Staging

The following staging, grading, and tumor marker information is directly cited from the NCI web page "Staging: Questions & Answers" and "Tumor Grade: Questions & Answers" facts sheet. For additional information double click http://www.cancer.gov for direct access to the NCI web page.

Key Points:

- Staging describes the extent or severity of an individual's cancer
- Knowing the stage of the disease helps the doctor plan a person's treatment and estimate prognosis
- The TMN staging system is based on the extent of tumor (T), spread of the lymph nodes (N), and metastasis (M) spread to other body parts
- Most cancers can be described in stages; stage I, stage II, stage III, or stage IV
- Physical exams, imaging procedures, laboratory tests, pathology reports, and surgical reports provide information to determine the stage of the cancer

Staging:

Staging describes the extent or severity of an individual's cancer based on the extent of spread in the body. Staging is important because:

- Helps to plan the patient's treatment
- The stage can be used to estimate the person's prognosis
- Knowing the staging is important to identify clinical trials that may be suitable for a particular patient

Staging helps practitioners exchange information about patients. It also gives them a common language for evaluating the results of clinical trials and comparing the results of different trials.

Basis for staging:

Staging is based on knowledge of the way that cancer develops. Cancer cells divide and grow without control or order to form a mass of tissue, called a growth or tumor. As the tumor grows, it can invade nearby organs and tissues. Cancer cells can also break away from the tumor and enter the vascular or lymphatic system, cancer can spread from the primary site to form new tumors in the organs. The spread of cancer is called metastasis.

Common Elements of Staging:

Staging systems for cancer have evolved over time. They continue to change as scientists learn more about cancer. Some staging systems cover many types of cancer: others focus on a particular type. The common elements considered in most staging systems are:

- Location of the primary tumor
- Tumor size and number of tumors
- Lymph node involvement (spread of cancer into lymph nodes)
- Cell type and tumor grade (how closely the cancer cells resemble normal tissue)
- Presence of metastasis

The TNM system:

The TNM system is one of the most commonly used staging systems. This system has been accepted by the International Union Against Cancer (UNICC) and the American Joint Committee on Cancer (AJCC). Most medical facilities use the TNM system as their main method for cancer reporting.

The TNM system is based on the extent of the tumor (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M). A number is added to each letter to indicate the size or extent of the tumor and the extent of spread.

Primary Tumor (T)

Tx	**Primary tumor cannot be evaluated**
T0	**No evidence of primary tumor**
Tis	**Carcinoma in situ (early cancer that has not spread to neighboring tissue)**
T1, T2, T3, T4	**Size and/or extent of the primary tumor**

Regional Lymph Nodes (N)

Nx	**Regional lymph nodes cannot be evaluated**
N0	**No regional lymph node involvement (no cancer found in the lymph nodes)**
N1, N2, N3	**Involvement of regional lymph nodes (number and/or extent of spread)**

Distant Metastasis (M)

Mx	**Distant metastasis cannot be evaluated**
M0	**No distant metastasis (cancer had not spread to other parts of the body)**
M1	**Distant metastasis (cancer has spread to distant parts of the body)**

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Examples:

Breast cancer T3, N2, M0 refers to a large tumor that has not spread outside the breast to nearby lymph nodes, but not to other parts of the body.

Prostate cancer T2, N0, M0 means that the tumor is located only in the prostate and has not spread to the lymph nodes or any other part of the body

The TNM combinations correspond to one of five stages. Criteria for stages differ for different types of cancer. For example, bladder cancer T3,N0,M0 is stage III; however, colon cancer T3, N0, M0 is stage II

Other Ways to Stage Tumors and Hematologic Disorders:

Most types of cancer have TMN designations, but some do not. Cancers of the and spinal cord are classified according to their cell type and grade. Different staging systems are also used for many cancers of the blood and bone marrow, such as lymphoma. The **Ann Arbor** staging classification is commonly used to stage lymphomas and has been adopted by both the AJCC and the UICC.

http://en.wikipedia.org/wiki/Ann_Arbor_staging

Other types of cancers of the blood and bone marrow including most leukemia, do not have a clear-cut staging system. Another staging system, developed by the **International Federation of Gynecology and Obstetrics (FIGO),** is used to stage cancers of the cervix, uterus, ovary, vagina, and vulva. This system uses the TNM format. Childhood cancers are staged using the TNM system or the staging criteria of the Children's Oncology Group, a group that conducts pediatric clinical trials.

Many cancer registries such as the NCI's Surveillance, epidemiology, and End Results Program (SEER), use summary staging. This system is used for all types of cancer. It groups cancer cases into five main categories;

- **In situ** is early cancer that is present only in the layer of cells in which it began
- **Localized** is cancer that is limited to the organ in which it began, without evidence of spread

- **Regional** is cancer that has spread beyond the original (primary) site nearby lymph nodes or organs and tissues
- **Distant** is cancer that had spread from the primary site to distant organs or distant lymph nodes
- **Unknown** is used to describe cases for which there is not enough information to indicate a stage

Types of Tests Used to Determine Staging:

The types of tests used for staging depend on the type of cancer. Tests include the following;

- Physical Exam: used to gather information about the cancer. The doctor examines the body looking, feeling, listening for any thing unusual. The exam may show the location and size of the tumor. It may also help to identify spread to lymph nodes and/or to other organs
- Imaging studies: produce direct internal visualization of tumors. Examples are x-ray, CT, PET, and MRI scans
- Pathology reports: include information about the size of the tumor, growth of the tumor into other tissues and organs, the type of cancer cells, and the grade of the tumor (how closely the cancer cells resemble normal tissue). A biopsy (the removal of cells or tissues for examination under a microscope) may be performed to provide information for the pathology report. Cytology reports also describe findings from the examination of cells in body fluid.
- Surgical reports: tell what is found during surgery. These reports describe the size and appearance of the tumor and often include observations about lymph nodes and nearby organs.

Try your hand at the Case study on staging and management of Lung Cancer. This is an advanced program. Do not be discouraged, this is for your learning only and will help you to understand how staging and grading of tumors help physicians to make treatment decisions. It is also a good overview of the most current recommended treatment approaches to advanced NSCLC. In order to participate in this program click on the following link:
http://www.projectsinknowledge.com/cp/Activity/indexb.cfm?showfile=b&jn=1789&sj=1795.03

The following tumor grading information is directly cited from the NCI web page "Tumor Grade: Questions & Answers" facts sheet. For additional information double click http://www.cancer.gov for direct access to the NCI web page.

Tumor Grade

Key Points:

- Tumor grade is a system used to classify cancer cells in terms of how abnormal they look under a microscope and how quickly the tumor is likely to grow and spread.
- A pathologist determines whether the tumor is benign or malignant and further describes the tumor grade
- Each type of cancer is graded using a different grading system
- Doctors consider the tumor grade and other factors when developing an individual treatment plan for a patient

What is a tumor?

Normally, cells grow and divide to produce new cells in a controlled and orderly manner. Sometimes, however, new cells continue to be produced when they are not needed. As a result, a mass of extra tissue called a tumor may develop. A tumor can be benign (not cancerous) or malignant (cancerous). Cells in malignant tumors are abnormal and divide without control or order. These cancerous cells can invade and damage nearby tissue, and spread to other body parts (metastasize).

Description of Tumor Grade:

Tumor grade is a system used to classify cancer cells in terms of how abnormal they look under a microscope and how quickly the tumor is likely to grow and spread. Many factors are considered when determining tumor grade, including the structure and growth pattern of the cells. The specific factors used to determine tumor grade vary with each type of cancer.

Histologic grade is also called *differentiation* which refers to how much the tumor cells resemble normal cells of the same tissue type. *Nuclear grade* refers to the size and shape of the nucleus in tumor cells and the percentage of tumor cells that are dividing.

Tumor grade should not be confused with the stage of a cancer. Cancer stage refers to the extent or severity of the cancer, based on factors such as the location of the primary tumor, tumor size, number of tumors, and lymph node involvement (spread of cancer into lymph nodes).

How is tumor grade determined?

If a tumor is suspected to be malignant, a sample of the tissue or the entire tumor is biopsied. A pathologist examines the tissue to determine whether the tumor is benign or malignant. The pathologist can also determine the tumor grade and identify other characteristics of the tumor cells. Based on the microscopic appearance of cancer cells, pathologists commonly describe tumor grade by four degrees of severity: grade 1, 2, 3, 4. The cells of grade 1 tumors resemble normal cells, and tend to grow and multiply slowly. Grade 1 tumors are generally considered the least aggressive. The cells of Grade 3 and 4 tumors do not look like normal cells of the same type. Grade 3 and 4 tumors tend to grow rapidly and spread faster than tumors of a lower grade.

AJCC recommends that following guidelines for grading tumors:

Grade:

Gx Grade cannot be assessed (undetermined)
G1 well-differentiated (low-grade)
G2 moderately differentiated (intermediate grade)
G3 poorly differentiated (high-grade)
G3 undifferentiated (high-grade)

Does the same grading scale apply to all tumors?

Grading systems are different for each type of cancer. For example, pathologists use the Gleason system to describe the degree of differentiation of prostate cancer cells. The Gleason system uses scores ranging from Grade 2-10. The lower scores describe well-differentiated, less aggressive tumors. Higher scores describe poorly differentiated, more aggressive tumors. Other grading systems include the Bloom-Richardson system for breast cancer and the Fuhrman system for kidney cancer.

Does tumor grade affect a patient's treatment options?

Doctors use tumor grade and many other factors, such as cancer stage, to develop an individual treatment plan for the patients and to predict the patient's prognosis. Generally, a lower grade indicates a better prognosis. However, the importance of tumor grade in planning treatment and estimating a patient's prognosis is greater for certain types of cancers, such as soft tissue sarcoma, primary brain tumors, lymphomas, and breast and prostate cancer.

The following tumor marker information is directly cited from the NCI web page "Tumor Marker Question & Answer" facts sheet. For additional information double click http://www.cancer.gov for direct access to the NCI web page

Tumor Markers

Tumor markers are substances that can often be detected in higher-than normal amounts in the blood, urine, or body tissues of some patients with certain types of cancers (Alberts & Goldberg, 2004; Breathnack, 2001; Edelman & Gandara, 2004; Glisson, Movsas, & Scott, 2007; Srinivasan & Kaye, 2001, National Comprehensive Cancer Network, 2007; Box & Russell, 2004; Wood, Muss, Solin, & Olopade, 2005; Chapman & Moore, 2005; Zisman, Belldegrun & Figlin, 2004; Ellerhorn, Cullinane, Coia, & Alberts, 2007; Held-Warmkessel, 2005). Tumor markers are produced either by the tumor itself or by the body in response to the presence of cancer or certain benign conditions.

Measurements of tumor marker levels can be useful when used along with x-rays or other tests in the detection and diagnosis of some types of cancer. However, measurements of tumor marker levels alone are not sufficient to diagnose cancer for the following reasons:

- Tumor marker levels may be elevated in people with benign conditions
- Tumor marker levels are not elevated in every person with cancer-especially in the early stages of disease
- Many tumor markers are not specific to a particular type of cancer; the level of a tumor marker can be raised by more than one type of cancer

In addition to their role in cancer diagnosis, some tumor marker levels are measured before treatment to help doctors plan appropriate therapy. In some types of cancer, tumor marker levels may also be measured during treatment to monitor a patient's response to treatment. A decrease or return to normal in the level of a tumor marker may indicate that the cancer has responded favorably to therapy. If the tumor marker level rises, it may indicate that the cancer is growing. Measurements of tumor marker levels may be used after treatment has ended as part of follow-up care to check for recurrence.

Currently the main use of tumor markers is to assess a cancers response to treatment and to check for recurrences. Scientists continue to study the use of tumor markers as well as their potential role in the early detection and diagnosis

of cancer (Alberts & Goldberg, 2004; Breathnack, 2001; Edelman & Gandara, 2004; Glisson, Movsas, & Scott, 2007; Srinivasan & Kaye, 2001, National Comprehensive Cancer Network, 2007; Box & Russell, 2004; Wood, Muss, Solin, & Olopade, 2005; Chapman & Moore, 2005; Zisman, Belldegrun & Figlin, 2004; Ellerhorn, Cullinane, Coia, & Alberts, 2007; Held-Warmkessel, 2005).

Common Tumor Markers:

Prostate Specific Antigen:

- Known as the PSA
- Present in low concentrations in the blood of all adult males
- Produced by normal and abnormal prostate cells
- Elevated levels may be found in the blood of men with benign prostate conditions (prostatitis, hyperplasia, or with malignant cells)
- An elevated PSA may signal that other tests are required
- Useful in monitoring the effectiveness of prostate cancer treatment and checking for recurrence after treatment has ended
- Doctors look for trends such as a steadily rising PSA
- Researchers are currently working on ways to increase the accuracy to the PSA test to distinguish BPH from cancer

CA 125:

- produced by a variety of cells
- particularly in ovarian cancer cells
- in those patients treated with chemotherapy a falling CA 125 level generally indicates that the cancer is responding to therapy
- increasing CA 125 levels during or after therapy may suggest a lack of response
- cancer conditions that will show an elevation are: uterus, cervix, pancreas, liver, colon, breast, lung and digestive tract
- non-cancerous conditions the show an elevation are: endometriosis, pelvic inflammatory disease, peritonitis, pancreatitis, liver disease, and any condition that inflames the pleura
- note that pregnancy and menstruation may also cause increases

Carcinoembryonic Antigen (CEA):

- normally found in small amounts in the blood of most healthy people
- may be elevated in people who have cancer and some benign conditions
- primary use is in for monitoring colorectal cancer, especially when the disease is spread (metastasized)

- may be used to check for recurrence of colorectal cancer
- other cancers that may cause and elevation: melanoma, lymphoma, breast, lung, pancreas, stomach, cervix, bladder, kidney, thyroid, liver, and ovary
- non-cancerous causes of elevation: inflammatory bowel disease, pancreatitis, and liver disease
- tobacco use can also cause higher-than normal levels

Alpha-Fetoprotein:

- normally produced by a developing fetus
- begin to decrease soon after birth
- are usually undetectable in the blood of a healthy adult (except during pregnancy)
- an elevated level of AFP strongly suggests the presence of either primary liver cancer or germ cell cancer (arising from the eggs or sperm of the ovary or testicles)
- non-cancerous causes of elevations are: cirrhosis, hepatitis, pregnancy

Human Chorionic Gonadotropin:

- normally produced by the placenta during pregnancy
- HCG is used to test for pregnancy (increases early within the first trimester)
- Used to screen for choriocarcinoma (rare uterine cancer)
- Elevated levels may indicate the presence of cancers of the testis, ovary, liver, stomach, pancreas, and lung
- Pregnancy and marijuana use can cause elevations

CA 19-9:

- Initially found in colorectal cancer patients
- Also identified in patients with stomach, pancreatic, and bile duct cancer
- Those who have pancreatic cancer with higher CA 19-9 levels will have more advanced disease
- Non-cancerous conditions that cause elevations are: gallstones, pancreatitis, cirrhosis of the liver, and cholecystitis

CA 27-29:

- Found in the blood of most breast cancer patients
- Levels may be used in conjunction with other procedures (mammograms and measurements of other tumor marker levels) to check for recurrence

- Can also be elevated in cancers of the; colon, stomach, kidney, lung, ovary, pancreas, uterus, liver
- Non-cancerous causes of elevations are: first trimester of pregnancy, endometriosis, ovarian cysts, benign breast disease, kidney disease, liver disease

Lactate Dehydrogenase (LDH):

- Protein found throughout the body
- Nearly every type of cancer can cause an elevation
- Cannot be used to diagnose
- Used to monitor treatment of the following cancers; testicular, Ewing's sarcoma, non-Hodgkin's lymphoma, and some types of leukemia
- Non-cancerous causes of elevations: heart failure, hypothyroidism, anemia, lung and liver disease

(Alberts & Goldberg, 2004; Breathnack, 2001; Edelman & Gandara, 2004; Glisson, Movsas, & Scott, 2007; Srinivasan & Kaye, 2001, National Comprehensive Cancer Network, 2007; Box & Russell, 2004; Wood, Muss, Solin, & Olopade, 2005; Chapman & Moore, 2005; Zisman, Belldegrun & Figlin, 2004; Ellerhorn, Cullinane, Coia, & Alberts, 2007; Held-Warmkessel, 2005).