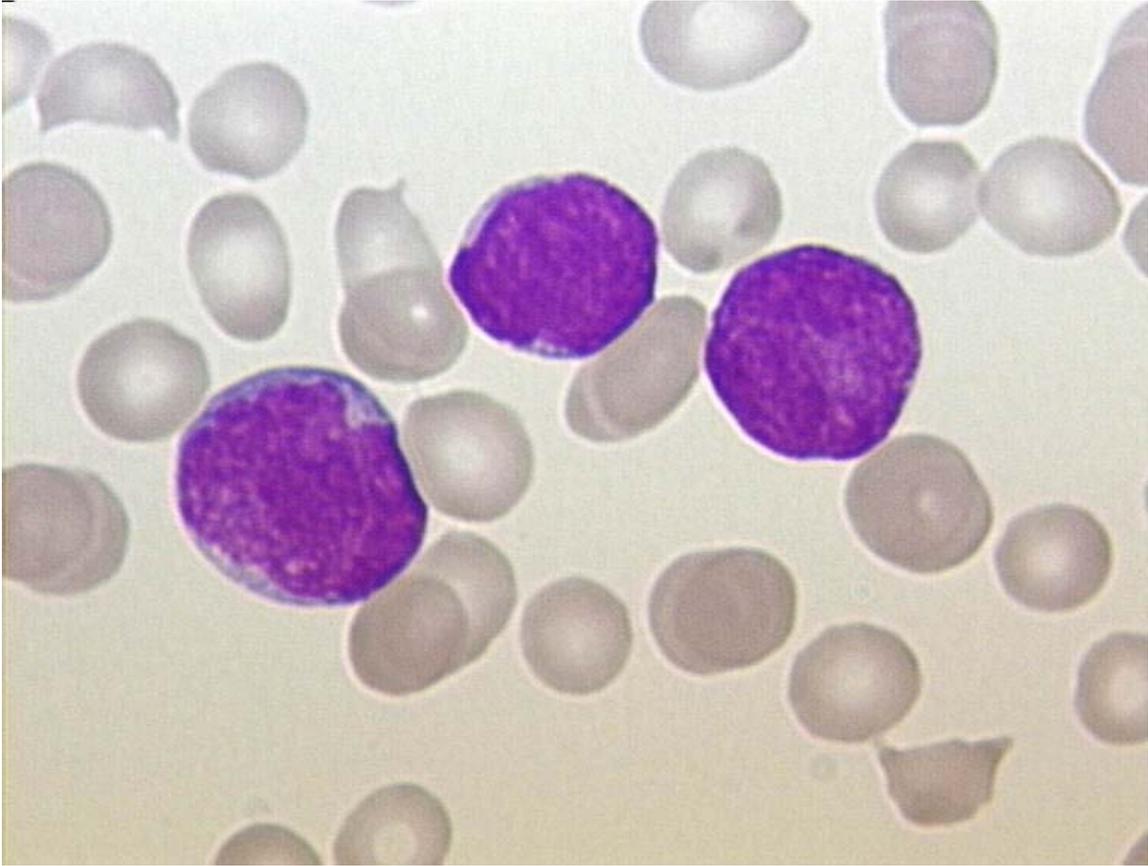
Radiation therapy

Radiation therapy (or radiotherapy) is used on painful bony areas, in high disease burdens, or as part of the preparations for a bone marrow transplant (total body irradiation). Radiation in the form of whole brain radiation is also used for central nervous system prophylaxis, to prevent recurrence of leukemia in the brain. Whole brain prophylaxis radiation used to be a common method in treatment of children's ALL. Recent studies showed that CNS chemotherapy provided results as favorable but with less developmental side effects. As a result, the use of whole brain radiation has been more limited. Most specialists in adult leukemia have abandoned the use o

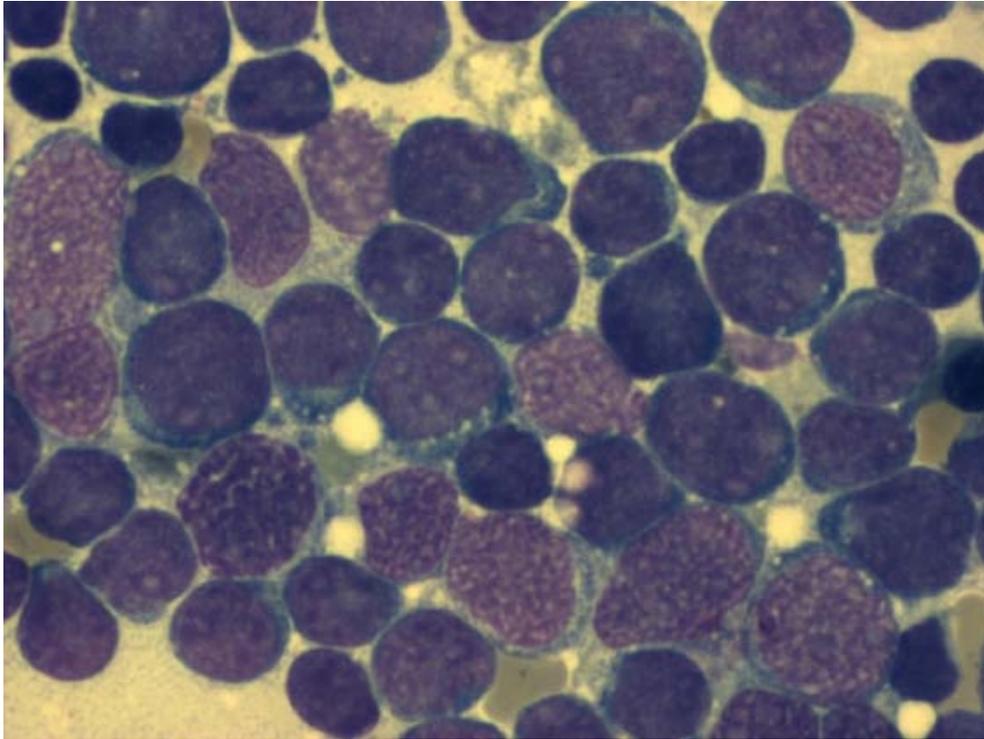
Epidemiology

In the US, the incidence of ALL is roughly 6000 new cases per year (as of 2009), or approximately 1 in 50,000. ALL accounts for approximately 70 percent of all childhood leukemia cases (ages 0 to 19 years), making it the most common type of childhood cancer. It has a peak incident rate of 2–5 years old, decreasing in incidence with increasing age before increasing again at around 50 years old. ALL is slightly more common in males than females. There is an increased incidence in people with Down Syndrome, Fanconi anemia, Bloom syndrome, Ataxia telangiectasia, X-linked agammaglobulinemia and Severe combined immunodeficiency.

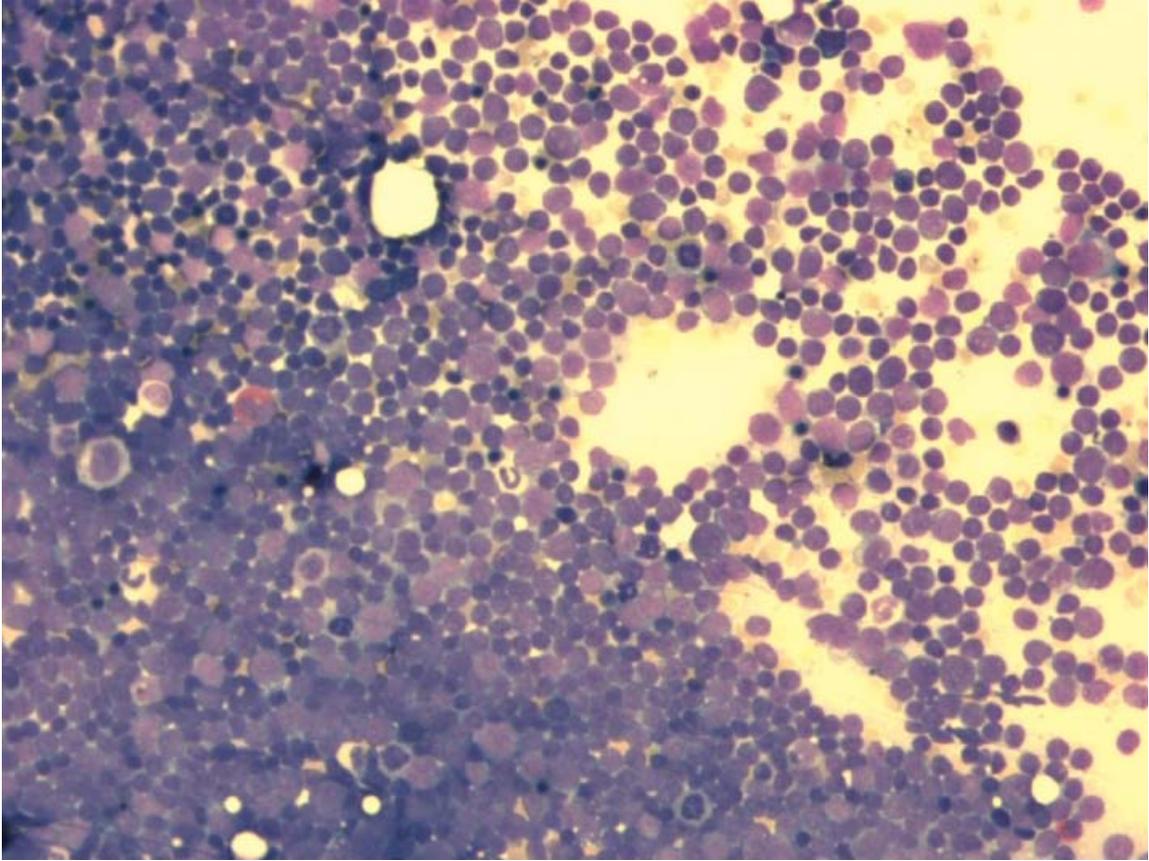
Additional images



acute lymphoblastic leukemia (ALL), peripheral blood of a child, Papanheim stain



bone marrow smear (large magnification) from a patient with acute lymphoblastic leukemia

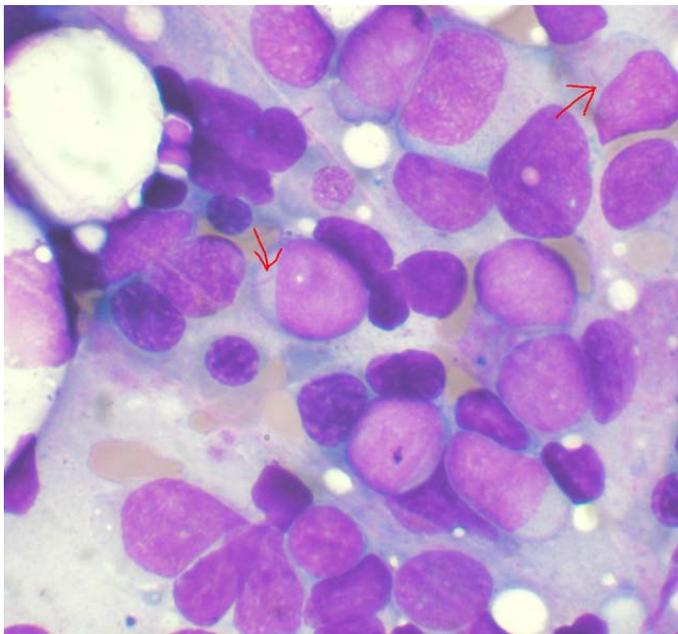


bone marrow smear from a patient with acute lymphoblastic leukemia

Chapter 14

Acute Myeloid Leukemia

Acute myeloid leukemia



Bone marrow aspirate showing acute myeloid leukemia.

Arrows indicate Auer rods.

ICD-10	C92.0
ICD-9	205.0
ICD-O:	M9861/3
OMIM	602439
DiseasesDB	203
eMedicine	med/34
MeSH	D015470

Acute myeloid leukemia (AML), also known as **acute myelogenous leukemia**, is a cancer of the myeloid line of blood cells, characterized by the rapid growth of abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells. AML is the most common acute leukemia affecting adults, and its incidence increases with age. Although AML is a relatively rare disease, accounting for approximately 1.2% of cancer deaths in the United States, its incidence is expected to increase as the population ages.

The symptoms of AML are caused by replacement of normal bone marrow with leukemic cells, which causes a drop in red blood cells, platelets, and normal white blood cells. These symptoms include fatigue, shortness of breath, easy bruising and bleeding, and increased risk of infection. Although several risk factors for AML have been identified, the specific cause of the disease remains unclear. As an acute leukemia, AML progresses rapidly and is typically fatal within weeks or months if left untreated.

AML has several subtypes; treatment and prognosis varies among subtypes. Five-year survival varies from 15–70%, and relapse rate varies from 78–33%, depending on subtype. AML is treated initially with chemotherapy aimed at inducing a remission; patients may go on to receive additional chemotherapy or a hematopoietic stem cell transplant. Recent research into the genetics of AML has resulted in the availability of tests that can predict which drug or drugs may work best for a particular patient, as well as how long that patient is likely to survive.

Classification

The two most commonly used classification schemata for AML, are the older French-American-British (FAB) system and the newer World Health Organization (WHO) system.

World Health Organization

The World Health Organization (WHO) classification of acute myeloid leukemia attempts to be more clinically useful and to produce more meaningful prognostic information than the FAB criteria. Each of the WHO categories contains numerous descriptive sub-categories of interest to the hematopathologist and oncologist; however, most of the clinically significant information in the WHO schema is communicated via categorization into one of the subtypes listed below.

The WHO subtypes of AML are:

Name	Description	ICD-O
AML with characteristic genetic abnormalities	<p>Includes:</p> <ul style="list-style-type: none"> • AML with translocations between chromosome 8 and 21 [t(8;21)] (ICD-O 9896/3); RUNX1/RUNX1T1 • AML with inversions in chromosome 16 [inv(16)] (ICD-O 9871/3); CBFB/MYH11 • APL with translocations between chromosome 15 and 17 [t(15;17)] (ICD-O 9866/3); RARA;PML 	Multiple
AML with multilineage dysplasia	<p>Patients with AML in this category generally have a high rate of remission and a better prognosis compared to other types of AML.</p> <p>This category includes patients who have had a prior myelodysplastic syndrome (MDS) or myeloproliferative disease (MPD) that transforms into AML. This category of AML occurs most often in elderly patients and often has a worse prognosis.</p>	M9895/3
AML and MDS, therapy-related	<p>This category includes patients who have had prior chemotherapy and/or radiation and subsequently develop AML or MDS. These leukemias may be characterized by specific chromosomal abnormalities, and often carry a worse prognosis.</p>	M9920/3
AML not otherwise categorized	<p>Includes subtypes of AML that do not fall into the above categories.</p>	M9861/3

Acute leukemias of ambiguous lineage (also known as mixed phenotype or biphenotypic acute leukemia) occur when the leukemic cells can not be classified as either myeloid or lymphoid cells, or where both types of cells are present.

French-American-British

The French-American-British (FAB) classification system divides AML into 8 subtypes, M0 through to M7, based on the type of cell from which the leukemia developed and its degree of maturity. This is done by examining the appearance of the malignant cells under light microscopy and/or by using cytogenetics to characterize any underlying chromosomal abnormalities. The subtypes have varying prognoses and responses to therapy. Although the WHO classification may be more useful, the FAB system is still widely used.

There are eight FAB subtypes.

Type	Name	Cytogenetics
M0	minimally differentiated acute myeloblastic leukemia	
M1	acute myeloblastic leukemia, without maturation	
M2	acute myeloblastic leukemia, with granulocytic maturation	t(8;21)(q22;q22), t(6;9)
M3	promyelocytic, or acute promyelocytic leukemia (APL)	t(15;17)
M4	acute myelomonocytic leukemia	inv(16)(p13q22), del(16q)
M4eo	myelomonocytic together with bone marrow eosinophilia	inv(16), t(16;16)
M5	acute monoblastic leukemia (M5a) or acute monocytic leukemia (M5b)	del(11q), t(9;11), t(11;19)
M6	acute erythroid leukemias, including erythroleukemia (M6a) and very rare pure erythroid leukemia (M6b)	
M7	acute megakaryoblastic leukemia	t(1;22)
M8	acute basophilic leukemia	

Uncommon phenotypes of acute myeloid leukemia

The morphologic subtypes of AML include many exceedingly rare types not included in the FAB system. All of them except acute myeloid dendritic cell leukemia acute eosinophilic leukemia and are included in the WHO classification. The following list shows these subtypes.

- Acute basophilic leukemia
- Acute eosinophilic leukemia
- Mast cell leukemia
- Acute myeloid dendritic cell leukemia
- Acute panmyelosis with myelofibrosis
- Myeloid sarcoma.

Signs and symptoms



Diffusely swollen gums due to infiltration by leukemic cells in a person with acute myelomonocytic leukemia

Most signs and symptoms of AML are caused by the replacement of normal blood cells with leukemic cells. A lack of normal white blood cell production makes the patient susceptible to infections; while the leukemic cells themselves are derived from white blood cell precursors, they have no infection-fighting capacity. A drop in red blood cell count (anemia) can cause fatigue, paleness, and shortness of breath. A lack of platelets can lead to easy bruising or bleeding with minor trauma.

The early signs of AML are often vague and non-specific, and may be similar to those of influenza or other common illnesses. Some generalized symptoms include fever, fatigue, weight loss or loss of appetite, shortness of breath, anemia, easy bruising or bleeding, petechiae (flat, pin-head sized spots under the skin caused by bleeding), bone and joint pain, and persistent or frequent infections.

Enlargement of the spleen may occur in AML, but it is typically mild and asymptomatic. Lymph node swelling is rare in AML, in contrast to acute lymphoblastic leukemia. The skin is involved about 10% of the time in the form of leukemia cutis. Rarely, Sweet's syndrome, a paraneoplastic inflammation of the skin, can occur with AML.

Some patients with AML may experience swelling of the gums because of infiltration of leukemic cells into the gum tissue. Rarely, the first sign of leukemia may be the development of a solid leukemic mass or tumor outside of the bone marrow, called a chloroma. Occasionally, a person may show no symptoms, and the leukemia may be discovered incidentally during a routine blood test.

Causes

A number of risk factors for developing AML have been identified, including: other blood disorders, chemical exposures, ionizing radiation, and genetics.

Preleukemia

"Preleukemic" blood disorders such as myelodysplastic syndrome or myeloproliferative disease can evolve into AML; the exact risk depends on the type of MDS/MPS.

Chemical exposure

Exposure to anti-cancer chemotherapy, in particular alkylating agents, can increase the risk of subsequently developing AML. The risk is highest about 3–5 years after chemotherapy. Other chemotherapy agents, specifically epipodophyllotoxins and anthracyclines, have also been associated with treatment-related leukemia. These treatment-related leukemias are often associated with specific chromosomal abnormalities in the leukemic cells.

Occupational chemical exposure to benzene and other aromatic organic solvents is controversial as a cause of AML. Benzene and many of its derivatives are known to be carcinogenic *in vitro*. While some studies have suggested a link between occupational exposure to benzene and increased risk of AML, others have suggested that the attributable risk, if any, is slight.

Radiation

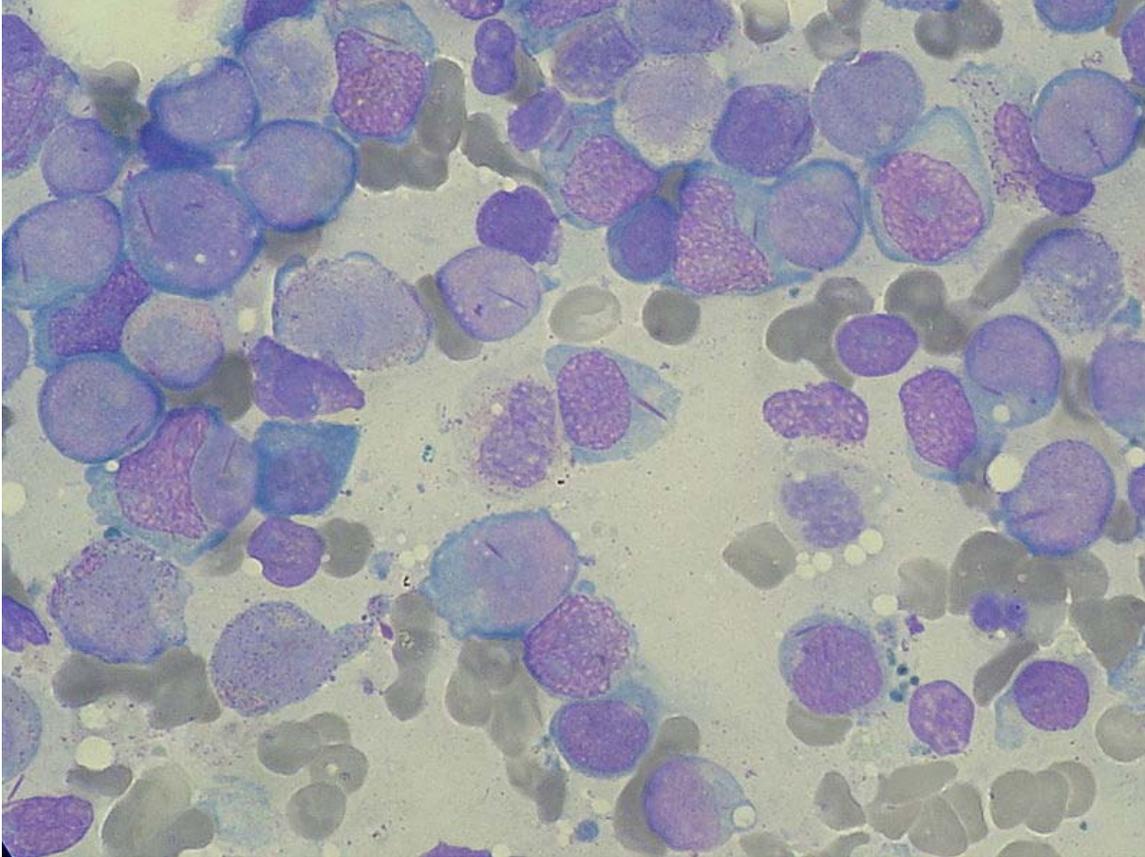
Ionizing radiation exposure can increase the risk of AML. Survivors of the atomic bombings of Hiroshima and Nagasaki had an increased rate of AML, as did radiologists exposed to high levels of X-rays prior to the adoption of modern radiation safety practices.

Genetics

A hereditary risk for AML appears to exist. There are numerous reports of multiple cases of AML developing in a family at a rate higher than predicted by chance alone. The risk of developing AML is increased threefold in first-degree relatives of patients with AML.

Several congenital conditions may increase the risk of leukemia; the most common is probably Down syndrome, which is associated with a 10- to 18-fold increase in the risk of AML.

Diagnosis



Bone marrow: myeloblasts with Auer rods seen in Acute Myeloid Leukemia (AML)

The first clue to a diagnosis of AML is typically an abnormal result on a complete blood count. While an excess of abnormal white blood cells (leukocytosis) is a common finding, and leukemic blasts are sometimes seen, AML can also present with isolated decreases in platelets, red blood cells, or even with a *low* white blood cell count (leukopenia). While a presumptive diagnosis of AML can be made via examination of the peripheral blood smear when there are circulating leukemic blasts, a definitive diagnosis usually requires an adequate bone marrow aspiration and biopsy.

Marrow or blood is examined via light microscopy as well as flow cytometry to diagnose the presence of leukemia, to differentiate AML from other types of leukemia (e.g. acute lymphoblastic leukemia), and to classify the subtype of disease. A sample of marrow or blood is typically also tested for chromosomal translocations by routine cytogenetics or fluorescent in situ hybridization. Genetic studies may also be performed to look for specific mutations in genes such as FLT3, nucleophosmin, and KIT, which may influence the outcome of the disease.

Cytochemical stains on blood and bone marrow smears are helpful in the distinction of AML from ALL and in subclassification of AML. The combination of a myeloperoxidase or Sudan black stain and a non specific esterase stain will provide the desired information in most cases. The myeloperoxidase or Sudan black reactions are most useful in establishing the identity of AML and distinguishing from ALL. The non-specific esterase stain is used to identify a monocytic component in AMLs and to distinguish a poorly differentiated monoblastic leukemia from ALL.

The diagnosis and classification of AML can be challenging, and should be performed by a qualified hematopathologist or hematologist. In straightforward cases, the presence of certain morphologic features (such as Auer rods) or specific flow cytometry results can distinguish AML from other leukemias; however, in the absence of such features, diagnosis may be more difficult.

According to the widely used WHO criteria, the diagnosis of AML is established by demonstrating involvement of more than 20% of the blood and/or bone marrow by leukemic myeloblasts. AML must be carefully differentiated from "pre-leukemic" conditions such as myelodysplastic or myeloproliferative syndromes, which are treated differently.

Because acute promyelocytic leukemia (APL) has the highest curability and requires a unique form of treatment, it is important to quickly establish or exclude the diagnosis of this subtype of leukemia. Fluorescent in situ hybridization performed on blood or bone marrow is often used for this purpose, as it readily identifies the chromosomal translocation (t[15;17]) that characterizes APL.

Pathophysiology

The malignant cell in AML is the myeloblast. In normal hematopoiesis, the myeloblast is an immature precursor of myeloid white blood cells; a normal myeloblast will gradually mature into a mature white blood cell. However, in AML, a single myeloblast accumulates genetic changes which "freeze" the cell in its immature state and prevent differentiation. Such a mutation alone does not cause leukemia; however, when such a "differentiation arrest" is combined with other mutations which disrupt genes controlling proliferation, the result is the uncontrolled growth of an immature clone of cells, leading to the clinical entity of AML.

Much of the diversity and heterogeneity of AML stems from the fact that leukemic transformation can occur at a number of different steps along the differentiation pathway. Modern classification schemes for AML recognize that the characteristics and behavior of the leukemic cell (and the leukemia) may depend on the stage at which differentiation was halted.

Specific cytogenetic abnormalities can be found in many patients with AML; the types of chromosomal abnormalities often have prognostic significance. The chromosomal translocations encode abnormal fusion proteins, usually transcription factors whose

altered properties may cause the "differentiation arrest." For example, in acute promyelocytic leukemia, the t(15;17) translocation produces a PML-RAR α fusion protein which binds to the retinoic acid receptor element in the promoters of several myeloid-specific genes and inhibits myeloid differentiation.

The clinical signs and symptoms of AML result from the fact that, as the leukemic clone of cells grows, it tends to displace or interfere with the development of normal blood cells in the bone marrow. This leads to neutropenia, anemia, and thrombocytopenia. The symptoms of AML are in turn often due to the low numbers of these normal blood elements. In rare cases, patients can develop a *chloroma*, or solid tumor of leukemic cells outside the bone marrow, which can cause various symptoms depending on its location.

Treatment

First-line treatment of AML consists primarily of chemotherapy, and is divided into two phases: *induction* and *postremission* (or *consolidation*) therapy. The goal of *induction* therapy is to achieve a complete remission by reducing the amount of leukemic cells to an undetectable level; the goal of *consolidation* therapy is to eliminate any residual undetectable disease and achieve a cure. Hematopoietic stem cell transplantation is usually considered if induction chemotherapy fails or after a patient relapses, although transplantation is also sometimes used as front-line therapy for patients with high-risk disease.

Induction

All FAB subtypes except M3 are usually given induction chemotherapy with cytarabine (ara-C) and an anthracycline (such as daunorubicin or idarubicin). This induction chemotherapy regimen is known as "7+3" (or "3+7"), because the cytarabine is given as a continuous IV infusion for seven consecutive days while the anthracycline is given for three consecutive days as an IV push. Up to 70% of patients will achieve a remission with this protocol. Other alternative induction regimens, including high-dose cytarabine alone or investigational agents, may also be used. Because of the toxic effects of therapy, including myelosuppression and an increased risk of infection, induction chemotherapy may not be offered to the very elderly, and the options may include less intense chemotherapy or palliative care.

The M3 subtype of AML, also known as acute promyelocytic leukemia, is almost universally treated with the drug ATRA (all-*trans*-retinoic acid) in addition to induction chemotherapy. Care must be taken to prevent disseminated intravascular coagulation (DIC), complicating the treatment of APL when the promyelocytes release the contents of their granules into the peripheral circulation. APL is eminently curable with well-documented treatment protocols.

The goal of the induction phase is to reach a *complete remission*. Complete remission does not mean that the disease has been cured; rather, it signifies that no disease can be detected with available diagnostic methods. Complete remission is obtained in about

50%–75% of newly diagnosed adults, although this may vary based on the prognostic factors described above. The length of remission depends on the prognostic features of the original leukemia. In general, all remissions will fail without additional *consolidation* therapy.

Consolidation

Even after complete remission is achieved, leukemic cells likely remain in numbers too small to be detected with current diagnostic techniques. If no further *postremission* or consolidation therapy is given, almost all patients will eventually relapse. Therefore, more therapy is necessary to eliminate non-detectable disease and prevent relapse — that is, to achieve a cure.

The specific type of postremission therapy is individualized based on a patient's prognostic factors and general health. For good-prognosis leukemias (i.e. inv(16), t(8;21), and t(15;17)), patients will typically undergo an additional 3–5 courses of intensive chemotherapy, known as *consolidation* chemotherapy. For patients at high risk of relapse (e.g. those with high-risk cytogenetics, underlying MDS, or therapy-related AML), allogeneic stem cell transplantation is usually recommended if the patient is able to tolerate a transplant and has a suitable donor. The best postremission therapy for intermediate-risk AML (normal cytogenetics or cytogenetic changes not falling into good-risk or high-risk groups) is less clear and depends on the specific situation, including the age and overall health of the patient, the patient's personal values, and whether a suitable stem cell donor is available.

For patients who are not eligible for a stem cell transplant, immunotherapy with a combination of histamine dihydrochloride (Ceplene) and interleukin-2 (Proleukin) after the completion of consolidation has been shown to reduce the absolute relapse risk by 14%, translating to a 50% increase in the likelihood of maintained remission.

Relapsed AML

For patients with relapsed AML, the only proven potentially curative therapy is a hematopoietic stem cell transplant, if one has not already been performed. In 2000, the monoclonal antibody-linked cytotoxic agent gemtuzumab ozogamicin (Mylotarg) was approved in the United States for patients aged more than 60 years with relapsed AML who are not candidates for high-dose chemotherapy.

Patients with relapsed AML who are not candidates for stem cell transplantation, or who have relapsed after a stem cell transplant, may be offered treatment in a clinical trial, as conventional treatment options are limited. Agents under investigation include cytotoxic drugs such as clofarabine as well as targeted therapies such as farnesyl transferase inhibitors, decitabine, and inhibitors of MDR1 (multidrug-resistance protein). Since treatment options for relapsed AML are so limited, another option which may be offered is palliative care.

For relapsed acute promyelocytic leukemia (APL), arsenic trioxide has been tested in trials and approved by the Food and Drug Administration. Like ATRA, arsenic trioxide does not work with other subtypes of AML.

Prognosis



t(9;11)

Chromosomal translocation (9;11), associated with AML

Acute myeloid leukemia is a curable disease; the chance of cure for a specific patient depends on a number of prognostic factors.

Cytogenetics

The single most important prognostic factor in AML is cytogenetics, or the chromosomal structure of the leukemic cell. Certain cytogenetic abnormalities are associated with very good outcomes (for example, the (15;17) translocation in acute promyelocytic leukemia). About half of AML patients have "normal" cytogenetics; they fall into an intermediate risk group. A number of other cytogenetic abnormalities are known to associate with a poor prognosis and a high risk of relapse after treatment.

The first publication to address cytogenetics and prognosis was the MRC trial of 1998:

Risk Category	Abnormality	5-year survival	Relapse rate
Good	t(8;21), t(15;17), inv(16)	70%	33%
Intermediate	Normal, +8, +21, +22, del(7q), del(9q), Abnormal 11q23, all other structural or numerical changes	48%	50%
Poor	-5, -7, del(5q), Abnormal 3q, Complex cytogenetics	15%	78%

Later, the Southwest Oncology Group and Eastern Cooperative Oncology Group and, later still, Cancer and Leukemia Group B published other, mostly overlapping lists of cytogenetics prognostication in leukemia.

Myelodysplastic syndrome

AML which arises from a pre-existing myelodysplastic syndrome or myeloproliferative disease (so-called *secondary AML*) has a worse prognosis, as does *treatment-related AML* arising after chemotherapy for another previous malignancy. Both of these entities are associated with a high rate of unfavorable cytogenetic abnormalities.

Other prognostic markers

In some studies, age >60 years and elevated lactate dehydrogenase level were also associated with poorer outcomes. As with most forms of cancer, performance status (i.e. the general physical condition and activity level of the patient) plays a major role in prognosis as well.

FLT3 internal tandem duplications (ITDs) have been shown to confer a poorer prognosis in AML. Treating these patients with more aggressive therapy, such as stem-cell transplantation in first remission, has not been shown to enhance long-term survival, so this prognostic feature is of uncertain clinical significance at this point. ITDs of *FLT3* may be associated with leukostasis.

Researchers are investigating the clinical significance of *c-KIT* mutations in AML. These are prevalent, and clinically relevant because of the availability of tyrosine kinase inhibitors, such as imatinib and sunitinib that can block the activity of *c-KIT* pharmacologically.

Other genes being investigated as prognostic factors or therapeutic targets include *CEBPA*, *BAALC*, *ERG*, and *NPM1*.

Overall expectation of cure

Cure rates in clinical trials have ranged from 20–45%; however, it should be noted that clinical trials often include only younger patients and those able to tolerate aggressive therapies. The overall cure rate for all patients with AML (including the elderly and those unable to tolerate aggressive therapy) is likely lower. Cure rates for promyelocytic leukemia can be as high as 98%.

Epidemiology

Acute myeloid leukemia is a relatively rare cancer. There are approximately 10,500 new cases each year in the United States, and the incidence rate has remained stable from 1995 through 2005. AML accounts for 1.2% of all cancer deaths in the United States.

The incidence of AML increases with age; the median age at diagnosis is 63 years. AML accounts for about 90% of all acute leukemias in adults, but is rare in children. The rate of *therapy-related AML* (that is, AML caused by previous chemotherapy) is rising; therapy-related disease currently accounts for about 10–20% of all cases of AML. AML is slightly more common in men, with a male-to-female ratio of 1.3:1.

There is some geographic variation in the incidence of AML. In adults, the highest rates are seen in North America, Europe, and Oceania, while adult AML is rarer in Asia and Latin America. In contrast, childhood AML is less common in North America and India than in other parts of Asia. These differences may be due to population genetics, environmental factors, or a combination of the two.

History



Alfred Velpeau

The first published description of a case of leukemia in medical literature dates to 1827, when French physician Alfred-Armand-Louis-Marie Velpeau described a 63-year-old florist who developed an illness characterized by fever, weakness, urinary stones, and

substantial enlargement of the liver and spleen. Velpeau noted that the blood of this patient had a consistency "like gruel", and speculated that the appearance of the blood was due to white corpuscles. In 1845, a series of patients who died with enlarged spleens and changes in the "colors and consistencies of their blood" was reported by the Edinburgh-based pathologist J.H. Bennett; he used the term "leucocythemia" to describe this pathological condition.

The term "leukemia" was coined by Rudolf Virchow, the renowned German pathologist, in 1856. As a pioneer in the use of the light microscope in pathology, Virchow was the first to describe the abnormal excess of white blood cells in patients with the clinical syndrome described by Velpeau and Bennett. As Virchow was uncertain of the cause of the white blood cell excess, he used the purely descriptive term "leukemia" (Greek: "white blood") to refer to the condition.

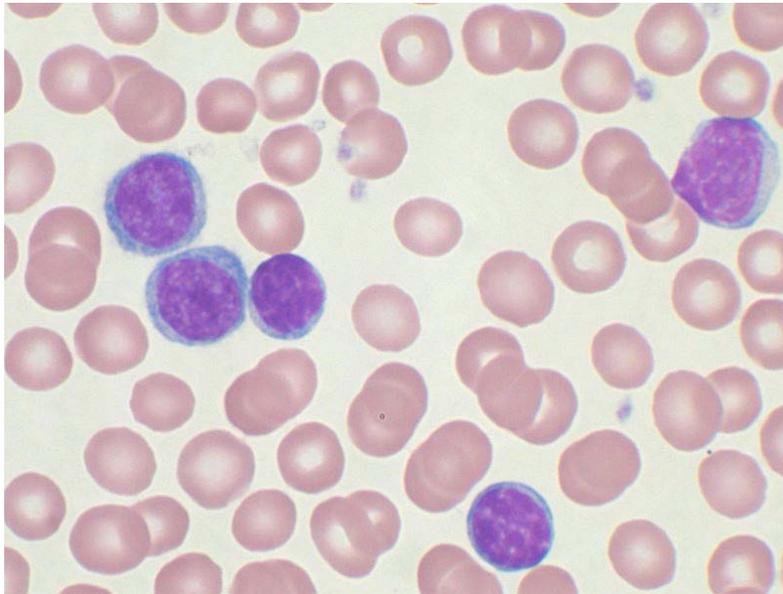
Further advances in the understanding of acute myeloid leukemia occurred rapidly with the development of new technology. In 1877, Paul Ehrlich developed a technique of staining blood films which allowed him to describe in detail normal and abnormal white blood cells. Wilhelm Ebstein introduced the term "*acute leukemia*" in 1889 to differentiate rapidly progressive and fatal leukemias from the more indolent chronic leukemias. The term "myeloid" was coined by Neumann in 1869, as he was the first to recognize that white blood cells were made in the bone marrow (Greek: μυελός, *myelos* = (bone) marrow) as opposed to the spleen. The technique of bone marrow examination to diagnose leukemia was first described in 1879 by Mosler. Finally, in 1900 the myeloblast, which is the malignant cell in AML, was characterized by Otto Naegeli, who divided the leukemias into *myeloid* and *lymphocytic*.

In 2008, AML became the first cancer genome to be fully sequenced. DNA extracted from leukemic cells were compared to unaffected skin. The leukemic cells contained acquired mutations in several genes that had not previously been associated with the disease.

Chapter 15

B-cell Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia



Peripheral blood smear showing CLL cells

ICD-10	C91.1
ICD-9	204.1
ICD-O:	M9823/3 (CLL) 9670/3 (SCL)
DiseasesDB	2641
MedlinePlus	000532
eMedicine	med/370

B-cell chronic lymphocytic leukemia (B-CLL), also known as **chronic lymphoid leukemia (CLL)**, is the most common type of leukemia. Leukemias are cancers of the white blood cells (leukocytes). CLL affects B cell lymphocytes. B cells originate in the bone marrow, develop in the lymph nodes, and normally fight infection by producing antibodies. In CLL, the DNA of a B cell is damaged, so that it cannot produce antibodies. Additionally, B cells grow out of control and accumulate in the bone marrow and blood, where they crowd out healthy blood cells. CLL is a stage of **small lymphocytic lymphoma (SLL)**, a type of B-cell lymphoma, which presents primarily in the lymph nodes. CLL and SLL are considered the same underlying disease, just with different appearances.

CLL is a disease of adults, but, in rare cases, it can occur in teenagers and occasionally in children (inherited). Most (>75%) people newly diagnosed with CLL are over the age of 50, and the majority are men.

Most people are diagnosed without symptoms as the result of a routine blood test that returns a high white blood cell count, but, as it advances, CLL results in swollen lymph nodes, spleen, and liver, and eventually anemia and infections. Early CLL is not treated, and late CLL is treated with chemotherapy and monoclonal antibodies.

DNA analysis has distinguished two major types of CLL, with different survival times. CLL that is positive for the marker ZAP-70 has an average survival of 5 years. CLL that is negative for ZAP-70 has an average survival of more than 25 years. Patients with slowly-progressing disease can be reassured and may not need any treatment in their lifetimes.

Clinical staging

Staging, determining the extent of the disease, is done with the Rai staging system or the Binet classification and is based primarily on the presence, or not, of a low platelet or red cell count. Early stage disease does not need to be treated.

Gene mutation status

Recent publications suggest that two or three prognostic groups of CLL exist based on the maturational state of the cell. This distinction is based on the maturity of the lymphocytes as discerned by the immunoglobulin variable-region heavy chain (IgV_H) gene mutation status. High risk patients have an immature cell pattern with few mutations in the DNA in the IgV_H antibody gene region whereas low risk patients show considerable mutations of the DNA in the antibody gene region indicating mature lymphocytes.

Since assessment of the IgV_H antibody DNA changes is difficult to perform, the presence of either cluster of differentiation 38 (CD38) or Z-chain-associated protein kinase-70 (ZAP-70) may be surrogate markers of high risk subtype of CLL. Their expression correlates with a more immature cellular state and a more rapid disease course.

Fluorescence in situ hybridization (FISH)

In addition to the maturational state, the prognosis of patients with CLL is dependent on the genetic changes within the neoplastic cell population. These genetic changes can be identified by fluorescent probes to chromosomal parts using a technique referred to as fluorescent in situ hybridization (FISH). Four main genetic aberrations are recognized in CLL cells that have a major impact on disease behavior.

1. Deletions of part of the short arm of chromosome 17 (del 17p), which target the cell cycle regulating protein p53 are particularly deleterious. Patients with this abnormality have significantly short interval before they require therapy and a shorter survival. This abnormality is found in 5–10% of patients with CLL.
2. Deletions of the long arm on chromosome 11 (del 11q) are also unfavorable although not to the degree seen with del 17p. The abnormality targets the ATM gene and occurs infrequently in CLL (5–10%).
3. Trisomy 12, an additional chromosome 12, is a relatively frequent finding occurring in 20–25% of patients and imparts an intermediate prognosis.
4. Deletion of the long arm of chromosome 13 (del 13q) is the most common abnormality in CLL with roughly 50% of patients with cells containing this defect. These patients have the best prognosis and most will live many years, even decades, without the need for therapy. The gene targeted by this deletion is a segment coding for microRNAs miR-15a and miR-16-1.

Array-based Karyotyping

Array-based karyotyping is a cost-effective alternative to FISH for detecting chromosomal abnormalities in CLL. Several clinical validation studies have shown >95% concordance with the standard CLL FISH panel.

Related diseases

In the past, cases with similar microscopic appearance in the blood but with a T cell phenotype were referred to as T-cell CLL. However, it is now recognized that these so-called T-cell CLLs are in fact a separate disease group and are currently classified as T-cell prolymphocytic leukemias.

CLL should not be confused with acute lymphoblastic leukemia, (ALL) a highly aggressive and highly treatable leukemia most commonly diagnosed in children.

Symptoms and signs

Most people are diagnosed without symptoms as the result of a routine blood test that returns a high white blood cell count. Less commonly, CLL may present with enlarged lymph nodes without a high white blood cell count or no evidence of the disease in the blood. This is referred to as *small lymphocytic lymphoma*. In some individuals the disease comes to light only after the neoplastic cells overwhelm the bone marrow resulting in anemia producing tiredness or weakness.

Diagnosis

The disease is easily diagnosed. CLL is usually first suspected by the presence of a lymphocytosis, an increase in one type of the white blood cell, on a complete blood count (CBC) test. This frequently is an incidental finding on a routine physician visit. Most often the lymphocyte count is greater than 4000 cells per microlitre (μl) of blood but can be much higher. The presence of a lymphocytosis in an elderly individual should raise strong suspicion for CLL and a confirmatory diagnostic test, in particular flow cytometry, should be performed unless clinically unnecessary.

The diagnosis of CLL is based on the demonstration of an abnormal population of B lymphocytes in the blood, bone marrow, or tissues that display an unusual but characteristic pattern of molecules on the cell surface. This atypical molecular pattern includes the co-expression of cells surface markers cluster of differentiation 5 (CD5) and cluster of differentiation 23 (CD23). In addition, all the CLL cells within one individual are clonal, that is genetically identical. In practice, this is inferred by the detection of only one of the mutually exclusive antibody light chains, kappa or lambda, on the entire population of the abnormal B cells. Normal B lymphocytes consist of a stew of different antibody producing cells resulting in a mixture of both kappa and lambda expressing cells. The lack of the normal distribution of kappa and lambda producing B cells is one basis for demonstrating clonality, the key element for establishing a diagnosis of any B cell malignancy (B cell Non-Hodgkin lymphoma).

The combination of the microscopic examination of the peripheral blood and analysis of the lymphocytes by flow cytometry to confirm clonality and marker molecule expression is needed to establish the diagnosis of CLL. Both are easily accomplished on a small amount of blood. A flow cytometer is an instrument that can examine the expression of molecules on individual cells in fluids. This requires the use of specific antibodies to marker molecules with fluorescent tags recognized by the instrument. In CLL, the lymphocytes are genetically clonal, of the B cell lineage (express marker molecules cluster of differentiation 19 (CD19) and CD20), and characteristically express the marker molecules CD5 and CD23. These B cells resemble normal lymphocytes under the microscope, although slightly smaller, and are fragile when smeared onto a glass slide giving rise to many broken cells (smudge cells).

Differential diagnosis

Hematologic disorders that may resemble CLL in their clinical presentation, behavior, and microscopic appearance include mantle cell lymphoma, marginal zone lymphoma, B cell prolymphocytic leukemia, and lymphoplasmacytic lymphoma.

- B cell prolymphocytic leukemia (B PLL), is a related but more aggressive disorder, has cells with similar phenotype but that are significantly larger than normal lymphocytes and have a prominent nucleolus. The distinction is important as the prognosis and therapy differs from CLL.
- Hairy cell leukemia is also a neoplasm of B lymphocytes but the neoplastic cells have a distinct morphology under the microscope (hairy cell leukemia cells have delicate, hair-like projections on their surface) and unique marker molecule expression.

All the B cell malignancies of the blood and bone marrow can be differentiated from one another by the combination of cellular microscopic morphology, marker molecule expression, and specific tumor-associated gene defects. This is best accomplished by evaluation of the patient's blood, bone marrow and occasionally lymph node cells by a pathologist with specific training in blood disorders. A flow cytometer is necessary for cell marker analysis and the detection of genetic problems in the cells may require visualizing the DNA changes with fluorescent probes by fluorescent in situ hybridization (FISH).

Treatment

CLL treatment focuses on controlling the disease and its symptoms rather than on an outright cure. CLL is treated by chemotherapy, radiation therapy, biological therapy, or bone marrow transplantation. Symptoms are sometimes treated surgically (splenectomy removal of enlarged spleen) or by radiation therapy ("de-bulking" swollen lymph nodes).

Initial CLL treatments vary depending on the exact diagnosis and the progression of the disease, and even with the preference and experience of the health care practitioner. There are dozens of agents used for CLL therapy.

Decision to treat

While generally considered incurable, CLL progresses slowly in most cases. Many people with CLL lead normal and active lives for many years—in some cases for decades. Because of its slow onset, early-stage CLL is, in general, not treated since it is believed that early CLL intervention does not improve survival time or quality of life. Instead, the condition is monitored over time to detect any change in the disease pattern.

The decision to start CLL treatment is taken when the patient's clinical symptoms or blood counts indicate that the disease has progressed to a point where it may affect the patient's quality of life.

Clinical "staging systems" such as the Rai 4-stage system and the Binet classification can help to determine when and how to treat the patient.

Determining when to start treatment and by what means is often difficult; studies have shown there is no survival advantage to treating the disease too early. The National Cancer Institute Working Group has issued guidelines for treatment, with specific markers that should be met before it is initiated.

Chemotherapy

Combination chemotherapy regimens are effective in both newly-diagnosed and relapsed CLL. Combinations of fludarabine with alkylating agents (cyclophosphamide) produce higher response rates and a longer progression-free survival than single agents:

- **FC** (fludarabine with cyclophosphamide)
- **FR** (fludarabine with rituximab)
- **FCR** (fludarabine, cyclophosphamide, and rituximab)
- **CHOP** (cyclophosphamide, doxorubicin, vincristine and prednisolone)

Although the purine analogue fludarabine was shown to give superior response rates than chlorambucil as primary therapy, there is no evidence that early use of fludarabine improves overall survival, and some clinicians prefer to reserve fludarabine for relapsed disease.

Alkylating agents approved for CLL include bendamustine and cyclophosphamide.

Monoclonal antibodies such as alemtuzumab (directed against CD52), rituximab (directed against CD20), and Arzerra (ofatumumab)(directed against CD20).

Stem cell transplantation

Allogeneic bone marrow (stem cell) transplantation is rarely used as a first-line treatment for CLL due to its risk. There is increasing interest in the use of reduced-intensity allogeneic stem cell transplantation, which offers the prospect of cure for selected patients with a suitable donor.

Younger patients that are at high risk for dying from CLL might consider hematopoietic stem cell transplantation (HSCT). Autologous stem cell transplantation, a lower-risk form of treatment using the patient's own blood cells, is not curative. Myeloablative (bone marrow killing) forms of allogeneic stem cell transplantation, a high-risk treatment using blood cells from a healthy donor, may be curative for some patients, but most patients cannot tolerate the treatment. An intermediate level, called *reduced-intensity conditioning allogeneic stem cell transplantation*, may be better tolerated by older or frail patients.

Refractory CLL

"Refractory" CLL is a disease that no longer responds favorably to treatment. In this case more aggressive therapies, including lenalidomide, flavopiridol, and bone marrow (stem cell) transplantation, are considered. The monoclonal antibody, alemtuzumab (directed against CD52), may be used in patients with refractory, bone marrow-based disease.

Complications

Chronic lymphocytic leukemia may transform into Richter's syndrome, a term used to describe the development of fast-growing diffuse large B cell lymphoma, prolymphocytic leukemia, Hodgkin disease, or acute leukemia in a patient who has chronic lymphocytic leukemia. Its incidence is estimated to be around 5%.

Epidemiology

CLL is a disease of older adults and is rarely encountered in individuals under the age of 40. Thereafter, the disease incidence increases with age.

In the United States during 2009, about 16,000 new cases are expected to be diagnosed, and 4,400 patients are expected to die from CLL. Because of the prolonged survival, which was typically about ten years in past decades, but which can extend to a normal life expectancy, the prevalence (number of people living with the disease) is much higher than the incidence (new diagnoses).

Subclinical "disease" can be identified in 3.5% of normal adults, and in up to 8% of individuals over the age of 70. That is, small clones of B cells with the characteristic CLL phenotype can be identified in many healthy elderly persons. The clinical significance of these cells is unknown.

Of all cancers involving the same class of blood cell, 7% of cases are CLL/SLL.

Complications: hypogammaglobulinemia leading to recurrent infection, warm autoimmune haemolytic anaemia in 10–15% of patients, transformation to high grade lymphoma, Richter's transformation.

Rates of CLL are somewhat elevated in people that had been exposed to certain chemicals. Under U.S. Department of Veterans' Affairs regulations, Vietnam veterans who served in-country or in the inland waterways of Vietnam and who later develop CLL are presumed to have contracted it from exposure to Agent Orange and may be entitled to compensation.

Prognosis

Prognosis depends on the subtype. The overall 5-year survival rate (all forms of CLL together) is about 50%.

Research directions

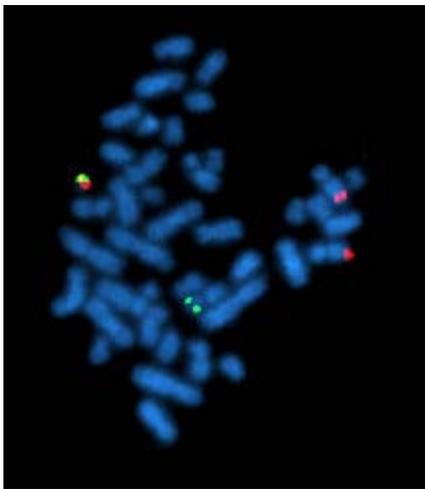
There is considerable research activity studying the many treatments individually or in combination with each other.

Current research is comparing different forms of bone marrow transplants to determine which patients are the best candidates and which approach is best in different situations.

Chapter 16

Chronic Myelogenous Leukemia

Chronic myelogenous leukemia



The Philadelphia chromosome as seen by metaphase FISH.

ICD-10	C92.1
ICD-9	205.1
ICD-O:	M9875/3
DiseasesDB	2659
MedlinePlus	000570
eMedicine	med/371
MeSH	D015464

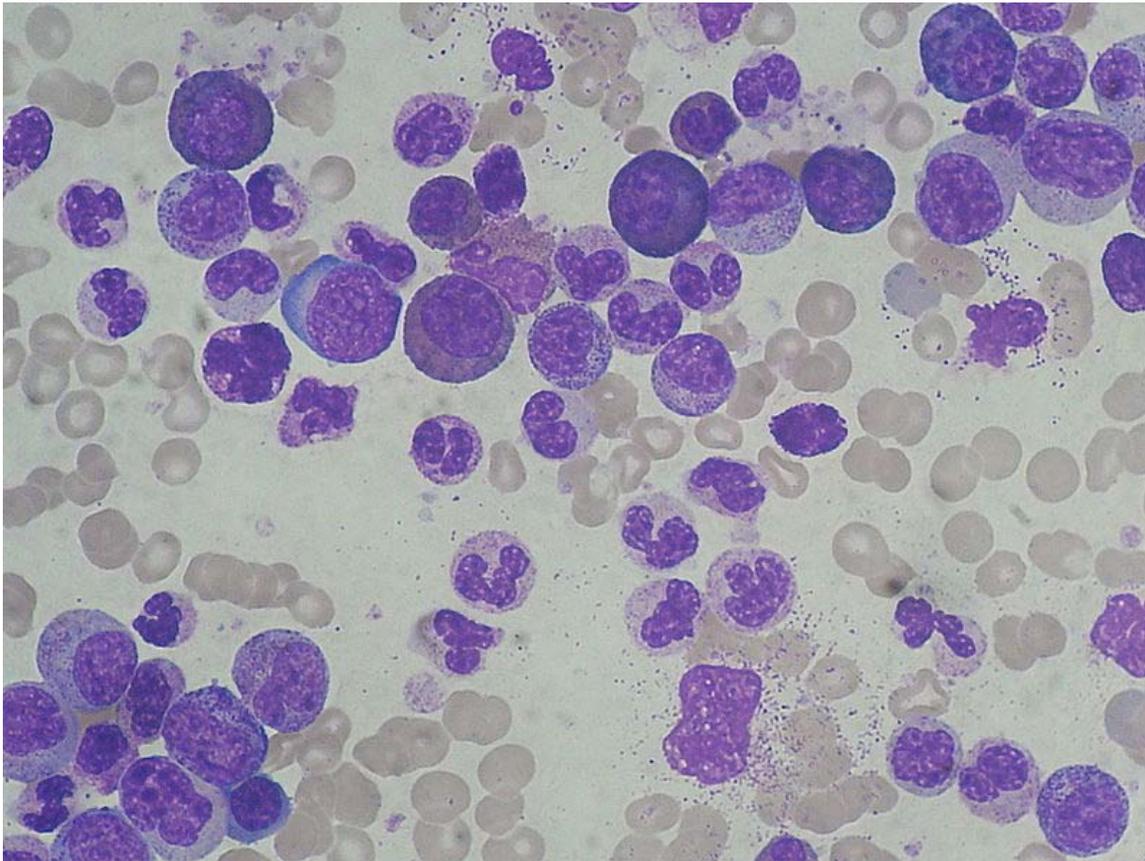
Chronic myelogenous (or myeloid) leukemia (CML), also known as **chronic granulocytic leukemia (CGL)**, is a cancer of the white blood cells. It is a form of leukemia characterized by the increased and unregulated growth of predominantly myeloid cells in the bone marrow and the accumulation of these cells in the blood. CML

is a clonal bone marrow stem cell disorder in which proliferation of mature granulocytes (neutrophils, eosinophils, and basophils) and their precursors is the main finding. It is a type of myeloproliferative disease associated with a characteristic chromosomal translocation called the Philadelphia chromosome. It is now treated with imatinib and other targeted therapies, which have dramatically improved survival.

Signs and symptoms

Patients are often asymptomatic at diagnosis, presenting incidentally with an elevated white blood cell count on a routine laboratory test. In this setting, CML must be distinguished from a leukemoid reaction, which can have a similar appearance on a blood smear. Symptoms of CML may include: enlarged spleen, malaise, low-grade fever, gout, increased susceptibility to infections, anemia, and thrombocytopenia with easy bruising (although an *increased* platelet count (thrombocytosis) may also occur in CML).

Diagnosis



Peripheral blood (MGG stain): marked leucocytosis with granulocyte left shift

CML is often suspected on the basis on the complete blood count, which shows increased granulocytes of all types, typically including mature myeloid cells. Basophils and eosinophils are almost universally increased; this feature may help differentiate CML

from a leukemoid reaction. A bone marrow biopsy is often performed as part of the evaluation for CML, but bone marrow morphology alone is insufficient to diagnose CML.

Ultimately, CML is diagnosed by detecting the Philadelphia chromosome. This characteristic chromosomal abnormality can be detected by routine cytogenetics, by fluorescent in situ hybridization, or by PCR for the *bcr-abl* fusion gene.

Controversy exists over so-called *Ph-negative* CML, or cases of suspected CML in which the Philadelphia chromosome cannot be detected. Many such patients in fact have complex chromosomal abnormalities which mask the (9;22) translocation, or have evidence of the translocation by FISH or RT-PCR in spite of normal routine karyotyping. The small subset of patients without detectable molecular evidence of *bcr-abl* fusion may be better classified as having an undifferentiated myelodysplastic/myeloproliferative disorder, as their clinical course tends to be different from patients with CML.

Pathophysiology

CML was the first malignancy to be linked to a clear genetic abnormality, the chromosomal translocation known as the Philadelphia chromosome. This chromosomal abnormality is so named because it was first discovered and described in 1960 by two scientists from Philadelphia, Pennsylvania, USA: Peter Nowell of the University of Pennsylvania and David Hungerford of the Fox Chase Cancer Center at Temple University.

In this translocation, parts of two chromosomes (the 9th and 22nd by conventional karyotypic numbering) switch places. As a result, part of the BCR ("breakpoint cluster region") gene from chromosome 22 is fused with the ABL gene on chromosome 9. This abnormal "fusion" gene generates a protein of p210 or sometimes p185 weight (p is a weight measure of cellular proteins in kDa). Because *abl* carries a domain that can add phosphate groups to tyrosine residues (a tyrosine kinase), the *bcr-abl* fusion gene product is also a tyrosine kinase.

The fused BCR-ABL protein interacts with the interleukin 3 β (c) receptor subunit. The BCR-ABL transcript is continuously active and does not require activation by other cellular messaging proteins. In turn, BCR-ABL activates a cascade of proteins which control the cell cycle, speeding up cell division. Moreover, the BCR-ABL protein inhibits DNA repair, causing genomic instability and making the cell more susceptible to developing further genetic abnormalities. The action of the BCR-ABL protein is the pathophysiologic cause of chronic myelogenous leukemia. With improved understanding of the nature of the BCR-ABL protein and its action as a tyrosine kinase, targeted therapies have been developed (the first of which was imatinib mesylate) which specifically inhibit the activity of the BCR-ABL protein. These tyrosine kinase inhibitors can induce complete remissions in CML, confirming the central importance of *bcr-abl* as the cause of CML.

Classification

CML is often divided into three phases based on clinical characteristics and laboratory findings. In the absence of intervention, CML typically begins in the *chronic* phase, and over the course of several years progresses to an *accelerated* phase and ultimately to a *blast crisis*. Blast crisis is the terminal phase of CML and clinically behaves like an acute leukemia. One of the drivers of the progression from chronic phase through acceleration and blast crisis is the acquisition of new chromosomal abnormalities (in addition to the Philadelphia chromosome). Some patients may already be in the accelerated phase or blast crisis by the time they are diagnosed.

Chronic phase

Approximately 85% of patients with CML are in the chronic phase at the time of diagnosis. During this phase, patients are usually asymptomatic or have only mild symptoms of fatigue or abdominal fullness. The duration of chronic phase is variable and depends on how early the disease was diagnosed as well as the therapies used. Ultimately, in the absence of curative treatment, the disease progresses to an accelerated phase.

Accelerated phase

Criteria for diagnosing transition into the accelerated phase are somewhat variable; the most widely used criteria are those put forward by investigators at M.D. Anderson Cancer Center, by Sokal et al., and the World Health Organization. The WHO criteria are perhaps most widely used, and define the accelerated phase by any of the following:

- 10–19% myeloblasts in the blood or bone marrow
- >20% basophils in the blood or bone marrow
- Platelet count <100,000, unrelated to therapy
- Platelet count >1,000,000, unresponsive to therapy
- Cytogenetic evolution with new abnormalities in addition to the Philadelphia chromosome
- Increasing splenomegaly or white blood cell count, unresponsive to therapy

The patient is considered to be in the accelerated phase if any of the above are present. The accelerated phase is significant because it signals that the disease is progressing and transformation to blast crisis is imminent.

Blast crisis

Blast crisis is the final phase in the evolution of CML, and behaves like an acute leukemia, with rapid progression and short survival. Blast crisis is diagnosed if any of the following are present in a patient with CML:

- >20% myeloblasts or lymphoblasts in the blood or bone marrow

- Large clusters of blasts in the bone marrow on biopsy
- Development of a chloroma (solid focus of leukemia outside the bone marrow)

Treatment

Chronic phase

Chronic phase CML is treated with inhibitors of tyrosine kinase, the first of which was imatinib mesylate (marketed as Gleevec or Glivec; previously known as STI-571). In the past, antimetabolites (e.g. cytarabine, hydroxyurea), alkylating agents, interferon alfa 2b, and steroids were used, but these drugs have been replaced by imatinib. Imatinib was approved by the United States FDA in 2001 and specifically targets BCR/abl, the constitutively activated tyrosine kinase fusion protein caused by the Philadelphia chromosome translocation. It is better tolerated and more effective than previous therapies. The IRIS study is an international study that compared interferon/cytarabine combination with imatinib. Long term follow up demonstrating the superiority of imatinib regimens is clear cut. However, the data of this study which allowed cross-over to Glivec have never been presented in an intent to treat analysis. It is not yet known whether Glivec treatment following cytarabine/interferon is better than Glivec alone in the long term. Bone marrow transplantation was also used as initial treatment for CML in younger patients before the advent of imatinib and, while it can often be curative, there was a high rate of transplant-related mortality. The transplant-related mortality rate as of 2010 is less than 5%.

As described below, a number of newer drugs are being used to treat the minority of patients who develop imatinib resistance. Trials such as SPIRIT 2 are being carried out, to evaluate these newer drugs as 'upfront' therapy for patients with newly diagnosed chronic phase CML.

To overcome imatinib resistance and to increase responsiveness of TK inhibitors, two novel agents have been developed. The first, dasatinib, is a TK inhibitor that blocks several oncogenic proteins and was approved by the US FDA in 2007 to treat CML patients who are either resistant to or intolerant of imatinib. Another TK inhibitor, nilotinib, has also been approved by the US FDA for the same indication. Nilotinib is designed to bind more tightly than imatinib to the Bcr-Abl abnormal fusion protein responsible for chronic myeloid leukemia. Dasatinib is being compared with Imatinib for first-line therapy in the SPIRIT 2 trial being undertaken in the United Kingdom. Study on the combination of alpha Interferon with Imatinib is currently recruiting in higher risk patients in chronic phase CML.

Dasatinib and nilotinib failed to overcome the imatinib resistance caused by the T315I mutation. All current treatments for this mutation are experimental. Recently Chemgenex released results of their open-label Phase 2/3 study (CGX-635-CML-202) which investigated the use of omacetaxine, administered subcutaneously in CML patients who had failed imatinib and who have the highly drug-resistant T315I kinase domain mutation. In October 2010, ponatinib, a small molecule, oral drug developed by Ariad

Pharmaceuticals, was entered into evaluation in a pivotal Phase 2 trial. Ponatinib, a pan-BCR-ABL inhibitor, has shown ongoing strong efficacy in its continuing Phase 1 trial in treatment of the T315I mutation CML, as well as all other known mutations. This drug has also been granted orphan status.

Stem cell transplantation is an option for patients who developed T315I mutation.

In 2005 favourable results of vaccination were reported with the *BCR/abl* p210 fusion protein in patients with stable disease, with GM-CSF as an adjuvant.

Prognosis

In one analysis of several clinical studies, three different risk groups were identified based on a prognostic scoring system that includes several variables: age, spleen size, blast count, platelet count, eosinophil count and basophil count. In the lowest risk group, the median survival time was 98 months. In the middle group, the median was 65 months, and in the highest risk group, the median was about 42 months. Of all patients analyzed, the longest survival time was 117 months. However, this study pre-dates the advent of treatments using targeted therapy. A follow-up on patients using imatinib published in the New England Journal of Medicine shows an overall survival rate of 89% after five years.

Epidemiology

CML occurs in all age groups, but most commonly in the middle-aged and elderly. Its annual incidence is 1–2 per 100,000 people, and slightly more men than women are affected. CML represents about 15–20% of all cases of adult leukemia in Western populations. The only well-described risk factor for CML is exposure to ionizing radiation; for example, increased rates of CML were seen in people exposed to the atomic bombings of Hiroshima and Nagasaki.