SWOG

QUALITY ASSURANCE DEPARTMENT

Cancer Staging

an overview for the research professional

Version 8/21/24

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Staging

Overview of the Staging of Cancer

Accurate staging is necessary to evaluate the results of treatment & clinical trials.[2]

Staging is a process by which the extent of a patient's disease is determined in order to provide the physician information to determine treatment options and prognostic indicators[1]. In clinical trials, it is paramount that all the patients registered to the study have the correct stage as indicated in the eligibility criteria. This is important for several reasons. 1) If all the patients do not have the correct stage, no conclusions can be made from the study related to the effectiveness of the intervention within a given disease type. In this scenario, all the patients on the study were accepting a risk, without valuable knowledge being acquired. 2) The study is proposed based on experience from prior clinical studies. Based on this information, it is projected to benefit the planned group of patients. If the patient does not meet the staging requirement, it may not benefit them or may cause serious side effects. This could be a safety issue that study personnel need to understand and could also be a legal issue. If a patient is registered to a clinical trial that they are not eligible for, and they have a negative outcome, the institution could be held ethically & legally responsible for the patient's injury. 3) Standardized language gives a benchmark for defining prognosis & determining the best approach for treatment of a disease.[2] 4) Using common language allows for the harmonization of contributions to cancer

ICON KEY

- Valuable information
- Terminology
- Staging Manual
- Test your knowledge

TNM staging is essential to phase II & III studies, in which the primary goal of the study is to determine response in a specific stage of a specific disease.

treatment throughout the world[2]. It is also important to note that cancer program accreditation from the American College of Surgeons Commission on Cancer requires that patients be staged as a key determinant of treatment choice.

Staging of disease can occur at different time points throughout the course of the disease. To properly stage a patient's cancer, it is important to determine the time point in a patient's care. These points in time are termed *classifications* and are based on the time of evaluation and management of the disease. Information is gathered during the relevant time frame, sometimes referred to as a *staging window*. The two predominant classifications are the clinical and pathological.

Classification: The time point in the patient's disease continuum when staging occurs.

Staging Window: The time frame when relevant information is obtained.

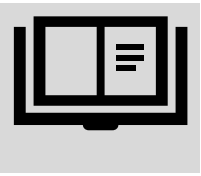
The clinical stage is based on tests that are done *before* surgery or treatment. The pathological stage is based on clinical stage information supplemented or modified by operative findings and pathological evaluation of the resected specimen.[2] This can be done at different time points, such as prior to treatment, when the primary tumor is removed, or after treatment to evaluate response to therapy. The pathology report will use a prefix letter 'y' &/or 'p' to distinguish if the stage is being given after treatment. Staging at the time of retreatment for a recurrence or disease progression is referred to as recurrence classification or retreatment classification.[2]

Neoadjuvant: Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery.

Restaging: Staging information must be determined to confirm eligibility. Sometimes a study requires the reporting of the stage of disease at the time of study entry. In this case, the initial stage at diagnosis is not what is entered on the CRF. Restaging after definitive treatment is sometimes seen with a prefix 'r' before the TNM. This may be requested if the extent of the disease, just prior to entering the study, is what the statisticians require. Therefore, the institution may need to restage the cancer if they are entering the study at the time of recurrence or progression. This does not require the initial stage at diagnosis to be changed in the medical record.

Staging Date: The last date of a test or procedure to gather staging information, not the date the patient sees the physician.

The AJCC Staging System



There are several staging systems available depending on the type of disease. The most common system for staging or categorizing the extent for solid tumors is the tumor, node, metastasis system. (TNM). Other staging systems are specific to a particular type of cancer (e.g., brain, spinal cord and hematologic cancers). This staging system was developed by the American Joint Commission on Cancer (AJCC) in Cooperation with the TNM Committee of the Union for International Cancer Control (UICC).[2] This system allows for consistency in staging worldwide as noted above. Using a staging system allows for accurate communication of information about the status of a malignancy to other medical professionals without ambiguity.[6]

The current manual of the AJC is the 8th edition. It is important to verify which version of the AJCC manual is to be used. This is usually indicated in section 4 of the protocol. In general protocols activated prior to 2018 most likely use the 7th edition while protocols activated during or after 2018 will use the 8th addition.

TNM Staging System

The AJCC TNM staging system is determined by the extent of cancer for the tumor, lymph nodes and distant metastases in the body. The T, N and M, have a set of categories, most often defined by a number (e.g., T1, N2). The description of the anatomy features is specific for each disease site and describes the extent of the disease. These categories are then combined, in a fashion for each cancer type, into prognostic staging groups. The term stage only refers to the aggregate information from TNM, and not the individual T, N, or M categories.[2]

T: The primary tumor extent
N: Regional lymph nodes
M: Distant metastases

Regional Lymph Node: A lymph node that drains lymph from the region around a tumor.

In the TNM system, there is a number or letter after each letter. This number gives more information about the extent of the cancer. Some disease sites have subcategories to facilitate reporting of more detailed information. If there is uncertainty in assigning a subcategory, the patient is assigned to the general category. If uncertain or incomplete information precludes subcategory assignment, which may result in different stage groups or study eligibility, a subcategory assignment may still be required. In that case, the general category, the physician/managing team categorization, or the lower or less advanced subcategory should be used.[2] See the following tables:

Category	Defined by:
T	**TX:** Primary tumor cannot be measured. **T0:** Primary tumor cannot be found. **Tis:** Carcinoma in situ (in the same place, not spread to nearby tissue) **T1, T2, T3, T4**: The size &/or extent of the primary tumor. The higher the number after the T, the larger the tumor or the more it has grown into nearby tissue.
N	**NX:** Cancer in nearby lymph nodes cannot be measured. **N0:** There is no cancer in nearby lymph nodes. **N1, N2, N3:** Refers to the number and location of lymph nodes that contain cancer. The higher the number after the N, the more lymph nodes that contain cancer.
M	**M0:** No evidence of spreading to other parts of the body. **M1:** Cancer has spread to other parts of the body. (*There is no MX designation in the 8th ed. The absence of any clinical history or physical findings suggestive of metastases is sufficient to assign the clinical M0 category*)[2]

Second primary: A term used to describe a new primary cancer that occurs in a person who has had cancer in the past. It can be a different cancer or a cancer in the same organ, but different histology.

During staging, there are terms or categories that may also be used to describe the location of the cancer. These terms are noted in the table on the next page.

Term	Definition[3]
In situ	Abnormal cells are present but have not spread to nearby tissue.
Localized	Cancer is limited to the place where it started, with no sign that it has spread.
Regional	Cancer has spread to nearby lymph nodes, tissues or organs.
Distant	Cancer has spread to distant parts of the body.
Unknown	There is not enough information to determine the stage.

Match the following for breast cancer:

a. **T** category ____ disease in axillary lymph node

b. **N** category ____ bone lesion (+) on biopsy

c. **M** category ____ tumor, right breast, 3 cm

Answer

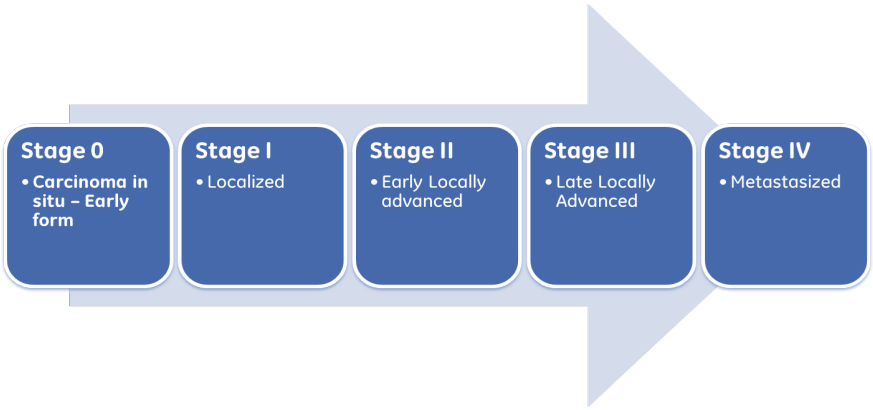
Prognostic Stage Groups

Once TNM is assigned, patients are categorized into staging groups. A staging group identifies patients with similar prognoses, usually with a statistically significant difference in outcomes between stage groups. Patients within a stage group have similar outcomes.[2] If the stage is incorrect, the findings of the study may be flawed, as there can be no reliable statistical comparison. This is why it is so important that the patient has the correct stage when registering to a clinical study.

Staging groups are denoted by Roman numerals from I to IV with increasing severity of disease and generally with worsening overall prognosis. Stage I tumors are small without regional disease or nodes and have a more favorable survival compared to those with stage IV, who have distant metastases, and a poorer likelihood of surviving their disease.[6]

The TNM letters and subcategories are grouped differently for different malignancies. See the following table for general information on cancer stages.

Stage	Definition[3]
Stage 0	Abnormal cells are present but have not spread to nearby tissue. Also called carcinoma in situ, or CIS. CIS is not cancer but may become cancer.
Stage I, II & III	Cancer is present. The higher the number, the larger the cancer tumor and the more it has spread into nearby tissue.
Stage IV	The cancer has spread to distant parts of the body.



The oncologist initially determined the stage of disease based on his expertise and professional judgement, the location of the tumor in the body, the size of the tumor, and evidence of disease through physical examination. How is this staging defined?

a. Clinical Staging
b. Pathologic staging
c. Surgical staging
d. All of the above

Answer

Prognostic Factors

In some cancers prognostic factors are required, in addition to TNM to assign a stage group. These tumor-specific factors are categories not related to the anatomy and are clearly defined if required for a particular disease site. Factors shown to effect outcome or response to therapy can include grade, histology, mitotic rate, nuclear grade and tumor markers.

Factor	Definition[2, 3]
Tumor grade	The description of tumor cells based on how abnormal (differentiated) they look under a microscope. • G1: Well differentiated (low grade) • G2: Moderately differentiated (intermediate grade) • G3: Poorly differentiated (high grade) • G4: Undifferentiated (high grade)
Histology	The microscopic assessment whereby a tumor is categorized according to the normal tissue type or cell type it most closely resembles.
Mitotic rate	The assessment of how many dividing cells are present, which is a measure of how fast the tumor cells are growing.
Nuclear grade	An evaluation of the size and shape of the nucleus in tumor cells.
Tumor marker	A substance found in tissue, blood or other body fluids that may be a sign of cancer. Most tumor markers are made by both normal and cancer cells, but they are made in large amounts by cancer cells.

Documenting Staging in the Medical Record

All staging information must be documented in the medical record. The criteria for evaluating each part of the TNM system are outlined in the AJCC Cancer Staging Manual and are defined for each disease site.[1] All information may not be available to the pathologist. Therefore, the final T, N, M categories and stage may not be fully assessed from pathology reports and should be assigned by the managing physician(s). Clinical evaluation by physical examination alone frequently underestimates the extent of cancer burden at the time of patient presentation[2]. Staging should be a collaborative approach and requires working with other professionals to finalize the correct stage. This is frequently done in the setting of a tumor board. All information for the staging of cancer should be found in the patient's medical record in the initial clinical evaluations and consultations, follow-up reports, endoscopy reports, operative and pathology reports, radiology and nuclear medicine reports.

Pathology Reports:

A pathologic diagnosis is needed to identify which disease stage to utilize. A pathologist confirms a diagnosis of cancer after careful examination of a tissue sample. Tissue may be obtained by aspiration, fine needle biopsy, punch biopsy, excisional biopsy or cytology. Cancer cells develop from a specific type of tissue, and generally retain characteristics of the cell of origin, even if it is metastasized to another location in the

body. The pathologist summarizes findings in the pathology report.[4] Pathology reports follow standard nomenclature in a structured report, usually termed the *Synoptic Report*. These standards are published by the College of American Pathologists (CAP). Synoptic reporting requires specific data elements (e.g., tumor size, grade, lymphatic invasion), in a specific format in surgical pathology reports (see example to the below).

Synoptic Report: The standard nomenclature in a pathology report that lists the various requirements, such as the size of tumor, lymphatic invasion and grade of tumor.

SYNOPTIC SUMMARY:

MACROSCOPIC:

Specimen Type: Wedge resection
Laterality: Right
Tumor Site: Lower Lobe Lung
Tumor Size: 1.8 cm

MICROSCOPIC

Histologic Type: Squamous Carcinoma
Histologic Grade: G3 (poorly differentiated)
Margins: Uninvolved by invasive carcinoma, nearest margin 3 mm
Direct Extension of Tumor: Not identified
Venous Invasion: Absent
Lymphatic Invasion: Absent
Pathologic Staging:
Primary Tumor (pT): pT1
Regional Lymph Nodes (pN): pN0
Number Examined: 6 (fragments)
Number Involved: 0
Distant Metastasis (pM): pMx

Previously, surgical pathology reports were free text, highly narrative, and prone to omission of necessary data and inconsistencies in formation.[5] Each pathology department is required to have a copy of their current CAP certificate on file in their regulatory binder. The CAP certificate documents that the laboratory operates by specific standards and results can be trusted.

There are other letters that can be seen on a pathology. A lower-case prefix describes the time point in a patient's cancer continuum when stage is assigned. See the following table for their definition.

Classification	Definition[2]
c	Clinical
p	Pathological
yc	Post neoadjuvant therapy – clinical
Yp	Post neoadjuvant therapy – pathological
r	Recurrence or retreatment
a	autopsy

A cancer cell's appearance may sometimes make it difficult for the pathologist to determine what type of cancer is present in the specimen. Usually, this is because the cells have changed in such a way that they no longer look like the original tissue (undifferentiated). In these cases, pathologists may use other types of tests to help in identifying the cancer. Both normal and cancer cells have markers either on the cell or produced by the cell or other cells in response to the cancer. These markers can be identified with various stains or special testing, to identify the type of cancer. Below is a list of some of these tests.

Test	Definition[3]
Immunophenotyping	The use of antibodies to identify cells based on the types of antigens or markers on the surface of the cells
Immunohistochemistry	Utilization of antibodies to check for certain antigens. The antibodies are linked to an enzyme or a fluorescent dye that is activated when the antibody binds to the antigen which allows it to be seen under the microscope. Example: ER, PR & HER2.
Flow Cytometry	The presence of tumor markers such as antigens or proteins are measured. The cells are stained with a light-sensitive dye and passed through a beam of light. The measurements are based on how the stained cells react to the beam of light. Examples are the CD markers, such as CD20, CD138 etc.
Genomic Testing	Determines the entire genetic makeup of a specific organism or cell type. It can find changes in areas of the genome, such as mutations.
Cytogenetics	The study of chromosomes, to identify changes in chromosomes, including broken, missing, rearranged or extra chromosomes.
FISH	Identification of genes or chromosomes in cells and tissue. Pieces of DNA that contain a fluorescent dye are made and added to a cell or tissue. These pieces of DNA bind to certain genes or areas on chromosomes and light up when viewed under a special light. FISH can be used to identify where a specific gene is located on a chromosome, how many copies of the gene are present, and any chromosomal abnormalities.

Imaging Reports:

Imaging allows assessment of the tumor's size, location and relationship to normal anatomy structures, as well as the existence of nodal &/or distant metastatic disease.[2] The American College of Radiology Appropriateness Criteria maintains guidelines and criteria for use of imaging and interventional radiology procedures for many aspects of cancer care. Radiologists should use standardized nomenclature and structured report

formats such as those recommended by the Radiological Society of North America (RSNA). Without consistent terminology for anatomy locations, it is difficult to track target & non-target lesions between radiologists &/or institutions.

Computed tomography (CT) and magnetic resonance (MR) imaging are the most commonly used imaging modalities, although positron emission tomography (PET, often combined with CT), ultrasound, and plain film radiography also play important roles in various clinical situations.

When reviewing radiology reports, it is important to recognize the difference between a nodule and a node. Nodule refers to a tumor, where a node refers to a lymph node.

When using a PET scan for RECIST criteria, the scan must be of diagnostic quality as stated in the protocol (usually in Section 10).

What documents need to be reviewed to assess the complete staging of a patient with Melanoma?

a. CT Scan
b. Physical Exam
c. Pathology Report
d. A & C
e. A, B, C

Answer

Multiple primary tumors:

Multiple cancer may occur in the same organ and may be diagnosed at or about the same time (synchronous) or at separate time points (metachronous). For the purpose of staging, the following definitions apply.

Tumor	Definition[2]
Synchronous	Cancers occurring in the same organ (including paired organs) that are identified with a diagnosis date ≤ 4 months apart, or that are identified at the time of surgery for the first cancer if that surgery is part of the planned first course of therapy. (*m* suffix may be used to indicate multiple tumors in a single organ)
Metachronous	Cancers occurring in the same organ system that are identified with diagnosis dates > 4 months from each other. Staged as a new cancer by using the applicable TNM disease site system.
T0	There is no evidence of a primary tumor, but the body site is suspected. Clinical suspicion exists of a primary tumor, with evidence of regional or distant metastases.
Unknown	T0 is not used for a cancer whose site of origin cannot be determined. For example, when the histology is not specific for a particular primary, and for which no actual site is identified.

Staging at Recurrence or Retreatment (rTNM)

Classification of T, N and M for recurrence or retreatment is denoted by use of the lowercase *r* prefix. The recurrence or retreatment classification is assigned if a cancer recurs after an interval during which the patient has been considered cancer-free (disease-free interval), or if the cancer progresses and the patient has never been disease-free (even if no retreatment is planned).[2]

Studies may ask for the current stage of the patient. In general, restaging at the time of recurrence does not affect the initially assigned clinical and pathological stages at diagnosis. Many institutions do not assign a new stage at the time of recurrence or progression. So, this may need to be determined by looking at the scans, pathology or other documents to determine the recurrent stage. If the Baseline CRF requests the stage at time of recurrence, then the initial stage at diagnosis is not what is reported. For instance, if the patient had a T3 lesion, that was removed by surgery, they could not be T3 at restaging, they would be TX, as the primary was removed.

Glossary

Adjuvant therapy	Treatment designed to eradicate microscopic foci of metastatic disease after local control with surgery, radiation or both.
Biomarkers	A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Also called molecular marker and signature molecule.
Breslow Thicknes	A measure of how deeply a melanoma tumor has grown into the skin. The tumor thickness is usually measured from the top of the tumor to the deepest tumor cells. If the tumor is ulcerated, it is measured from the base of the ulcer to the deepest tumor cells.
CD	Cluster of Differentiation. CD molecules are cell surface markers which are very useful for identification of certain types of cancer
Clark Level	A system for describing how deep skin cancer has spread into the skin. Levels I-V describe the layers of skin involved.
Contralateral	Having to do with the opposite side of the body.
De novo	The first occurrence of cancer in the body.
Distant Mets	Refers to cancer that has spread from the original tumor to distant organs or distant lymph nodes.
Extra capsular extension	Invasion of tumor cells in a lymph node beyond the lymph node capsule and involving the perinodal fat.
Gleason Score	A way of describing prostate cancer based on how abnormal the cancer cells in a biopsy sample look under a microscope and how quickly they are likely to grow and spread.
Grade	A description of a tumor based on how abnormal the cancer cells and tissue look under a microscope and how quickly the cancer cells are likely to grow and spread.

Histology	The type of tissue and cells seen under the microscope
in situ	In its original place. For example, in carcinoma in situ, abnormal cells are found only in the place where they first formed. They have not spread.
In-transit Met	Dermal &/or subcutaneous metastases identified at a distance of > 2cm from the primary melanoma in the region between the primary and the first echelon of regional lymph nodes.
Ipsilateral	On the same side of the body as another structure or a given point.
Isolated Tumor Cells (ITC)	Small clusters of cells not larger than 0.2 mm, or single tumor cells, or fewer than 200 cells in a single histologic cross-section.
Localized	Describes disease that is limited to a certain part of the body. For example, localized cancer is usually found only in the tissue or organ where it began and has not spread to nearby lymph nodes or to other parts of the body.
Lymphovascular invasion	The presence of tumor cells within an endothelium-lined space.
Matted (nodes)	A group of fused lymph nodes. Matted lymph nodes may be a sign of certain conditions, such as infection, sarcoidosis, or lymphoma.
Metachronous	Cancers occurring in the same organ system that are identified with diagnosis dates > 4 months from each other. Staged as a new cancer by using the applicable TNM disease site system.
Micrometastases	Tumor deposits > 0.2 mm & < 2 mm
Macrometastases	Tumor deposit > 2 mm
Micro invasion	An invasive cancer with no focus measured larger than 1 mm^2.
Microsatellite	A small group of tumor cells in an area beside or below, but separate from, the primary melanoma. Microsatellite tumors can only be seen with a microscope. Having a microsatellite tumor is a sign that the melanoma has spread from where it first formed.

Mitotic rate (MR)	A measure of how fast cancer cells are dividing and growing. To find the mitotic rate, the number of cells dividing in a certain amount of cancer tissue is counted. Mitotic rate is used to help find the stage of melanoma and other types of cancer. Higher mitotic rates are linked with lower survival rates.
Natural killer cells (NK)	A group of large, granular lymphocytes that have the intrinsic ability to recognize and destroy some virally infected cells and some tumor cells.
Neoadjuvant	Treatment administered before other therapies.
Nuclear grade	An evaluation of the size and shape of the nucleus in tumor cells and the percentage of tumor cells that are in the process of dividing or growing.
Occult	Cancer in which the site of the primary tumor cannot be found.
Receptor	A molecule inside or on the surface of a cell that binds to a specific substance and causes a specific effect in the cell.
Regional lymph node	A lymph node that drains lymph from the region around a tumor.
Second primary	A term used to describe a new primary cancer that occurs in a person who has had cancer in the past. Second primary cancers may occur months or years after the original primary was diagnosed and treated.
Staging	Performing exams and tests to learn the extent of the cancer within the body, especially whether the disease has spread from where it first formed to other parts of the body.
Synchronous	Cancers occurring in the same organ (including paired organs) that are identified with a diagnosis date $\leq$ 4 months apart, or that are identified at the time of surgery for the first cancer if that surgery is part of the planned first course of therapy. (*m* suffix may be used to indicate multiple tumors in a single organ)
Synoptic report	The standard nomenclature in a pathology report that lists the various requirements, such as the size of tumor, lymphatic invasion and grade of tumor.

TNM	A system of cancer staging in which T stands for the extent of the primary tumor, N stands for the presence or absence and extent of regional lymph node metastasis and M stands for the presence or absence of distant metastasis.
Tumor marker	A product produced by a cancer cell or in response to the presence of cancer, which may be released into the circulation or may remain associated with the cancer cell.
Undifferentiated or anaplastic	Characterized by a loss of differentiation of cells, an irreversible alteration in adult cells toward more primitive cell types; a characteristic of cancer cells.

Answers

Overview:

Page 5: N, M, T

Page 6: A

Page 9: E

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