Staging of Cancer

Mary Linton Peters
Richard S. Pieters, MD
James Liebmann, MD
Geoffrey Graeber, MD

Notes & Additional Reading

Summary and Key Points

1. Staging of cancer occurs prior to the beginning of treatment, or at the first definitive surgery. Clinical staging, which includes radiography and exam findings, takes place initially. Pathologic staging, which is obtained from surgical specimens, can be acquired during the course of surgical treatment. Patients then carry either the clinical stage or the pathologic stage for the duration of their illness.

2. Because the initial clinical or pathologic stage is carried for the duration of a patient's illness, patients with Stage I disease who later develop metastases still have Stage I disease – any given cancer is only staged once.

3. Specific criteria are revised periodically, but the principles of TNM classification are constant for all solid tumors:

   - **T** describes the size or extent of local invasion of the primary tumor
   - **N** describes regional lymph node involvement
   - **M** describes metastatic disease
   - **G** describes the pathologic grade of the primary tumor

   The TNM classification translates to Stage groupings, generally 0-4.

4. Some cancers, including sarcomas, include G (grade) in the Stage Grouping.

5. Cancer stages are created to provide prognostic information and guide treatment decisions.

6. Leukemia, lymphoma, some pediatric malignancies, and a few rare adult malignancies use different staging systems that do not rely on TNM information.

7. Restaging, a term in common use for reassessing a patient's current disease state, is a misnomer.

8. The American College of Surgeons requires pretreatment staging on the chart of each patient. All patients can be staged clinically. Pathologic staging provides more accurate information and is the one most physicians use if available.

9. Staging systems are periodically revised and it is important to know which version was used.

Overview

The "stage" of a cancer is a short-hand way of describing the extent of cancer in a patient. Stage is based on macroscopic involvement of tissues by cancer. By contrast, the "grade" of a cancer is a pathologist's interpretation of how well (low grade) or poorly (high grade) differentiated a tumor is. Cancer grade, therefore, is a microscopic description of malignancy. This chapter will describe principles of cancer staging.

When considering treatments for cancer, one of the first considerations is the stage of disease. Early stage disease has the best prognosis and can be most effectively treated; in some cases curing the disease entirely is a realistic goal. Late stage disease may be considered inoperable or incurable, with treatment focusing on palliation of symptoms and prolonging life. Treatment paradigms are developed for each stage of disease, and clinical trials use disease staging to segregate outcomes. The stage of disease must therefore be determined prior to any therapeutic intervention.

For solid tumors, the tumor node metastasis (TNM) system is used. Although the specific categories differ by tumor type and are periodically revised, the TNM system itself is a common language for most cancers. For hematologic cancers, most pediatric and some rare adult tumor types,[1] staging systems customized to the tumor type are used.

Staging

Clinical stage includes physical exam findings and imaging results. Imaging is generally performed to determine the extent of primary disease and to search for possible metastasis. Imaging techniques include X Ray, CT, MRI, and PET. Scans may encompass the area

YouTube: Understanding Lung Cancer, Part III: Staging (3:18)

[1] Examples: Wilm's tumor, CNS tumors, and esthesioneuroblastoma

of the primary lesion, typical sites for metastasis (spine, bone, brain, liver), and symptomatic areas. Any new or changed lesions found by imaging are considered suspicious for metastatic disease. Careful evaluation of regional lymph node basins may reveal enlarged nodes.

Pathologic stage includes the results of primary tumor resection, lymph node biopsies, and biopsies of any suspected metastasis at presentation. If the definitive surgery follows neoadjuvant treatment, the results are reported as "y stage", but the clinical stage is carried as the patient's actual stage.[2]

Biopsies

As part of the staging process, fine needle aspirate (FNA) or core biopsies may be performed of the primary tumor, enlarged regional lymph node, or site of possible metastasis. Biopsies generally have a high specificity but poor sensitivity. This implies that a biopsy positive for malignant cells is diagnostic and adequate for pathologic staging of nodes or metastases. However, the absence of malignant cells in a biopsy sample is not sufficient to rule out cancer in patients with a high index of suspicion, and the suspicion is sufficient to include the site in clinical staging.

The presence of malignant cells informs the TNM staging process in several ways:

- **pT**: Biopsy is insufficient to define pathologic T Stage; pathologic staging requires resection of the primary
- **pN**: Confirms presence of malignant cells in regional lymph nodes
- **pM**: Confirms presence of distant metastatic disease

[2] cStage III, T4N1M0, yStage II: T1 N1 M0

If biopsy is not possible or results are not available, staging can be done based solely on imaging and physical exam. In this case, the stage is annotated with the prefix "c" to indicate clinical staging without biopsy information.

T: Tumor

There are several different categories of primary tumor classification based mainly on the size or extent of local invasion of the tumor. Typically the T is determined by imaging studies, although in the case of some palpable masses this can be supplemented by direct measurement.

For certain cancers, including breast, carcinoma in situ is staged Tis, and grouped as Stage 0.

Table 1.

T Stage	Breast Cancer	Lung Cancer
T1	Tumor < 2cm (largest dimension)	Tumor < 3cm (largest dimension)
T2	Tumor > 2cm and < 5cm	Tumor > 3cm and < 7cm
T3	Tumor > 5 cm	Tumor > 7 cm
T4	Tumor invaded chest wall, skin, or other neighboring structures	Tumor invaded mediastinum, heart, or other neighboring structures

Note: If there is no detectable primary tumor, but there is nodal or metastatic disease, the classification T0 is used. Tis is used to designate in situ disease with no risk of nodal involvement or metastasis. If the tumor has grown sufficiently large that it directly invades neighboring organs, it typically is classified T4 even if the tumor itself is relatively small.

N: Node

The definition of a regional lymph node varies by the tumor location and local anatomy. N0 is used to indicate the lack of any suspicious lymph nodes on imaging and exam, or pathology.

If the patient has enlarged lymph nodes on exam or imaging, ideally these should be biopsied to determine if there is any malignancy

present. If biopsy cannot be performed, is non-diagnostic, or is negative in the face of substantial clinical suspicion, the clinician may opt for the classification Nx. This indicates that node status cannot be assessed clinically. Often this Nx status is revised following surgical resection, although this may not be possible if the patient receives chemotherapy or radiation therapy prior to node dissection (neoadjuvant therapy).

If regional lymph nodes are found to have malignant cells, the number and location of the involved nodes is designated with N1, N2, and N3 classifications. Table 2 illustrates the AJCC N classifications for breast and lung cancer.

Table 2. AJCC N classifications for breast and lung cancer

N Stage	Breast Cancer	Lung Cancer
N0	No regional lymph node involvement	No regional lymph node involvement
N1	Ipsilateral axillary nodes (freely mobile)	Ipsilateral intrapulmonary, peribronchial, or hilar nodes
N2	Ipsilateral axillary nodes (fixed or matted) OR ipsilateral internal mammary nodes	Ipsilateral mediastinal or subcarinal nodes
N3	Ipsilateral infraclavicular nodes or ipsilateral supraclavicular nodes OR both axillary and internal mammary nodes	Contralateral nodes or supraclavicular nodes

Note: If nodes have previously been removed for another purpose, the patient is defined as Nx. There are many subclassifications regarding the type of cells seen and the number of nodes involved, designated N1a, N1b, etc.

M: Metastasis

Metastases are distant spread of disease to unrelated organs via either hematogenous or lymphatic spread. Metastatic disease is assessed both via a complete physical exam and imaging studies. Neurological signs and new, localized bone pain are frequent

warning signs for metastasis. Bone scans, PET, and head CT are often used to check for metastasis in patients with a high clinical suspicion. This may be based on symptoms or exam findings, or may be due to a high T or N status. Typically M classification correlates with higher T and N stages, although it is possible to have metastasis with T1 or N0 disease.

If there is evidence of distant metastasis, the patient is classified M1. Otherwise the patient is M0. Occasionally the Mx classification is used if there is high suspicion but no clinical or radiographic evidence of distant disease.

TNM to Staging

Once the TNM classification is determined, this can be used to determine the clinical or pathologic stage of disease. There are typically at least 32 different TNM classifications possible (T1-4, N0-3, M0-1), even without considering various modifiers and subclasses. This is an unwieldy number that is not necessary for high-level discussion of disease severity and potential treatment response. Therefore the many different TNM categories are grouped into Stages I-IV. Typically metastatic disease (M1) is Stage IV, regardless of the T or N classification. Based on the AJCC Staging Manual, ,7th edition, a simplified example is shown in Table 3:

Table 3. AJCC lung cancer staging

Lung Cancer	N0	N1	N2	N3
T1	T1N0M0	T1N1M0	T1N2M0	T1N3M0
T2	T2N0M0	T2N1M0	T2N2M0	T2N3M0
T3	T3N0M0	T3N1M0	T3N2M0	T3N3M0
T4	T4N0M0	T4N1M0	T4N2M0	T4N3M0
Any T	AnyTAnyNM1			

Lung Cancer:

Green: Stage I (T1N0M0)

Blue: *Stage II (T1N1M0, T2N0M0, T2N1M0, T3N0M0)*

Orange: *Stage III (T1N2M0, T2N2M0, T3N1M0, T3N2M0, T4N0M0, T4N1M0, T4N2M0, anyTN3M0)*

Stage IIIA (T1N2M0, T2N2M0, T3N2M0)

Stage IIIB (anyTN3M0, T4anyNM0)

Red: *Stage IV (anyTanyNM1)*

Pathology

If the tumor and/or regional nodes are removed surgically, more extensive pathological examination is performed. This does not change the patient's clinical staging, which reflects the state of the malignancy prior to the initiation of treatment. The post-surgical information can be annotated with the prefix "p" to designate a pathological stage (pTNM). The American College of Surgeons requires pretreatment staging on the chart of each patient, which is clinical. All patients can be staged clinically. Pathologic staging provides far more accurate information and is the one most physicians use if available.

If patients receive neoadjuvant chemotherapy or radiotherapy, the size of the tumor (T), number of involved nodes (N), and presence of metastasis (M) might all be reduced. This does not change the patient's official staging, although the new information may be annotated with the prefix "yp" to designate a pathological stage after neoadjuvant treatment. The ypTNM stage does not take the place of the TNM stage, but can provide additional information.

Leukemia, Brain Cancer, etc

Some malignancies are not easily described by the TNM system. Due to their diffuse nature, leukemias are not staged. Accurate pathologic description of leukemias (e.g., acute vs. chronic, myeloid vs. lymphoid, etc.) is very important in determining prognosis and

treatment options for patients. In contrast to leukemias, primary cancers of the brain rarely spread outside of the brain. T stage is relevant in brain tumors. It should be readily apparent that the N and M components of the TNM system are meaningless for a malignancy that does not spread away from its primary organ. Like leukemias, the pathologic description of brain tumors is critically important to predicting prognosis and guiding treatment options for patients.

Progression

A patient's tumor will retain the initial clinical or pathologic staging regardless of disease development. If the primary tumor progresses (T), develops nodal involvement (N) or metastasizes (M), the patient's disease stage does not change, but is noted that the disease has progressed along certain dimensions. The term restaging is heard very often when a reassessment of the current state of a patient's disease is needed, but is a misnomer because it confuses people.

Revisions of Staging Systems

Since the goal of the staging system is to provide prognostic information to the patient and to compare groups of patients with similar prognosis, the staging system for a given cancer may be revised over time based on a review of outcomes for a large number of patients. In addition, changes in technology, usually imaging technology, may lead to improvements in staging systems.

As imaging improves (for example as CT or PET scans become more available), suspicious nodes may be visualized, moving patients into a higher stage grouping than they would have been in based only on older imaging and physical examination. This group of patients will do better than expected for the new higher stage, but would have had the worst prognosis in the former, lower stage.

Will Rogers, a famous American comedian from Oklahoma, stated that when the Okies moved to California (during the Dust Bowl era) they improved the intelligence of both Oklahoma and California.

Therefore, moving them improves the outcome of both the lower and the higher stage overall. This effect is referred to as the Will Rogers effect. These changes and the reasons behind them, are very important to understand which staging version was used when a data driven oncology paper is considered, both academically and clinically.

Thought Questions

1. What did Will Rogers mean when he said that "When the Okies moved to California (during the Dust Bowl era) they improved the intelligence of both Oklahoma and California." Why is it important to understand "the Will Rogers Effect" in oncology?
2. Why do oncologists not change the stage of a patient when they "restage" that patient? What are they trying to accomplish by "restaging"?
3. What is the difference between clinical staging and pathologic staging? If staging is based on diagnostic imaging, what is that called?
4. How do advances in imaging affect staging?
5. Prior to 2011, non-small cell lung cancers presenting with malignant pleural effusions were considered stage IIIb disease. Beginning in January, 2011, these lung cancers were reclassified as stage IV. How do staging system revisions affect interpretation of clinical studies? How could the 2011 change in the lung cancer staging be considered an example of "the Will Rogers effect"?

Glossary

Cancer stage- Describes disease extent, provides prognostic information and guides treatment decisions

Clinical staging- Initial radiography and exam findings

CT- X-ray computed tomography, a series of X-rays that are digitally processed to produce a 3 dimensional map of the density of the body part being imaged. The patient receives a higher dose of radiation than is received in an X-ray.

Grade- A determination of how well or poorly differentiated cancer cells appear to be based on microscopic assessment of a tumor

specimen

MRI- Magnetic resonance imaging, a medical imaging technique wherein the patient is placed in a strong magnetic field. In such fields, hydrogen nuclei give different responses to low-energy radio frequencies according to the local chemical environment. From these responses, 3 dimensional maps of body tissue types are produced. MRI scans are not associated with radiation exposure and are useful in contrasting soft tissues.

Neoadjuvant- Administration of a therapy in preparation for a main treatment. Examples include hormone therapy, radiation therapy and chemotherapy, which may shrink the tumor and make the main treatment safer and/or more effective.

Pathologic staging- Obtained from surgical specimens

PET Scan- Positron emission tomography, a medical imaging technique wherein positron-emitting tracer is incorporated into (usually) a glucose analog and injected into the body. The complex is taken up by the body tissues, with greater uptake in metabolically active areas. As positrons are emitted, they collide with electrons, and produce pairs of gamma ray photons moving in opposite directions, which are detected and localized. This forms a 3-dimensional map of areas of maximal tracer uptake in the body.

TNM Staging System- A common staging system developed by the American Joint Committee on Cancer

X ray- Photons with a shorter wavelength than ultraviolet light are created and passed through the tissues of interest. Dense objects absorb more of the photons, casting a shadow on the sensor on the other side of the body part.

References

AJCC (American Joint Committee on Cancer) Cancer Staging Manual, 7th ed, Edge, SB, Byrd, DR, Compton, CC, et al (Eds), Springer-Verlag, New York, 2010.

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