Principles of Cancer Staging

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INTRODUCTION AND OVERVIEW

The extent or *stage* of cancer at the time of diagnosis is a key factor that defines prognosis and is a critical element in determining appropriate treatment based on the experience and outcomes of groups of previous patients with similar stage. In addition, cancer stage often is a key component of inclusion, exclusion, and stratification criteria for clinical trials. Indeed, accurate staging is necessary to evaluate the results of treatments and clinical trials, to facilitate the exchange and comparison of information across treatment centers and within and between cancer-specific registries, and to serve as a basis for clinical and translational cancer research. At the national and international levels, a cohesive approach to the classification of cancer provides a method of clearly conveying clinical experience to others without ambiguity.

Cancer treatment requires assessment of the extent and behavior of the tumor and patient-related factors. Several cancer staging systems are used worldwide. Differences among these systems stem from the needs and objectives of users in clinical medicine and in population surveillance. The most clinically useful staging system is the tumor, node, and metastasis (TNM) staging system developed by the American Joint Committee on Cancer (AJCC) in collaboration with the Union for International Cancer Control (UICC), herein referred to as the AJCC TNM staging system. The AJCC TNM system classifies cancers by the size and extent of the primary tumor (T), involvement of regional lymph nodes (N), and the presence or absence of distant metastases (M), supplemented in recent years by evidence-based prognostic and predictive factors. There is a TNM staging algorithm for cancers of virtually every anatomic site and histology, with the primary exception of pediatric cancers.

Philosophy of Revisions to the TNM Staging System

The AJCC and UICC periodically modify the AJCC TNM staging system in response to newly acquired clinical and pathological data and an improved understanding of cancer biology and other factors affecting prognosis. Periodic and, to the extent possible, evidence-based revision is a key feature that makes this staging system the most clinically useful among staging systems and accounts for its widespread use worldwide. However, because changes in staging systems may make it difficult to compare outcomes of patients over time, evidence-based changes to this staging system are made with deliberate care.

In general, the revision cycle for AJCC TNM staging has historically been 5 to 7 years. This approach provides sufficient time for implementation of changes in clinical management and cancer registry operations and for relevant examination and discussion of data supporting changes in staging. Table 1.1 shows the publication year for each version of the AJCC TNM system up through this current *AJCC Cancer Staging Manual*, 8th Edition. The *AJCC Cancer Staging Manual*, 7th Edition was used for cancer patients diagnosed on or after January 1, 2010. The 8th Edition published in this manual is effective for cancer patients diagnosed on or after January 1, 2018. The AJCC recognizes that rapidly evolving evidence may necessitate more frequent updates of AJCC TNM staging in the future, and anticipates providing more frequent updates for disease sites as new and validated evidence becomes available. Moreover, the AJCC also recognizes that as clinical cancer care continues to evolve and incorporates factors that are not used to determine stage but that provide key information on specific outcomes and/or expected benefit from specific therapies, new,

To access the AJCC cancer staging forms, please visit www.cancerstaging.org.

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Table 1.1 *AJCC Cancer Staging Manual* editions

Edition	Publication	Effective dates for cancer diagnoses
1st	1977	1978–1983
2nd	1983	1984–1988
3rd	1988	1989–1992
4th	1992	1993–1997
5th	1997	1998–2002
6th	2002	2003–2009
7th	2009	2010–2017
8th	2016	2018–

validated clinical tools will be needed to help clinicians efficiently and accurately use these important data to enhance clinical care (see Anatomic Staging and the Evolving Use of Nonanatomic Factors).

Comprehensive Analysis of Staging Rules and Nomenclature

In January 2012, the AJCC and UICC initiated a comprehensive analysis of staging nomenclature: the AJCC–UICC Lexicon Project. This effort focused on harmonization of their collective staging taxonomies with each other and with international standards. This group concluded that terminology should be categorized into four main groups: (1) anatomic stage—disease extent and timing/classification; (2) tumor profile—characterization of tumor (e.g., biomarkers, viral load); (3) patient profile—age, gender, race, and health status; and (4) environment—availability of treatment and quality of imaging. This joint project thus far has encompassed two working groups—anatomic stage and tumor profile—to thoroughly review the existing nomenclature and standard definitions. The patient profile and environment categories will be addressed in future work.

The Content Harmonization Core (CHC) is one of seven AJCC "cores" developed to inform a more uniform 8th Edition effort. The CHC had its first meeting in August 2014. Building upon the work of the AJCC–UICC Lexicon Project, its charge was to review and update the general staging rules and nomenclature (published in Chapter 1 of the 7th Edition) and to develop a more precise language of cancer to enhance the accuracy of the staging system. A goal of this effort is to standardize technical terms and concepts as well as conflicting terms and usage. Once it identified key issues, the CHC worked with thought leaders and organizations to clarify and ensure precise, standardized, and clear definitions and rules for staging to the extent possible; for some terms and concepts, however, unequivocal clarity could not be achieved (and is noted in the chapter). The work product of the CHC is reflected in this chapter, and provides overall rules for staging that apply across all tumor sites. In most cases, the rules are unchanged from previous versions of TNM; to the extent possible, ambiguities have been resolved. Although the rules generally apply across all disease sites, there are some exceptions as to how these rules are applied to specific disease sites. Wherever possible, such exceptions are noted, both in this chapter and in the appropriate disease site chapters.

Assigning Stage: Role of the Managing Physician

Staging requires the collaborative effort of many professionals, including the managing physician, pathologist, radiologist, cancer registrar, and others. The pathologist plays a central role. An accurate microscopic diagnosis is essential to the evaluation and treatment of cancer. Pathologists must also accurately report several anatomic, histologic, and morphologic characteristics of tumors, as well as key biologic features. Pathological reporting is best accomplished by using standardized nomenclature in a structured report, such as the synoptic reports or cancer protocols defined by the College of American Pathologists (CAP). In addition, for some cancers, measurements of other factors, including biochemical, molecular, genetic, immunologic, or functional characteristics of the tumor or normal tissues have become important or essential elements to improve tumor classification. Some of the growing repertoire of techniques that supplement standard histologic evaluation used to characterize tumors and their potential behavior and response to treatment include immunohistochemistry (IHC), cytogenetic analysis, and genetic characterization in the form of mutational analysis. Similarly, imaging specialists must provide concise and unambiguous reports on the extent of cancer as identified on a variety of imaging studies.

Although the pathologist and the radiologist provide important staging information, and may provide important T-, N-, and/or M-related information, stage is defined ultimately from the synthesis of an array of patient history and physical examination findings supplemented by imaging and pathology data. Only the managing physician can assign the patient's stage, because only (s)he routinely has access to all the pertinent information from physical examination, imaging studies, biopsies, diagnostic procedures, surgical findings, and pathology reports.

Related Publications to Facilitate Staging

In the interest of promoting high-quality care, and to facilitate international collaboration in cancer research and comparison of data among different clinical studies, the AJCC uses information from other organizations and publications to facilitate staging, including:

- *World Health Organization Classification of Tumours, Pathology and Genetics*. Since 1958, the World Health Organization (WHO) has had a program aimed at providing internationally accepted criteria for the histologic classification of tumors. The series contains definitions, descriptions, and illustrations of tumor types and related nomenclature (WHO: World Health Organization Classification of Tumours. Various editions. Lyon, France: IARC Press, 2000–2016).
- *WHO International Classification of Diseases for Oncology (ICD-O), 3rd edition*. ICD-O is a numeric classification and coding system by topography and morphology (WHO: ICD-O-3 International Classification of Diseases for Oncology. 3rd ed. Geneva: WHO, 2000).
- *American College of Radiology Appropriateness Criteria®*. The American College of Radiology (ACR) maintains guidelines and criteria for use of imaging and interventional radiology procedures for many aspects of cancer care. This includes the extent of imaging recommended for the diagnostic evaluation of the extent of disease of the primary tumor, nodes, and distant metastases for several cancer types. The ACR Appropriateness Criteria® are updated regularly (http://www.acr.org/ac).
- *CAP Cancer Protocols*. CAP publishes standards for pathology reporting of cancer specimens for all cancer types and cancer resection types. These specify the elements necessary for the pathologist to report the extent and characteristics of cancer specimens (http://www.cap.org).
- *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®).* The National Comprehensive Cancer Network (NCCN) provides practice guidelines for most types of cancer. These guidelines are updated at least annually. They include recommendations for diagnostic evaluation and imaging of the primary tumor and screening for metastases for each cancer type that may be useful to guide staging (http://www.nccn.org).
- *American Society of Clinical Oncology (ASCO) Guidelines.* ASCO develops guidelines and technical assessments for an array of clinical situations and tools. These include disease- and modality- specific guidelines and assessments of tools, such as the use of biomarkers in certain cancers. These guidelines may be found at the ASCO website: www.asco.org.

Anatomic Staging and the Evolving Use of Nonanatomic Factors

Historically, cancer staging has been based solely on the anatomic extent of cancer, and the 8th Edition approach remains primarily anatomic. However, an increasing number of nonanatomic cancer- and host-related factors provide critical prognostic information and may predict the benefit of specific therapies. Among factors shown to affect patient outcome and/or response to therapy are the clinical and pathological anatomic extent of disease; the reported duration of signs or symptoms; the gender, age, and health status of the patient; the tumor type and grade; and specific biological properties of the cancer and host. Clinicians often use pure anatomic extent of disease in defining treatment, but in many cases, they supplement TNM-based staging with other factors to counsel patients and offer specific treatment recommendations. As more of these and other factors are embraced, applying them in practice will become increasingly complex. This will make it essential to initiate strategies to develop clinically validated prognostic tools and incorporate them into practice to enhance patient management and overall clinical decision making, ideally while maintaining a core anatomic-based structure of staging. Such an integrated approach may reduce the potential for the de facto anatomically constrained TNM system to be rendered obsolete by fostering incorporation of an unprecedented and rapidly evolving understanding of the biology of human cancer. See also Chapter 4, Risk Assessment Models, for more information on AJCC-initiated efforts to embrace development of clinically validated tools.

As introduced in this chapter and detailed throughout this cancer staging manual, in many of the revised AJCC staging algorithms, prognostic factors have been incorporated into stage groupings for specific disease sites where indicated. Because this practice was initiated in a limited fashion in previous editions, most prognostic factors in use, if validated, have been done so only for patients with specific types of disease stratified largely by anatomic stage (e.g., Gleason score in early-stage prostate cancer and genomic profiles in women with node-negative breast cancer). It is important to recognize that even with these advances, anatomic extent of disease remains central to defining cancer prognosis. Inclusion of anatomic extent also maintains the ability to compare patients in a similar fashion across both contemporary and historical treatment regimens and eras, as well as patient populations for whom new prognostic factors cannot be obtained because of cost, available expertise, reporting systems, and/or other logistical issues.

AJCC TNM STAGING SYSTEM: CLASSIFICATIONS, CATEGORIES, AND RULES FOR STAGING

The AJCC TNM stage for each cancer type is built by defining the anatomic extent of cancer for the tumor (T), lymph nodes (N), and distant metastases (M), supplemented in some cases with nonanatomic factors. For each of the T, N, and M, there is a set of categories, most often defined by a

number (e.g., T1, N2). The description of the anatomic factors is specific for each disease site. These descriptors and the nomenclature for TNM have been developed and refined over many editions of the *AJCC Cancer Staging Manual* by experts in each disease and by cancer registrars who collect the information, taking into consideration the behavior and natural history of each type of cancer. These elements are then combined, in a fashion set forth for each cancer type, into prognostic stage groups (often called "stage groups").

Importantly, the term *stage* should be used only to describe the aggregate information resulting from T, N, and M category designations (i.e., based on T, N, and M classifications) combined with any prognostic factors relevant to the specific disease. The term *stage* should not be used to describe individual T, N, or M category designations that often are mistakenly referred to as "stage."

Assigning the T, N, and M categories follows general rules described in the tables in this chapter. These rules apply to all cancer sites, with relatively few exceptions. These exceptions are defined in the relevant disease-specific chapters.

Rules are repeated throughout this chapter to facilitate easy reference based on the topic.

Before delineating the specific rules for T, N, and M categorization and for generating prognostic stage groups, it is important to first delineate the time points, termed *classifications*, at which staging information is collected and reported.

TNM Staging Classification: Clinical, Pathological, Posttherapy, Recurrence, and Autopsy

Stage may be defined at several time points in the care of the cancer patient. To properly stage a patient's cancer, it is essential to first determine the time point in a patient's care. These points in time are termed *classifications*, and are based on time during the continuum of evaluation and management of the disease. Then, T, N, and M categories are assigned for a particular classification (clinical, pathological, posttherapy, recurrence, and/or autopsy) by using information obtained during the relevant time frame, sometimes also referred to as a *staging window*. These staging windows are unique to each particular classification and are set forth explicitly in the following tables. The prognostic stage groups then are assigned using the T, N, and M categories, and sometimes also site-specific prognostic and predictive factors.

Among these classifications, the two predominant are clinical classification (i.e., pretreatment) and pathological classification (i.e., after surgical treatment).

Clinical Classification (cTNM)

Clinical stage classification is based on patient history, physical examination, and any imaging done before initiation of treatment. Imaging study information may be used for clinical staging, but clinical stage may be assigned based on whatever information is available. No specific imaging is required to assign a clinical stage for any cancer site. When performed within this framework, biopsy information on regional lymph nodes and/or other sites of metastatic disease may be included in the clinical classification.

Clinical evaluation by physical examination often underestimates the extent of cancer burden at the time of patient presentation. Although imaging is not required to assign clinical stage, clinical imaging has become increasingly important, and for many cancer sites, imaging is essential to stage solid tumors accurately. Imaging allows assessment of the tumor's size, location, and relationship to normal anatomic structures, as well as the existence of nodal and/or distant metastatic disease. 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 have important roles in various clinical situations. Thus, a new section was added to the disease site chapters to provide context-specific imaging information. To adequately and comprehensively communicate essential information, radiologists should use standardized nomenclature and structured report formats, such as those recommended by the Radiological Society of North America (RSNA) reporting initiative (http://www.rsna.org/Reporting_Initiative.aspx). In addition to providing key information for assigning the T, N, and M categories, clinical imaging is invaluable for guiding biopsies and surgical resections. Later in the course of a patient's treatment, imaging also often plays an important role in monitoring response to treatment.

Pathological Classification (pTNM)

Pathological stage classification is based on clinical stage information supplemented/modified by operative findings and pathological evaluation of the resected specimens. This classification is applicable when surgery is performed before initiation of adjuvant radiation or systemic therapy.

Posttherapy or Post Neoadjuvant Therapy (ycTNM and ypTNM)

Stage determined after treatment for patients receiving systemic and/or radiation therapy alone or as a component of their initial treatment, or as neoadjuvant therapy before planned surgery, is referred to as posttherapy classification. It also may be referred to as post neoadjuvant therapy classification.

Recurrence or Retreatment (rTNM)

Staging classifications at the time of retreatment for a recurrence or disease progression is referred to as recurrence classification. It also may be referred to as retreatment classification.

Autopsy (aTNM)

Staging classification for cancers identified only at autopsy is referred to as autopsy classification.

Defining T, N, M, and Prognostic Factor Categories

The T, N, and M designations are referred to as categories. The category criteria for defining anatomic extent of disease are specific for tumors at different anatomic sites and sometimes for tumors comprising different histologic types arising from similar anatomic sites. For example, the size of the tumor is a key factor in breast cancer but has no impact on prognosis in colorectal cancer, in which the depth of invasion or extent of the cancer is the primary prognostic feature. In summary, the T, N, and M category criteria are defined separately for each tumor and histologic type.

In addition to anatomic-based T, N, and M information, the AJCC recommends collection of key prognostic factors for specific cancer sites (as detailed in each site chapter) that in some cases are used to define T, N, or M and/or may be used to define stage groupings critical to prognosis and/or helpful to guide patient care and to ensure uniformity in comparative research and reporting environments.

The AJCC includes additional factors that play a role in the calculation of the AJCC Prognostic Stage Group for a disease site. If available and applicable to the disease site, so-called Prognostic Factors Required for Stage Grouping can modify the calculation of stage based only on TNM. These factors are involved in the calculation of stage in several disease sites, such as breast and prostate.

A different system for designating the extent of disease and prognosis is necessary for certain types of tumors, such as Hodgkin and other lymphomas. In these circumstances, other categories are used instead of T, N, and M, and for lymphoma, only the stage group is defined. General staging rules are presented in this chapter, and the specifics for each type of disease are detailed in the respective disease site–specific chapters.

AJCC Prognostic Stage Groups

For the purposes of tabulation and to analyze the care of patients who generally have a similar prognosis, T, N, and M are grouped into *prognostic stage groups*, commonly referred to as stage groups. As introduced earlier, a stage group is determined from aggregate information on the primary tumor (T), regional lymph nodes (N), and distant metastases (M), as well as any specified prognostic factors for certain cancer types. Stage groups are based primarily on anatomic information, supplemented by selected prognostic factors in some disease sites. Stage groups are defined for each of the classifications: clinical stage group and pathological stage group.

Documenting Cancer Stage in the Medical Record

All staging classifications—and, most importantly, clinical and pathological classifications—should be documented in the medical record. The documentation in the record should include the type of classification (e.g., clinical or pathological); T, N, and M categories; relevant prognostic factor categories; and the stage grouping. Clinical stage generally is used to define primary therapy. TNM-based clinical stage also is important because it may be the only common denominator across all cancers of a certain anatomic site and histology. Examples include lung cancer, advanced gastrointestinal tumors, and head and neck cancers, for which surgery may not be performed, and others, such as prostate cancer, for which surgical resection for limited disease may not be applicable. In such scenarios, it may be impossible to compare patients for whom information is obtained solely by clinical staging strategies with those undergoing surgical resection and for whom pathological staging is performed. The importance of clinical stage was reinforced in 2008 when the American College of Surgeons Commission on Cancer (CoC) introduced the requirement that clinical stage be documented in all cancer patients as part of its cancer program standards, as a key determinant of treatment choice. Pathological staging is used to define a more precise prognosis and to plan other therapies as required.

Many options exist for documenting staging data in the medical record. Examples of source documents in the medical record that may contain patient-specific cancer staging information include initial clinical evaluations and consultations, operative reports, imaging studies, pathology reports, discharge summaries, and follow-up reports. Physicians are encouraged to enter the stage of cancer in every record of clinical encounters with the cancer patient. Paper or electronic staging forms may be useful to record stage in the medical record as well as to facilitate communication of staging data to a cancer registry. A form for recording cancer staging data will be made available for each disease site on www.cancerstaging.org.

T, N, and M category information as well as disease site-specific prognostic factor data should be included in pathology reports whenever these data are available. Pathologists should use the appropriate AJCC-specified data elements as defined by the CAP Cancer Protocols. However, the determination of stage usually involves synthesis of

information from multiple sources, including clinical data, imaging studies, and pathology reports. Because all this information may not be available to the reporting pathologist, final T, N, and M categories and stage may not be fully assessed from pathology reports alone and should be assigned by the managing physician(s).

TNM and Prognostic Stage Group Tables

TNM information in each chapter provides precise criteria and rules for categorizing the T, N, or M of a patient for the relevant classification (e.g., clinical, pathological). This information is used to assign prognostic stage groups based on the assigned T, N, and M categories (with other prognostic factors if required for that specific cancer type).

Elements of TNM tables	Description
Classification	A lower case prefix describes the time point in a patient's cancer continuum when stage is assigned, including: • c: clinical • p: pathological • yc: post neoadjuvant (radiation or systemic) therapy—clinical • yp: post neoadjuvant (radiation or systemic) therapy—pathological • r: recurrence or retreatment • a: autopsy
Category	T-, N-, and M-specific data are used to assign a cancer site–specific T, N, and M category for a patient at a given classification. Generally, the higher the T, N, or M category, the greater the extent of the disease and generally the worse the prognosis. *Note*: Exceptions exist in which T-, N-, or M-specific category elements may represent unique characteristics of the cancer but not necessarily worse prognosis. For example, N1c in colon cancer does not represent greater nodal disease burden than N1a or N1b, but rather a unique situation.
Subcategory	Some disease sites have subcategories devised to facilitate reporting of more detailed information and often more specific prognostic information. Examples: • breast cancer: T1mi, T1a, T1b, T1c • breast cancer: N2a, N2b • prostate cancer: M1a, M1b, M1c *Note*: If there is uncertainty in assigning a subcategory, the patient is assigned to the general category. For example, a breast cancer reported clinically as <2 cm without further specification is assigned T1 and cannot be assigned T1a, T1b, or T1c. If uncertain or incomplete information precludes subcategory assignment, which may result in different stage groups or management paradigms, 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.
AJCC prognostic stage groups (stage groups)	AJCC prognostic stage groups are assigned based on disease site–specific T, N, and M categories and relevant prognostic factors to group patients with similar prognosis and/or treatment approach. For each cancer type in which prognostic factors are used to assign stage groups, a separate stage group may be assigned based solely on anatomic categories so as to allow stage group comparisons among patients who have and do not have available prognostic factor information.

T, N, M and Prognostic Factor Category Criteria

The three categories—T, N, and M—and the prognostic factors collectively describe, with rare exceptions, the extent of tumor, including local spread, regional nodal involvement, and distant metastasis. It is important to stress that each component (T, N, and M) is referred to as a *category*. The term *stage* is used when T, N, and M and cancer site–specific required prognostic factors are combined. The criteria for T, N, and M are defined separately for cancers in different anatomic locations and/or for different histologic types.

This category…	Is defined by…
T	The size and/or contiguous extension of the primary tumor. *Note*: The roles of the size component and the extent of contiguous spread are specifically defined for each cancer site.
N	Cancer in the regional lymph nodes as defined for each cancer site, including • absence or presence of cancer in regional node(s), and/or • number of positive regional nodes, and/or • involvement of specific regional nodal groups, and/or • size of nodal metastasis or extension through the regional node capsule, and/or • In-transit and satellite metastases, somewhat unique manifestations of nonnodal intralymphatic regional disease, usually found between the primary tumor site and draining nodal basins. *Note*: For melanoma and Merkel cell carcinoma, nonnodal regional metastasis, such as satellites and in-transit metastases, may be included in the N categorization (see the melanoma and Merkel cell carcinoma chapters for specifics). For colorectal carcinoma, mesenteric tumor deposits without remaining nodal architecture are included in the N category.
M	The absence or presence of distant metastases in sites and/or organs outside the local tumor area and regional nodes as defined for each cancer site. For some cancer sites, the location and volume or burden of distant metastases are included.

This category…	Is defined by…
Prognostic factors required for stage grouping	The prognostic factors required for stage grouping have such a strong correlation with prognosis that they are included in the AJCC Prognostic Stage Groups table. It is important to collect these factors in cancer registries and databases to measure their impact on prognosis.

Primary Tumor (T) Categories

Primary tumor categories have specific notations to describe the existence, size, or extent of the tumor.

Tumor category…	Is assigned when there is…
TX	No information about the T category for the primary tumor, or it is unknown or cannot be assessed *Note*: Use of the TX category should be minimized.
T0	No evidence of a primary tumor
Tis	Carcinoma *in situ* **Examples of exceptions include**: Tis for *in situ* melanoma of the skin, germ cell neoplasia *in situ* for testis, and high-grade dysplasia in colorectal carcinoma.
T1, T2, T3, or T4	Primary invasive tumor, for which a higher category generally means • an increasing size • an increasing local extension, or • both

Regional Lymph Node (N) Categories

Categorizing regional lymph node involvement depends on its existence and extent.

Regional node category…	Is assigned when there is…
NX	No information about the N category for the regional lymph nodes, or it is unknown or cannot be assessed *Note:* Use of NX should be minimized.
N0	No regional lymph node involvement with cancer and for some disease sites, nonnodal regional disease as noted earlier
N1, N2, or N3	Evidence of regional node(s) containing cancer, with • an increasing number, and/or • regional nodal group involvement, and/or • size of the nodal metastatic cancer deposit, or • non-nodal regional disease as noted earlier for melanoma and Merkel cell carcinoma, and for colorectal carcinoma

Distant Metastasis (M) Categories

The distant metastasis category specifies whether distant metastasis is present.

Distant metastasis category…	Is assigned when there is…
M0	No evidence of distant metastasis
M1	Distant metastasis

Notes: There is no designation of MX. The absence of any clinical history or physical findings suggestive of metastases in a patient who has not undergone any imaging is sufficient to assign the clinical M0 category (cM0).
There is no designation of pM0. Biopsy or other pathological information is required to assign the pathological M1 category. Patients with a negative biopsy of a suspected metastatic site are classified as clinical M0 (cM0).

Distant Metastasis: Selected Locations

The M1 category may be specified further according to the location of distant metastases.

Location	Notation
Pulmonary	PUL
Osseous	OSS
Hepatic	HEP
Brain	BRA
Distant lymph nodes	LYM
Bone marrow	MAR
Pleura	PLE
Peritoneum	PER
Adrenal	ADR
Distant skin	SKI
Other	OTH

Unknown Designation: X

The X designation is used if information on a specific T or N category is unknown; such cases usually cannot be assigned a stage. Therefore, TX and NX should be used only if absolutely necessary. Of note, there is no MX category.

Exceptions: TX

Stage may be assigned when the TNM stage group results in Any T or Any N with M1, which includes TX or NX. These are classified as Stage IV. Examples include:

- TX NX M1, or
- TX N3 M1.

Stage may be assigned when the TNM stage group results in Any T or Any N with M0, which includes TX or NX. Examples include:

- TX N1 M0 Stage III in melanoma clinical stage
- T4 NX M0 Stage III in pancreas

MX is Not a Valid M Category

The MX category was eliminated from the AJCC and UICC TNM systems in the *AJCC Cancer Staging Manual*, 6th Edition. Unless there is clinical or pathological evidence of distant metastases, the patient is classified as clinical M0 and denoted as cM0. It is not necessary to perform any imaging or invasive studies to categorize a patient as cM0. A history and physical examination are all that is needed to assign cM0. The M category must always be known and reported to assign a stage group.

Pathologists should not report an M category unless appropriate for the specimen evaluated. CAP Cancer Protocols require documentation of distant metastases as pM1 only if present in the specimen(s) provided to the pathologist. If the pathologist does not review and report on a metastatic specimen, or if a biopsy is performed of a possible distant metastasis and the biopsy does not show cancer, then there should be no mention of the M category in the pathology report, or the pathologist should designate the M category as "not applicable." The term *MX* should not be used in the pathology report.

The managing physician should stage a patient for whom a biopsy performed for possible distant metastasis does not demonstrate cancer as cM0; there is no pM0 designation. Only the managing physician can assign cM0 after taking into account physical examination, imaging, and other information.

AJCC Prognostic Stage Groups

The purpose of defining and assigning stage groups is to generate a reproducible and easily communicated summary of staging information. The staging tables generally group patients with similar prognoses, usually with a statistically significant separation in outcomes between stage groups. Patients within a stage group generally have similar outcomes, even though their burden of disease may vary. Exceptions to this general stage group convention are noted in each chapter where relevant. For example, to retain an anatomic- and TNM-based staging system in melanoma, some prognostic overlap was allowed between patients with Stage IIC melanoma and those with Stage IIIA melanoma; many patients with Stage IIIA disease have a prognosis more favorable than that of patients with Stage IIC disease.

Stage groups are denoted by Roman numerals from I to IV with increasing extent of disease and generally with worsening overall prognosis. Stage I generally indicates cancers that are smaller or less deeply invasive without regional disease or nodes, Stages II and III define patients with increasing tumor or nodal extent, and Stage IV identifies those who present with distant metastases (M1) at diagnosis.

The term *Stage 0* is used to denote carcinoma *in situ* (or melanoma *in situ* for melanoma of the skin or germ cell neoplasia *in situ* for testicular germ cell tumors) and generally is considered to have no metastatic potential. Stage 0 is determined by microscopic examination of the primary tumor. Stage I through Stage IV subgroups are denoted by capital letters—for example, A, B, or C—according to cancer site stage grouping definitions and are used to expand the main groupings to provide more refined prognostic information.

Prognostic Factors Required for Stage Grouping

For some cancer types, in addition to T, N, and M categories, prognostic factors are required to assign a stage group. Examples include tumor grade, age at diagnosis, histologic type, mitotic rate, serum tumor markers, hormone receptors, hereditary factors, prostate-specific antigen, and Gleason score. Specifically, cancer site–specific prognostic factors populate nonanatomic categories and are defined clearly if required for a particular disease site.

These factors generally constitute categories used with the TNM categories to assign prognostic stage groups. In some cases in which factors are used in stage groups, an X category is provided for use by the managing physician if the factor is not available. Generally, in cases in which the factor is absent and X is not provided as an option, the physician's determination or lowest category (best prognosis) of the factor is used to assign the stage group.

In contrast, cancer registry data collection should record *X* or *unknown* if the prognostic factor is not available, and should not use the lowest category. This allows for accurate analysis of the data.

GENERAL STAGING RULES

These general rules apply to the application of T, N, and M categories for all anatomic sites and classifications.

Topic	Rules
Microscopic confirmation	• Microscopic confirmation is necessary for TNM classification, including clinical classification (with rare exception). • In rare clinical scenarios, patients who do not have any biopsy or cytology of the tumor may be staged. This is recommended in rare clinical situations, only if the cancer diagnosis is NOT in doubt. In the absence of histologic confirmation, survival analysis may be performed separately from staged cohorts with histologic confirmation. Separate survival analysis is not required if clinical findings support a cancer diagnosis and specific site. **Example**: Lung cancer diagnosed by CT scan only, that is, without a confirmatory biopsy
Time frame/staging window for determining clinical stage	Information gathered about the extent of the cancer is part of clinical classification: • from date of diagnosis before initiation of primary treatment or decision for watchful waiting or supportive care to one of the following time points, whichever is shortest: ○ 4 months after diagnosis ○ to the date of cancer progression if the cancer progresses before the end of the 4 month window; data on the extent of the cancer is only included before the date of observed progression
Time frame/staging window for determining pathological stage	Information including clinical staging data and information from surgical resection and examination of the resected specimens—if surgery is performed before the initiation of radiation and/or systemic therapy—from the date of diagnosis: • within 4 months after diagnosis • to the date of cancer progression if the cancer progresses before the end of the 4-month window; data on the extent of the cancer is included only before the date of observed progression • and includes any information obtained about the extent of cancer up through completion of definitive surgery as part of primary treatment if that surgery occurs later than 4 months after diagnosis and the cancer has not clearly progressed during the time window *Note*: Patients who receive radiation and/or systemic therapy (neoadjuvant therapy) before surgical resection are not assigned a pathological category or stage, and instead are staged according to post neoadjuvant therapy criteria.
Time frame/staging window for staging post neoadjuvant therapy or posttherapy	After completion of neoadjuvant therapy, patients should be staged as: • yc: posttherapy clinical After completion of neoadjuvant therapy followed by surgery, patients should be staged as: • yp: posttherapy pathological The time frame should be such that the post neoadjuvant surgery and staging occur within a time frame that accommodates disease-specific circumstances, as outlined in the specific chapters and in relevant guidelines. *Note*: Clinical stage should be assigned before the start of neoadjuvant therapy.
Progression of disease	If there is documented progression of cancer before therapy or surgery, only information obtained before the documented progression is used for clinical and pathological staging. Progression does not include growth during the time needed for the diagnostic workup, but rather a major change in clinical status. Determination of progression is based on managing physician judgment, and may result in a major change in the treatment plan.
Uncertainty among T, N, or M categories, and/or stage groups: rules for clinical decision making	If uncertainty exists regarding how to assign a category, subcategory, or stage group, the lower of the **two possible** categories, subcategories, or groups is assigned for • T, N, or M • prognostic stage group/stage group Stage groups are for patient care and prognosis based on data. Physicians may need to make treatment decisions if staging information is uncertain or unclear. *Note*: Unknown or missing information for T, N, M or stage group is never assigned the lower category, subcategory, or group.
Uncertainty rules do not apply to cancer registry data	If information is not available to the cancer registrar for documentation of a subcategory, the main (umbrella) category should be assigned (e.g., T1 for a breast cancer described as <2 cm in place of T1a, T1b, or T1c). If the specific information to assign the stage group is not available to the cancer registrar (including subcategories or missing prognostic factor categories), the stage group should not be assigned but should be documented as unknown.
Prognostic factor category information is unavailable	If a required prognostic factor category is unavailable, the category used to assign the stage group is: • X, or • If the prognostic factor is unavailable, default to assigning the anatomic stage using clinical judgment.
Grade	The recommended histologic grading system for each disease site and/or cancer type, if applicable, is specified in each chapter and should be used by the pathologist to assign grade. The cancer registrar will document grade for a specific site according to the coding structure in the relevant disease site chapter.

Topic	Rules
Synchronous primary tumors in a single organ: *(m)* suffix	If multiple tumors of the same histology are present in one organ: • the tumor with the highest T category is classified and staged, and • the *(m)* suffix is used • An example of a preferred designation is: pT3(m) N0 M0. • If the number of synchronous tumors is important, an acceptable alternative designation is to specify the number of tumors. For example, pT3(4) N0 M0 indicates four synchronous primary tumors. *Note*: The *(m)* suffix applies to multiple invasive cancers. It is not applicable for multiple foci of *in situ* cancer or for a mixed invasive and *in situ* cancer.
Synchronous primary tumors in paired organs	Cancers occurring at the same time in each of paired organs are staged as separate cancers. Examples include breast, lung, and kidney. **Exception:** For tumors of the thyroid, liver, and ovary, multiplicity is a T-category criterion, thus multiple synchronous tumors are not staged independently.
Metachronous primary tumors	Second or subsequent primary cancers occurring in the same organ or in different organs outside the staging window are staged independently and are known as metachronous primary tumors. Such cancers are not staged using the *y* prefix.
Unknown primary or no evidence of primary tumor	If there is no evidence of a primary tumor, or the site of the primary tumor is unknown, staging may be based on the clinical suspicion of the organ site of the primary tumor, with the tumor categorized as T0. The rules for staging cancers categorized as T0 are specified in the relevant disease site chapters. **Example**: An axillary lymph node with an adenocarcinoma in a woman, suspected clinically to be from the breast, may be categorized as T0 N1 (or N2 or N3) M0 and assigned Stage II (or Stage III). **Examples of exception**: The T0 category is not used for head and neck squamous cancer sites, as such patients with an involved lymph node are staged as unknown primary cancers using the "Cervical Nodes and Unknown Primary Tumors of the Head and Neck" system (T0 remains a valid category for human papillomavirus [HPV]- and Epstein–Barr virus [EBV]-associated oropharyngeal and nasopharyngeal cancers).
Date of diagnosis	It is important to document the date of diagnosis, because this information is used for survival calculations and time periods for staging. The date of diagnosis is the date a physician determines the patient has cancer. It may be the date of a diagnostic biopsy or other microscopic confirmation or of clear evidence on imaging. This rule varies by disease site and shares similarities with the earlier discussion on microscopic confirmation.

STAGE CLASSIFICATIONS

Stage classifications are determined according to the point in time of the patient's care in relation to diagnosis and treatment. The five stage classifications are clinical, pathological, posttherapy/post neoadjuvant therapy, recurrence/retreatment, and autopsy.

Classification	Designation	Details
Clinical	cTNM or TNM	**Criteria:** used for all patients with cancer identified before treatment It is composed of diagnostic workup information, until first treatment, including: • clinical history and symptoms • physical examination • imaging • endoscopy • biopsy of the primary site • biopsy or excision of a single regional node or sentinel nodes, or sampling of regional nodes, with clinical T • biopsy of distant metastatic site • surgical exploration without resection • other relevant examinations *Note*: Exceptions exist by site, such as complete excision of primary tumor for melanoma.
Pathological	pTNM	**Criteria**: used for patients if surgery is the first definitive therapy It is composed of information from: • diagnostic workup from clinical staging combined with • operative findings, and • pathology review of resected surgical specimens

Classification	Designation	Details
Posttherapy or post neoadjuvant therapy	ycTNM and ypTNM	For purposes of posttherapy or post neoadjuvant therapy, *neoadjuvant therapy* is defined as systemic and/or radiation therapy given before surgery; primary radiation and/or systemic therapy is treatment given as definitive therapy without surgery. **yc** The yc classification is used for staging after primary systemic and/or radiation therapy, or after neoadjuvant therapy and before planned surgery **Criteria**: First therapy is systemic and/or radiation therapy **yp** The yp classification is used for staging after neoadjuvant therapy and planned post neoadjuvant therapy surgery. **Criteria:** First therapy is systemic and/or radiation therapy and is followed by surgery.
Recurrence or retreatment	rTNM	This classification is used for assigning stage at time of recurrence or progression until treatment is initiated. **Criteria**: Disease recurrence after disease-free interval or upon disease progression if further treatment is planned for a cancer that: • recurs after a disease-free interval or • progresses (without a disease-free interval) **rc** Clinical recurrence staging is assigned as rc. **rp** Pathological staging information is assigned as rp for the rTNM staging classification. This classification is recorded in addition to and does not replace the original previously assigned clinical (c), pathological (p), and/or posttherapy (yc, yp) stage classifications, and these previously documented classifications are not changed.
Autopsy	aTNM	This classification is used for cancers not previously recognized that are found as an incidental finding at autopsy, and not suspected before death (i.e., this classification does not apply if an autopsy is performed in a patient with a previously diagnosed cancer). **Criteria:** No cancer suspected prior to death Both clinical and pathological staging information is used to assign aTNM.

Clinical Classification

Classification of T, N, and M during the diagnostic workup time frame is denoted by use of a lower case *c* prefix: cT, cN, and cM0, cM1 or pM1, or the use of no prefix: T, N, M.

Clinical stage is important to record for all patients because:

- clinical stage is essential for selecting initial therapy, and
- clinical stage is critical for comparison across patient cohorts when some have surgery as a component of initial treatment and others do not.

Clinical stage may be the only stage classification by which comparisons can be made across all patients, because not all patients will undergo surgical treatment before other therapy, and response to treatment varies. Differences in primary therapy make comparing groups of patients difficult if that comparison is based on pathological assessment. For example, it is difficult to compare patients treated with primary surgery with those treated with chemotherapy or radiotherapy without surgery or neoadjuvant therapy.

Time frame: Clinical classification is based on any information gathered about the extent of the cancer from the time of diagnosis until the initiation of primary treatment or the decision for watchful waiting or supportive care, and is based on the shorter of two periods of time:

- within 4 months after diagnosis, or
- the time of cancer progression if the cancer progresses before the end of the 4-month window; data on the extent of the cancer is included only before the date of observed progression

Criteria: All patients with cancer identified before treatment.

Clinical classification is based on:

- clinical history and symptoms
- physical examination
- imaging
- endoscopy or surgical exploration without resection
- biopsy of the primary site, biopsy or excision of a single regional node or sentinel nodes, sampling of regional nodes with clinical T, or biopsy of a distant metastatic site

Clinical classification is based on evidence acquired from the date of diagnosis until initiation of primary treatment. Examples of primary treatment include definitive surgery, radiation therapy, systemic therapy, and neoadjuvant radiation and systemic therapy.

Importantly, clinical stage groups cannot be assigned for some cancer sites if the necessary minimum information to assign a clinical stage group is not available. Although this scenario is quite uncommon, it may occur—for example, if lymph nodes cannot be examined before surgical resection or if a cancer is identified and resected incidentally during surgery for another medical condition.

Component of clinical staging	Details
Assignment of stage by managing physician	Clinical stage is assigned based on a synthesis of clinical data from multiple sources and only by the managing physician, usually a surgical or medical oncologist. As noted earlier, the assignment of clinical stage also may include pathological data from biopsies.
Known or suspected tumor	Tumor must be known or suspected and have a diagnostic workup including at least a history and physical examination to assign a clinical stage. Incidental findings at the time of surgical treatment may not be assigned a clinical stage retrospectively.
Imaging studies	Imaging may be of value and useful, but imaging is not necessary to assign a clinical stage. Guidelines for diagnostic evaluation of individual cancer types are found in these publications: • ACR Appropriateness Criteria® http://www.acr.org/ac • NCCN Guidelines® http://www.nccn.org.
Impact of subsequent information	The clinical stage should not be changed based on: • subsequent information obtained from the pathological examination of resected tissue, or • information obtained after initiation of definitive therapy.

Clinical T (T or cT)

Assessment of the primary tumor is necessary to determine the cT category.

Component of cT	Details
Tumor size and extent	Based on physical examination, imaging, endoscopy, biopsy of the primary site (core through long axis), surgical exploration, or other relevant examinations. The most accurate size should be used, as some methods may overestimate the size. Therefore, the largest size may not be the most accurate and should not be used automatically. Guidance on which imaging technique(s) may be most accurate is discussed in site-specific chapters. Physicians should document the most accurate tumor size used for staging.
Tumor size in millimeters and rounding for T-category assignment	Primary tumor size is the most accurate/largest dimension and is • measured to the nearest whole millimeter, unless a smaller unit is specified in a specific disease site, and • rounded up or down as appropriate for assigning T category: ○ down when the numerals are between 1 and 4 ○ up when the numerals are between 5 and 9. **Examples:** • Tumor measured as 2.2 mm is recorded as 2 mm. • Tumor measured as 1.7 mm is recorded as 2 mm. • Tumor measured as 2.04 cm is recorded as 20 mm and would be grouped with ≤2 cm and not >2 cm. **Nonexhaustive exceptions**: • Melanoma: primary tumor measured to nearest 0.1 mm • Breast cancer: primary tumor >1.0 mm to 1.4 mm rounded to 2 mm (this avoids assigning the "microinvasion" category to cancer >1.0 mm)
Surgical exploration	Observations made at surgical exploration without resection are used to assign clinical categories. Biopsies of the primary site during surgical exploration without resection of the primary tumor are used for clinical categorization. **Exception**: This information also may be used for pathological T categorization if the biopsy provides histologic material corresponding to the highest possible T category for the specific cancer type, and if it meets other criteria described in stage group.

Component of cT	Details
Synchronous primary tumors in a single organ: *(m)* suffix	For multiple tumors in a single organ, T is assigned to the highest T category; the preferred designation is: • *m* suffix; for example, pT3(m) N0 M0 If the number of tumors is important, an acceptable alternative is: • number of tumors; for example, pT3(4) N0 M0 *Note*: The *(m)* suffix applies to multiple invasive cancers. It is not applicable to multiple foci of *in situ* cancer or a mixed invasive and *in situ* cancer.
Direct extension into an organ	Direct extension of a primary tumor into a contiguous or adjacent organ is classified as part of the tumor (T) classification and is not classified as metastasis (M). **Example:** Direct extension into the liver from a primary colon cancer would be in the T category and not in the M category.
Microscopic assessment of highest T category	If microscopic assessment of the primary site or regional tissue establishes the highest T category, it is: • assigned as cT, and • it also may be used for assignment of pT ONLY if there is microscopic confirmation of the highest pN. There must be microscopic confirmation of both the highest T and the highest N in order to assign a pathological stage group without resection of the primary site.
Unknown primary or no evidence of primary tumor	If there is no evidence of a primary tumor, or the site of the primary tumor is unknown, staging may be based on the clinical suspicion of the primary tumor, with the tumor categorized as T0. The rules for staging cancers categorized as T0 are specified in the relevant disease site chapters. **Examples of exception**: The T0 category is not used for head and neck squamous cancer sites, as such patients with an involved lymph node are staged as unknown primary cancers using the cervical lymph node system (T0 remains a valid category for HPV- and EBV-associated oropharyngeal and nasopharyngeal cancers).
Tis	*In situ* neoplasia identified during the diagnostic workup on a core or incisional biopsy is assigned cTis.
Any T	*Any T* includes all T categories except Tis. This includes TX and T0.

Clinical N (N or cN)

Assessment of the regional lymph nodes is necessary to determine the cN category.

Component of cN	Details
Lymph node assessment	Clinical regional lymph node assessment may be performed by physical examination and imaging. Clinical nodal category cN0 may be assigned based solely on physical examination. Imaging to assess regional lymph nodes is not required to assign clinical stage.
Node status not required in rare circumstances	For some cancer sites in which lymph node involvement is rare, patients whose nodal status is not determined to be positive for tumor should be designated as cN0. These circumstances are identified in specific disease chapters for these sites; NX is not listed as a category. **Example:** Bone and soft tissue sarcoma may use cN0 to assign the clinical stage group, that is, cT1 cN0 cM0.
Microscopic assessment for cN	Microscopic examination of regional nodes during the diagnostic workup is included in the clinical classification as cN. Microscopic examination or assessment may be by: • fine-needle aspiration (FNA), • core biopsy, • incisional biopsy, • excisional biopsy, or • sentinel node biopsy/procedure. This information also is included in the pathological staging if the patient has surgical resection as the first course of therapy. **Example**: Sentinel node biopsy performed before neoadjuvant therapy in breast cancer is designated as clinical (cN).
Sentinel lymph node	A sentinel lymph node (SLN) is a regional lymph node that receives direct afferent lymphatic drainage from a primary tumor site (e.g., breast, melanoma), and in many solid tumors it represents the regional lymph node(s) most likely to contain metastatic disease, if any are involved. More than one SLN may be present in a regional nodal basin, and some primary tumors (e.g., melanoma) may drain to more than one regional nodal basin. Sentinel nodes are identified by lymphatic mapping as evidenced by nodes that concentrate a colloidal material injected near the primary tumor or in the involved organ (the most commonly used agents for sentinel node biopsy are vital stains such as isosulfan blue and/or radiotracers such as technetium-99 (^{99}Tc)-sulfur colloid). In some circumstances, the managing physician also may label regional lymph nodes that are palpably abnormal during surgery as sentinel nodes. Nodes that do not concentrate colloidal material and are resected along with other sentinel nodes are nonsentinel nodes and are considered as part of the sentinel node procedure. Their resection is not coded as a separate nodal procedure or a lymph node dissection.

Component of cN	Details
Sentinel node (sn) and FNA or core biopsy (f)	To distinguish lymph nodes identified during diagnostic evaluation by sentinel node biopsy or FNA or core biopsy from those identified by physical examination and imaging, the following suffixes are used in assigning the clinical N (cN) category: If SLN biopsy is performed as part of the diagnostic workup: • the cN category should have the *sn* suffix; for example, cN1(sn). If an FNA or a core biopsy is performed on lymph nodes as part of the diagnostic workup: • the cN category should have the *f* suffix; for example, cN1(f).
Isolated tumor cells (ITCs): use of the *(i+)* designator	ITCs include single tumor cells or small clusters of cells ≤0.2 mm in greatest diameter, generally without stromal response in the lymph node. Such cells usually are found in the subcapsular nodal sinuses but may be seen within the nodal parenchyma. Because ITCs may represent in-transit tumor cells that are not proliferating within the node, lymph nodes with only ITCs usually are categorized as N0, with some exceptions. They are denoted as N0(i+). *The concepts regarding this staging rule continue to evolve, and further study is warranted. In the meantime, the staging rule serves as a guideline for uniformity and consistency in practice in recording information, and clinical judgment by the managing physician prevails.* **Exception:** In melanoma and Merkel cell carcinoma, tumor cell deposits defined here as ITCs are considered positive nodes and are designated as N1 or higher. *Note*: Cancer site–specific designators have been developed to identify ITCs in nodes. For example, N0(i+) in breast and gynecologic cancers applies to nodes with ITCs only.
Pathological techniques for ITCs or detection of micro-metastasis	ITCs or lymph node micro-metastases may be identified in lymph nodes by hematoxylin and eosin staining or by specialized pathological techniques, such as IHC for cytokeratin proteins for carcinomas. Specialized pathology techniques, such as IHC and molecular techniques, are not recommended for routine examination of lymph nodes. *The concepts regarding this staging rule continue to evolve, and further study is warranted.*
Nonmorphologic techniques for identifying ITCs: use of the *(mol+)* designator	Nonmorphologic techniques, including flow cytometry and reverse transcriptase polymerase chain reaction studies, may identify minimal deposits of cancer in lymph nodes. These deposits usually are classified as clinically node negative and are identified with the (mol+) designator: for example, cN0(mol+). *The concepts regarding this staging rule continue to evolve, and further study is warranted.*
Micro-metastases: use of the *mi* designator	Lymph node micro-metastases are defined as tumor deposits >0.2 mm but ≤2.0 mm. For certain disease sites, micro-metastases are denoted by using the *mi* designator: for example, cN1mi. *Further studies are needed to determine the significance of micro-metastases across many cancer sites.* *The concepts regarding this staging rule continue to evolve, and further study is warranted.*
Extranodal extension	Extranodal extension (ENE) is defined as the extension of a nodal metastasis through the lymph node capsule into adjacent tissues. *ENE* is the preferred terminology. It also is termed *extranodal spread*, *extracapsular extension*, or *extracapsular spread*.
Regional node metastasis invading a distant organ is ENE	A regional node extending into a distant structure or organ is categorized as ENE and is not considered distant metastatic disease.
Regional nodes when tumor involves more than one organ or structure	In rare cases in which a tumor involves more than one organ or structure, the regional nodes include the nodes of all involved structures, even if the nodes of the primary site are not involved. **Example**: If a primary transverse colon cancer invades the stomach, for staging purposes, the gastric regional nodes are considered regional for the transverse colon, even if the regional nodes of the colon are not involved.
Microscopic assessment of regional node is the highest N category	If microscopic assessment of the regional node is the highest N category, it is • assigned as cN, and • also may be used for the assignment of pN ONLY if there is microscopic confirmation of the highest pT. There must be microscopic evidence of both highest T and highest N to assign a pathological stage group without surgical resection of the primary site.
Any N	Any N includes all N categories, including NX and N0.

Clinical M Classification (cM and pM)

Assignment of the M category for clinical classification may be cM0, cM1, or pM1. The M category is based on clinical history, physical examination, any imaging results, and whether there is microscopic confirmation of the distant metastasis during the diagnostic workup. The terms pM0 and MX are NOT valid categories in the TNM system.

Component of clinical M	Details
No distant metastasis	**cM0** If there are no symptoms or signs of distant metastasis, M is categorized as clinically M0 (cM0). Evaluation methods include: • history and physical examination • imaging studies *Note*: Imaging studies may be used in assigning the M category but are not required to assign the cM0 category.
Clinical evidence of distant metastasis	**cM1** If there is clinical evidence of distant metastases on physical examination, imaging studies, or invasive procedures, but no microscopic evidence of the presumed distant metastases, M is categorized as clinically M1 (cM1). Examination methods include: • physical examination • imaging (if performed) • exploratory surgery and/or endoscopy (if performed)
Microscopic evidence of distant metastasis	**pM1** If there is microscopic evidence of distant metastatic disease, M is categorized as pathological M1 (pM1). Microscopic evidence includes: • cytology from FNA • core biopsy • incisional biopsy • excisional biopsy • resection
Use of pM1 for multiple distant metastases	**pM1** In patients who have distant metastases in multiple sites and have a cancer type for which M subcategories distinguish between one or more metastatic sites, microscopic evidence of one of these sites is necessary to assign the higher pM subcategory. In general, metastases to both sides of a paired organ are considered a single metastatic site of involvement (e.g., metastases to both lungs are designated metastasis to one distant site—lung). If clinical evidence of distant metastasis remains in other areas that are not or cannot be microscopically confirmed, cM1 is assigned.
pM1, both clinical and pathological Stage IV	**pM1** A patient may be staged as both clinical and pathological Stage IV if: • there is confirmatory microscopic evidence of a distant metastatic site during the diagnostic workup, which is categorized as pM1, and • T and N are categorized only clinically. **Example:** cT3 cN1 pM1 clinical Stage IV and cT3 cN1 pM1 pathological Stage IV
Circulating tumor cells and disseminated tumor cells: cM0(i+) category	**cM0(i+)** Patients with: • Circulating tumor cells (CTCs) in blood, or • Disseminated tumor cells (DTCs) in organs and micro-metastasis in bone marrow detected by IHC or molecular techniques are categorized as cM0(i+). The cM0(i+) category denotes the uncertain prognostic significance of these findings. *The concepts regarding this staging rule continue to evolve, and further study is warranted.*
Clinical suspicion and biopsy does not confirm distant metastatic disease	If there is clinical suspicion for distant metastases and a biopsy or excision does not confirm metastatic cancer, M is categorized as clinically M0 (cM0) or clinically M1 (cM1) based on the evaluation of other possible sites of distant metastatic disease. There is no TNM pM0 designation. *Note*: pM0 is not a valid category. If clinical evidence of distant metastasis remains in other areas that are not or cannot be confirmed microscopically, cM1 is assigned.
Unknown distant metastasis status	**MX does not exist** MX is not a valid category and cannot be assigned. Unless there is clinical or pathologic evidence of metastases, M is categorized as clinically negative: cM0.
Direct extension into an organ not M category	Direct extension from the primary tumor or lymph nodes into a contiguous or adjacent organ is not included in the M category but is used in the T and N category assignments as noted earlier. **Example**: Direct extension of a colon cancer into the liver is categorized as pT4 and cM0.
Definition of metastases timing	Metastases defined during the relevant time frame/staging window are classified as metastases (cM1/pM1) and are considered synchronous with diagnosis of the primary cancer. Metastases detected after the relevant time frame/staging window are not included in the initial staging and generally are considered recurrent cancer.

Pathological Classification

Classification of T, N, and M after surgical treatment is denoted by use of a lowercase *p* prefix: pT, pN, and cM0, cM1, or pM1.

Time frame: From date of diagnosis through surgical resection in the absence of cancer progression

Criteria: Surgery is first therapy

Pathological classification is based on the:

- clinical stage information (acquired before treatment), and supplemented/modified by
- operative findings, and
- pathological evaluation of the resected specimen(s).

Pathological stage is assigned for patients first treated with surgery. The surgical resection required for assignment of this classification is specified for each disease site, and ranges from resection of the tumor to complete resection of the organ and usually includes resection of at least some of the regional lymph nodes.

The purpose of pathological classification is to provide additional precise and objective data:

- for prognosis and outcomes, and
- to guide subsequent therapy.

Criteria for assigning pathological stage	
Component of pathological staging	**Details**
Assignment of pathological stage by managing physician	Pathological stage is based on a synthesis of clinical and pathological findings and is assigned only by the managing physician, such as a surgical, radiation, or medical oncologist.
Primary tumor surgical resection for pathological staging	The surgical resection criteria in the disease site must be met in order to assign a pathological stage. The extent of primary tumor surgical resection ranges from: • resection of the tumor, up to • complete resection of the organ, and • usually includes resection of at least some regional lymph nodes *Note*: Surgical resection criteria depend on the cancer site–specific information necessary to determine the need for adjuvant therapy and the patient's prognosis, including tumor (T) and regional nodes (N).
Basis of pathological staging	Pathological staging encompasses: • clinical staging information • the surgeon's operative findings • pathological evaluation of the resected specimen(s)
Imaging studies used in assigning pathological stage	Imaging studies performed after surgery are included in the pathological staging if they are within the time frame or staging window.
Unresectable tumor and assignment of pathological stage	If the highest T and N categories or the M1 category of the tumor are confirmed microscopically, even if a primary tumor technically cannot be removed or if it is unreasonable to remove it, the criteria for pathological staging are considered satisfied without total removal of the primary tumor. *Note*: Microscopic confirmation of the highest T and N does not necessarily require removal of that structure and may entail biopsy or FNA only. **Example:** Supraclavicular node involvement in inflammatory breast cancer in which inflammatory carcinoma was identified on the core needle breast biopsy and the supraclavicular node involvement is documented by FNA

Pathological T (pT)

The pathological assessment of the primary tumor generally is based on resection of the primary tumor.

Component of pT	Description
Tumor size and extent	Primarily based on size and local extension of the resected specimen The pathologist provides information to assign the pT category based on the specimen received, but this may not be the final pT used for staging assignment. Final pT is assigned by the managing physician and also may include clinical stage information and operative findings.
Tumor size in millimeters and rounding for T-category assignment	Primary tumor size is the most accurate/largest dimension and is: • measured to the nearest whole millimeter, unless a smaller unit is specified in a specific disease site, and • rounded up or down as appropriate for assigning T category: ○ down when the numerals are between 1 and 4 ○ up when the numerals are between 5 and 9 **Examples:** • Tumor measured as 2.2 mm is recorded as 2 mm. • Tumor measured as 1.7 mm is recorded as 2 mm. • Tumor measured as 2.04 cm is recorded as 20 mm, and would be grouped with ≤2 cm and not >2 cm **Nonexhaustive exceptions**: • Melanoma: primary tumor measured to nearest 0.1 mm • Breast cancer: primary tumor >1.0 mm to 1.4 mm rounded to 2 mm (this avoids assigning the "microinvasion" category to cancer >1.0 mm)

Component of pT	Description
Resection specimen role in pT category	pT category optimally is based on resection of a single specimen. If resected in several partial specimens at the same or separate operative setting, a reasonable estimate of size and extension should be made. The estimate of multiple specimens may be based on the best combination of gross and microscopic findings, and may include reconstruction of the tumor with the assistance of the radiologist and surgeon. See CAP Protocols for tumor-specific recommendations.
Impact on pT category of positive resection margins	The presence of microscopic cancer at the resection margin does not affect the assignment of the pT category, which is assigned based on findings in the resection specimen and at operation. In situations in which the surgeon has left behind grossly identified tumor in performing a noncurative resection, the T category should be based on all available clinical and pathological information.
Pathological tumor size variance based on assessment approach	Tumor size may vary based on whether it is measured on an unfixed or a fixed specimen. Size is often reported on the fixed specimen, and gross impression of tumor size may be adjusted based on microscopic examination. The pathologist should note potential alteration in tumor size caused by fixation if it might affect staging.
Synchronous primary tumors is a single organ: *(m)* suffix	For multiple tumors in a single organ, T is assigned to the highest T category; the preferred designation is: • *m* suffix; for example, pT3(m) N0 M0 If the number of tumors is important, an acceptable alternative is: • number of tumors; for example, pT3(4) N0 M0 *Note*: The *(m)* suffix applies to multiple invasive cancers. It is not applicable for multiple foci of *in situ* cancer, or for a mixed invasive and *in situ* cancer.
Direct extension into regional node	If a primary tumor directly extends into a regional lymph node, it is: • included in the N category as a positive regional lymph node • not included as a criterion for assigning the T category
Tumor nodule in node area not considered in T category	Rounded tumor nodules with smooth-contoured capsules in the regional nodal drainage area generally represent lymph nodes completely replaced with cancer and are classified as lymph nodes, unless there is clear evidence of residual blood vessel wall to justify classification as vascular involvement. They are not considered in the T category.
Direct extension into an organ	Direct extension of a primary tumor into a contiguous or adjacent organ is classified as part of the tumor (T) classification and is not classified as metastasis (M). **Example**: Direct extension of a primary colon cancer into the liver is categorized as T4 and is not in the M category.
Unresected tumor and highest T category	The pathological T (pT) category may be assigned without tumor resection if: • a biopsy of the primary tumor (cT) is performed and is adequate to evaluate the highest pT category. Other criteria, such as microscopic confirmation of the highest pN, must be met in order to assign pathological staging.
Disease sites have specific rules	Some disease sites have specific rules to guide assignment of pT. Refer to specific disease site chapters for further guidance.
Unknown primary or no evidence of primary tumor	If there is no evidence of a primary tumor, or the site of the primary tumor is unknown, staging may be based on clinical suspicion of the primary tumor, with the tumor categorized as T0. The rules for staging cancers categorized as T0 are specified in the relevant disease site chapters. **Examples of exception**: The T0 category is not used for head and neck squamous cancer sites, as such patients with an involved lymph node are staged as unknown primary cancers using the system for cervical nodes and unknown primary tumors of the head and neck (T0 remains a valid category for HPV- and EBV-associated oropharyngeal and nasopharyngeal cancers).
Tis and surgical resection criteria	*In situ* neoplasia identified from a surgical resection, as specified in the disease site pathological criteria, is assigned pTis. *In situ* neoplasia identified microscopically during the diagnostic workup may be used to assign the pathological stage pTis if the patient had a surgical resection and no residual tumor was identified.
Use of pTX	Since pathological assessment is generally based on resection of the primary tumor, pTX is rarely appropriate. It may be assigned when relevant specimens are not available for examination by the pathologist. It may also be assigned by the pathologist for a subsequent resection or multiple partial resections when tumor fragmentation precludes assessment of the pT category. In such cases, the managing physician should assign the pT and the stage based on the other available information. pTX may not be assigned if the pathological classification criteria of surgical resection, specified in each chapter, has not been met.
Any T	*Any T* includes all T categories except Tis. This includes TX and T0.

Pathological N (pN)

Pathological assessment of regional node involvement (pN) is necessary.

Component of pN	Details
Microscopic assessment for pN	Microscopic assessment of a regional node includes: • FNA cytology • Core biopsy • Incisional biopsy • Excisional biopsy • SLN biopsy/procedure • Regional lymph node dissection

Component of pN	Details
Requirements for assigning pN category	To assign a pN category, there must be: • pathological documentation of the presence or absence of cancer in at least one node, and • pathological assessment of the primary tumor (pT), except in cases of an unknown primary (T0)
	Note: It is not necessary to pathologically confirm the status of the highest N category to assign the pN. If pT is available (resection), then any microscopic evaluation of nodes is classified as pN. For example, assessment of the axillary nodes is sufficient to assign pN for breast cancer, and it is not necessary to microscopically confirm the status of supraclavicular nodes. Many cancer sites have specific recommendations regarding the minimum number of lymph nodes to be removed during lymph node dissection to provide optimal prognostic information. However, pathological categorization (pN) still applies even in cases in which fewer than the recommended number of lymph nodes are resected (e.g., a colon cancer resection specimen with only four pathologically negative lymph nodes is categorized as pN0). FNA and core needle biopsy of a node both satisfy the requirement that at least one regional node be microscopically examined.
Categorize N	pN generally is categorized by disease-specific rules based on: • number and/or • location of positive regional nodes and/or • size of the largest deposit of tumor cells in the node(s)
Size of regional nodal metastasis	Size of regional nodal metastasis generally is specified in disease site chapters and may be based on: • size of metastasis in the node, • size of the lymph node, or • size of the nodal mass, which may be a mass of matted nodes For some disease sites, the size of tumor metastasis within the regional lymph node is a criterion for the N category. If the size of the tumor in the regional nodal metastasis is unknown, the size of the involved lymph node may be used. The size of any mass, from a single node to a conglomerate mass of matted nodes, is used to determine the N category for some disease sites, such as head and neck. *Note:* Please refer to disease site chapters for specific criteria on assessment of size of regional nodal metastasis.
Direct extension into regional node is N category	If a primary tumor directly extends into a regional lymph node, it is: • included in the N category as a positive regional lymph node • not included as a criterion for assigning the T category
Tumor nodule in node area not considered in T category	Rounded tumor nodules with smooth-contoured capsules in the regional nodal drainage area generally represent lymph nodes completely replaced with cancer and are classified as lymph nodes, unless there is clear evidence of residual blood vessel wall to justify classification as vascular involvement. They are not considered in the T category.
Sentinel node or regional node excision	Microscopic examination of regional nodes without resection of the primary site (during the diagnostic workup) is included in the clinical classification as cN. Microscopic examination of regional nodes with surgical resection of the primary site (surgical treatment) is categorized as pN. **Example**: Sentinel node biopsy performed at the time of wide re-excision for melanoma (surgical treatment) is pathological (pN).
SLN	An SLN is a regional lymph node that receives direct afferent lymphatic drainage from a primary tumor site (e.g., breast, melanoma), and in many solid tumors represents the regional lymph node(s) most likely to contain metastatic disease, if any are involved. More than one SLN may be present in a regional nodal basin, and some primary tumors (e.g., melanoma) may drain to more than one regional nodal basin. Sentinel nodes are identified by lymphatic mapping, as evidenced by nodes that concentrate a colloidal material injected near the primary tumor or in the involved organ (the most commonly used agents for sentinel node biopsy are vital stains such as isosulfan blue and/or radiotracers such as ^{99}Tc-sulfur colloid). In some circumstances, the managing physician also may label regional lymph nodes that are palpably abnormal during surgery as sentinel nodes. Nodes that do not concentrate colloidal material and are resected along with other sentinel nodes are nonsentinel nodes, and are considered part of the sentinel node procedure. Their resection is not coded as a separate nodal procedure or a lymph node dissection.
Sentinel node (sn) and FNA or core biopsy (f)	If SLN biopsy is performed in the absence of complete dissection of the nodal basin: • the N category should have the *sn* suffix; for example, pN0(sn). If FNA or core biopsy is performed in the absence of a complete dissection of the nodal basin: • the N category should have the *f* suffix; for example, pN0(f). *Note*: This distinguishes it from a complete nodal dissection, for which the pN is assigned without the *(sn)* or *(f)* suffix.

Component of pN	Details
ITCs: use of the (i+) designator	ITCs include single tumor cells or small clusters of cells ≤0.2 mm in greatest diameter, generally without stromal response in the lymph node. These cells usually are found in the subcapsular nodal sinuses but may be seen within the nodal parenchyma. Because ITCs may represent tumor cells that are in transit that are not proliferating within the node, lymph nodes with only ITCs usually are categorized as N0, with some exceptions. They are denoted as N0(i+).
	The concepts regarding this staging rule continue to evolve, and further study is warranted. In the meantime, the staging rule serves as a guideline for uniformity and consistency in practice in recording information, and clinical judgment by the managing physician prevails. **Exception:** In melanoma and Merkel cell carcinoma, ITCs are considered positive nodes and are designated as N1 or higher. *Note*: There are cancer site–specific designators to identify ITCs in nodes. **Example:** N0(i+) in breast and gynecologic cancers applies to nodes with ITCs only.
Pathological techniques for ITCs or detection of micro-metastasis	ITCs or lymph node micro-metastases may be identified in lymph nodes by hematoxylin and eosin staining or by specialized pathological techniques, such as IHC for cytokeratin proteins for carcinomas. Specialized pathology techniques such as IHC and molecular techniques are not recommended for routine examination of lymph nodes. *The concepts regarding this staging rule continue to evolve, and further study is warranted.*
Nonmorphologic techniques for identifying ITCs: use of *(mol+)* designator	If used, nonmorphologic techniques, including flow cytometry and reverse transcriptase polymerase chain reaction studies, may identify minimal deposits of cancer in lymph nodes. These usually are classified as clinically node negative and identified with the *(mol+)* designator: for example, cN0(mol+). *The concepts regarding this staging rule continue to evolve, and further study is warranted.*
Micro-metastases: use of *mi* designator	Lymph node micro-metastases are defined as tumor deposits >0.2 mm but ≤2.0 mm. For certain disease sites, micro-metastases are denoted by using the *mi* designator: for example, cN1mi. Further studies are needed to determine the significance of micro-metastases across many cancer sites. *The concepts regarding this staging rule continue to evolve, and further study is warranted.*
Extranodal extension (ENE)	*ENE* is defined as the extension of a nodal metastasis through the lymph node capsule into adjacent tissues. ENE is the preferred terminology. It is sometimes also termed *extranodal spread*, *extracapsular extension*, or *extracapsular spread*.

Component of pN	Details
Regional node metastasis invading a distant organ is ENE	A regional node extending into a distant structure or organ is categorized as ENE and is not considered distant metastatic disease.
Recommended minimum number of lymph nodes	As noted in previous editions of the *AJCC Cancer Staging Manual*, as well as this 8th Edition, several cancer sites contain a recommendation regarding the minimum number of regional nodes to be surgically resected and pathologically analyzed for determination of the N category. These recommendations are offered as metrics for evaluation of quality review of the extent of surgical resection and resultant pathological analysis. These minimum benchmarks should not be construed as unique indicators for additional surgical resection or adjuvant therapy if the recommended nodal count has not been met. In cases in which fewer than the recommended optimal number of lymph nodes are removed, pathological node category (pN) should be assigned and complete pathological staging applied based on whatever number of nodes are reported. A suboptimal node count may lead to further dialogue between the surgeon and pathologist to support the opportunity for further evaluation (e.g., fat clearance techniques) of the node-bearing specimen to assure that a maximum node assessment is reached; however, this is not necessary to assign the pathological node category.
Node status not required in rare circumstances	For some cancer sites in which lymph node involvement is rare, patients whose nodal status is not determined to be positive for tumor should be designated as cN0. These circumstances are identified in specific disease site chapters for these sites; NX may not be listed as a category. The assignment of cN0 will ensure it is not confused with a case in which the nodes were microscopically proven to not contain tumor, that is, pN0. **Examples:** For bone and soft tissue sarcoma, cN0 may be used to assign the pathological stage group—that is, pT1 cN0 cM0. For melanoma, cN0 may be used to assign a pathological stage group for T1 melanoma.
Regional node invading a distant organ	Tumor involving a regional node and extending into a distant structure or organ is categorized as ENE and is not considered metastatic disease.
Regional nodes when a tumor involves more than one organ or structure	In the rare occurrence in which a tumor involves more than one organ or structure, the regional nodes include those of all involved structures, even if the nodes of the primary site are not involved. **Example**: If a transverse colon cancer invades the stomach, the gastric regional nodes would be considered regional for the transverse colon, even if the colon regional nodes were not involved.

Component of pN	Details
Unresectable tumor and highest N category	If the primary tumor and/or regional lymph nodes technically cannot be removed or it is clinically not indicated to remove them, the following criteria may be used to assign pathological stage: • microscopically confirmed highest T category, and • microscopically confirmed single node or nodes in the highest N category *Note*: Microscopic confirmation of the highest T and N categories may use biopsy or FNA only.
Any N	*Any N* includes all N categories. This includes NX and N0.

Pathological M Categorization (cM and pM)

Any of the M categories (cM0, cM1, or pM1) may be used with pathological stage grouping. The terms pM0 and MX are NOT valid categories in the TNM system.

Component of M for pathological staging	Details
No distant metastasis	**cM0** If there are no symptoms or signs of distant metastasis, the case is classified as clinically M0 (cM0). Evaluation includes: • history and physical examination • imaging studies performed *Note*: Imaging studies are NOT required to assign cM0.
Clinical evidence of distant metastasis	**cM1** Patients with clinical evidence of distant metastases by history, physical examination, imaging studies, or invasive procedures, but without microscopic evidence of the presumed distant metastases, are categorized as clinically M1 (cM1). Examination methods include: • physical examination • imaging • exploratory surgery or endoscopy
Microscopic evidence of distant metastasis	**pM1** Patients in whom there is microscopic evidence confirming distant metastatic disease are categorized as pathologically M1 (pM1). Microscopic evidence includes: • cytology from FNA • core biopsy • incisional biopsy • excisional biopsy • resection
Use of pM1 if there are multiple distant metastases	**pM1** In patients who have distant metastases in multiple sites, and have a cancer type for which M subcategories distinguish between one or more metastatic sites, microscopic evidence of one of these sites is necessary to assign the higher pM subcategory.
	In general, metastases to both sides of a paired organ are considered a single metastatic site of involvement (e.g., metastases to both lungs are assigned as metastasis to one distant site—lung). If clinical evidence of distant metastasis remains in other areas that are not or cannot be microscopically confirmed, cM1 is assigned.
pM1 may be used for both clinical and pathological Stage IV	**pM1** A patient may be staged as both clinical and pathological Stage IV if there is: • confirmatory microscopic evidence of a distant metastatic site during the diagnostic workup, which is categorized as pM1, and • T and N may be categorized only clinically. **Example:** cT3 cN1 pM1 clinical Stage IV, and cT3 cN1 pM1 pathological Stage IV
Circulating tumor cells and disseminated tumor cells: cM0(i+) category	**cM0(i+)** Patients with • CTCs, or • DTCs in organs and micro-metastasis in bone marrow, detected by IHC or molecular techniques, are categorized as cM0(i+). The cM0(i+) category denotes the uncertain prognostic significance of these findings. *The concepts regarding this staging rule continue to evolve, and further study is warranted.*
Clinical suspicion of metastasis, but biopsy does not confirm distant metastatic disease	If there is clinical suspicion of distant metastases and a biopsy or excision does not confirm metastatic cancer, M is classified as clinically M0 (cM0) or clinically M1 (cM1) based on the evaluation of other possible sites of distant metastatic disease. There is no TNM pM0 designation. ***Note:* pM0 is not a valid category** If clinical evidence of distant metastasis remains in other areas that are not or cannot be microscopically confirmed, cM1 is assigned.
Unknown distant metastasis status	**MX does not exist** MX is not a valid category and cannot be assigned. Unless there is clinical or pathologic evidence of metastases, M is categorized as clinically negative: cM0.
No direct extension in M category	Direct extension from the primary tumor or lymph nodes into a contiguous or adjacent organ is not included in the M category but is used in the T and N category assignments as noted earlier. **Example**: Direct extension of a colon cancer into the liver is categorized as pT4 and cM0.

Posttherapy or Post Neoadjuvant Therapy Classification (yTNM)

For purposes of posttherapy or post neoadjuvant therapy classification, *neoadjuvant therapy* is defined as systemic and/or radiation therapy given before surgery; primary radiation and/or systemic therapy is treatment given as definitive therapy without surgery.

Classification of T, N, and M after systemic or radiation treatment intended as definitive therapy, or after neoadjuvant therapy followed by surgery, is denoted by use of a lowercase *yc* or *yp* prefix, respectively: ycT, ycN, c/pM, and ypT, ypN, c/pM, respectively. The c/pM category may include cM0, cM1, or pM1.

yc

Time frame: After primary systemic and/or radiation therapy without subsequent surgical resection, or after neoadjuvant and before planned surgical resection

Criteria: First therapy is systemic and/or radiation therapy.

y-clinical (yc) classification is based on the:

- clinical history and physical examination and
- any imaging studies, if performed

Note: imaging studies may be considered standard practice, but are NOT required to assign yc categories.

yp

Time frame: The yp classification is used when staging after neoadjuvant therapy and planned post neoadjuvant therapy surgery. The time frame should be such that the post neoadjuvant therapy surgery and staging occur within a period that accommodates disease-specific circumstances, as outlined in the specific chapters and in relevant guidelines.

Criteria: First therapy is systemic and/or radiation therapy followed by surgery.

y-pathological (yp) classification is based on the:

- y-clinical stage information, and supplemented/modified by
- operative findings, and
- pathological evaluation of the resected specimen.

Observed changes between the clinical classification and the posttherapy classification may provide clinicians with information regarding the response to therapy. The clinical extent of response to therapy may guide the scope of planned surgery, and the clinical and pathological extent of response to therapy may provide prognostic information and guide the use of further adjuvant radiation and/or systemic therapy.

Examples of treatments that satisfy the definition of neoadjuvant therapy for a disease site may be found in sources such as the NCCN Guidelines, ASCO guidelines, or other treatment guidelines. Systemic therapy includes chemotherapy, hormone therapy, and immunotherapy. Not all medication given to a patient meets the criteria for neoadjuvant therapy (e.g., a short course, such as a few days of endocrine therapy in breast cancer or prostate cancer that is provided for variable and often unconventional reasons, should not be categorized as neoadjuvant therapy).

The time frame should be such that the post neoadjuvant therapy surgery and staging occur within a period that accommodates disease-specific circumstances, as outlined in the specific chapters and in relevant guidelines.

The post neoadjuvant therapy assessment of the T and N (yTNM) categories uses specific criteria. In contrast, the M category for post neoadjuvant therapy classification remains the same as that assigned in the clinical stage before initiation of neoadjuvant therapy (e.g., if there is a complete clinical response to therapy in a patient previously categorized as cM1, the M1 category is used for final yc and pc staging).

Component of posttherapy staging	Details
Assignment of stage by managing physician	Posttherapy or post neoadjuvant therapy stage is based on a synthesis of clinical and pathological findings and is assigned only by the managing physician, such as a surgical, radiation, or medical oncologist. Pathologists may provide T, N, and M information based on the specimens received to assist the managing physician in assigning the final stage. Radiologists may provide T, N, and M information based on imaging studies to assist the managing physician in assigning the final stage.
Use of yTNM	To use the yTNM classification, the extent of disease is assessed: • after systemic and/or radiation therapy as the primary treatment, and • after surgery when it follows the systemic and/or radiation therapy
Use of *y* prefix	The *y* prefix is always combined with either a clinical or pathological prefix, that is, ycTNM or ypTNM.
Time frame in the patient's care for use of yc and yp	• ycTNM denotes information gathered using clinical classification rules and methods: ○ after neoadjuvant systemic and/or radiation therapy, and ○ before surgical resection or if no surgery is performed. • ypTNM denotes information gathered using pathological classification rules and methods: ○ after neoadjuvant systemic and/or radiation therapy, and ○ after the surgical resection. **Examples:** • ycT and ycN with cM or pM • ypT and ypN with cM or pM.

Component of posttherapy staging	Details
Distant metastasis	The presence of distant metastases is classified by the M status defined during the clinical classification, cM or pM, before initiation of neoadjuvant radiation and/or systemic therapy. *Note:* Once distant metastasis is identified, that M category designation always remains, even if there no longer is evidence of the metastasis after neoadjuvant therapy. In this situation, the yc and yp stages always maintain the M1 category.
Complete pathological response	If a complete pathological response has occurred and the ypTNM is ypT0 ypN0 cM0, no stage group is assigned. *Note*: This situation is not classified as Stage 0, because such a designation would denote *in situ* neoplasia. Nonetheless, the individual T, N, and M categories should be documented as T0, N0, M0. The complete pathological response also may be documented by using the response designation.
Response to neoadjuvant therapy	It is important to record the response to neoadjuvant therapy. Consult disease site chapters for specific systems. For example, some disease sites include "complete," "partial," and "no response," whereas others consist of a numerical scoring system or a "regression score." If surgery is performed, it is critical to also assign the ypT and ypN for analysis of response to neoadjuvant therapy.
Mucin pools, necrosis, and other reactive changes not included in the assessment of residual cancer	Histologic confirmation of residual cancer requires identification of non-necrotic tumor cells. Mucin pools, necrosis, and other degenerative and reactive changes without viable-appearing tumor cells are insufficient for a diagnosis of residual cancer. Mucin pools and necrotic cells currently play no role in assigning the ypT and ypN.

Recurrence or Retreatment Classification (rTNM)

Classification of T, N, and M for recurrence or retreatment is denoted by use of the lowercase *r* prefix: rcT, rcN, rc/rpM, and rpT, rpN, rc/rpM. The rc/rpM may include rcM0, rcM1, or rpM1.

Time frame: From identification of recurrence or progression until treatment is initiated for rc, and from identification of recurrence or progression through surgical resection for rp

Criteria: Disease recurrence after disease-free interval, or disease progression

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).

Assessment of recurrence and retreatment follows specific criteria.

Recurrence/retreatment staging assessment criteria	
Component of recurrence/ retreatment staging	**Details**
Stage at initial diagnosis is not affected by recurrence	The initially assigned clinical and pathological stages at diagnosis do not change if a cancer recurs or progresses.
Use of *r* prefix	In staging for recurrence or retreatment, the *r* prefix is applied.
Information included: r classification	All information available at the time of recurrence or retreatment should be used to determine the rTNM stage, including clinical and pathological information. **Important**: Biopsy confirmation is not required but is encouraged if clinically feasible. **rc** The r-clinical (rc) classification is based on: • clinical history and physical examination and • any imaging studies, if performed *Note*: Imaging studies may be considered standard practice but are NOT required to assign rc categories. **rp** The r-pathological (rp) classification is based on: • r-clinical stage information, and supplemented/modified by • operative findings, and • pathological evaluation of the resected specimen.

Autopsy Classification (aTNM)

Classification of T, N, and M at autopsy is denoted by use of the lowercase *a* prefix: aT, aN, aM.

Time frame: At death

Criteria: Incidental finding of cancer at autopsy; cancer not suspected or evident before death (i.e., classification does not apply if autopsy is performed in a patent with a known cancer before death).

Autopsy assessment has specific criteria.

Component of autopsy staging	Details
Diagnosis at autopsy	Cancer must be diagnosed at autopsy. No prior suspicion or evidence of cancer before death.
Information included	All clinical and pathological information is included. It is obtained: • at time of death, and • through postmortem examination.

AJCC PROGNOSTIC STAGE GROUPS

Cancer patients with similar prognoses are grouped by using prognostic stage group tables. Clinical and pathological stage groups are defined for each case as appropriate. These disease-specific groups are composed of the following categories:

- cT, cN, and cM or pM
- pT, pN, and cM or pM
- factors for both groups, if applicable

Stage group assignment follows specific rules.

Rules for assigning prognostic stage groups (stage groups)	
Component of prognostic stage group	**Rule(s)**
Prognostic stage groups	Prognostic stage groups are based on combinations of T, N, M, and relevant prognostic factors and usually define groups of patients with similar outcomes to help define prognosis and appropriate treatment, as well as to enable comparisons of similar groups of patients between institutions and over time.
Categories and subcategories	When a category (e.g., T1) is identified in the stage group table, it includes all subcategories (e.g., for T1, this may include T1mi, T1a, T1b, etc.). However, If the specific subcategories are listed separately (e.g., T1a, T1b, N1mi), only the specific subcategory is included in the stage group.
Unknown T or N	A stage group cannot be assigned if X is used for either T or N. If a prognostic factor is X, it should be assigned based on TNM. **Exception:** Stage IV is always assigned if there is: • evidence of distant metastasis (cM1 or pM1), even if the T or N category is unknown (TX or NX). Stage may be assigned if the TNM stage group results in Any T or Any N with M0, which includes TX or NX. Examples include: • TX N1 M0 Stage III in melanoma clinical stage • T4 NX M0 Stage III in pancreatic cancer
Stage documentation in the medical record	The patient's medical record should be updated with any applicable stage group information as it is available, including: • clinical • pathological • posttherapy or post neoadjuvant therapy • recurrence or retreatment • autopsy Once assigned according to the appropriate rules and timing, the documented stage group does not change.

Rules for assigning prognostic stage groups (stage groups)	
Component of prognostic stage group	**Rule(s)**
Assigning stage with incomplete information	A presumptive stage to facilitate patient management may be used by the treating physician/management team. This is not a formal stage classification type in the TNM system. It is only for physician use in patient care. It should never be documented by cancer registries. During the diagnostic workup, the managing physician may assign a preliminary clinical stage based on the information known at that time, and may continually update the stage as the workup progresses. This approach commonly is used for cancer conferences (tumor boards) and other medical conversations. Once the final clinical stage is determined, these preliminary stages no longer are used and are replaced by the clinical stage. The stage(s) provisionally assigned during the diagnostic workup may be referred to as the *presumptive stage(s)*. In patient care, it may be appropriate for the managing physician to combine clinical and pathological T and N categories if only partial information is available in the pathological classification. Although this strategy may be used to plan treatment and to provide the patient with a stage group and prognosis, it does not represent the actual TNM stage and therefore is not used to assign a stage group.
Missing/unknown prognostic factor	If a required prognostic factor category is unavailable, the patient may still be staged. The stage group assigned is the: • group containing the prognostic factor X category, or • anatomic stage, assigned by default using clinical judgment
pM1 in stage groups	If a patient has microscopic confirmation of distant metastases (pM1) during the diagnostic workup, the patient may be classified as clinical Stage IV and pathological Stage IV, regardless of whether the T and N are classified by clinical or pathological means. **Example:** For pM1 and cT and cN, the patient may be assigned both: • clinical stage group, and • pathological stage group *Note*: This rule does not apply to patients with clinical metastases without microscopic confirmation. These patients may be staged only clinically.
cM or pM used in all stage groups	cM0, cM1, or pM1 may be used in any of the following stage groups: • clinical stage group • pathological stage group • post neoadjuvant therapy or primary radiation/systemic therapy clinical stage group • post neoadjuvant therapy pathological stage group • recurrence or retreatment stage group

Rules for assigning prognostic stage groups (stage groups)	
Component of prognostic stage group	**Rule(s)**
Microscopic evaluation without resection for assigning pathological classification	If the highest T and N categories of the tumor are confirmed microscopically, the criteria for pathological staging have been satisfied. This may occur if a primary tumor technically cannot be removed or if it is unreasonable to remove it, but the criteria for pathological staging have been satisfied without total removal of the primary tumor. *Note*: Microscopic confirmation of the highest T and N does not necessarily require removal of that structure and may include biopsy or FNA only. Please refer to disease sites for specific guidelines.
In situ neoplasia, Stage 0 for clinical classification	*In situ* neoplasia identified microscopically during the diagnostic workup is assigned as cTis cN0 cM0 clinical Stage 0.
In situ neoplasia, Stage 0 does not require node evaluation for pathological classification	*In situ* neoplasia is an exception to the stage grouping guidelines that otherwise require regional lymph node evaluation for pathological classification. By definition, *in situ* neoplasia has not involved any structures in the primary organ that would allow tumor cells to spread to regional nodes or distant sites. The primary tumor surgical resection criteria for pathological stage must be met in order to assign pathological Stage 0. Lymph node microscopic assessment is not necessary to assign pathological Stage 0 for *in situ* neoplasia; for example, pTis cN0 cM0 is staged as pathological Stage 0. *Notes*: • *In situ* neoplasia includes carcinoma *in situ* (CIS) and other *in situ* neoplasia. • Disease sites having two Stage 0 groups usually are denoted as 0is and 0a.
Noninvasive, Stage 0a	Ta is assigned for noninvasive papillary carcinoma in the renal pelvis and ureter, urinary bladder, and urethra. The stage group usually is 0a. The same rules apply to noninvasive tumors as those for *in situ* neoplasia. Noninvasive papillary carcinoma identified microscopically during the diagnostic workup is assigned as cTa cN0 cM0 clinical Stage 0a. Noninvasive papillary carcinoma identified on surgical resection meeting the criteria for pathological stage is assigned as pTa cN0 cM0 pathological Stage 0a.
Tis N1–3	In rare situations, whenever the pathology fails to reveal invasive cancer and shows Tis only with nodal involvement, the stage group may be assigned by the managing physician based on the N category as available for patient care. The cancer registry should document Tis with the appropriate N category and no stage group.

Rules for assigning prognostic stage groups (stage groups)	
Component of prognostic stage group	**Rule(s)**
	In melanoma, patients with histologically documented melanoma *in situ* disease only may develop regional metastasis. Biologically, this may represent melanoma metastasis associated with a regressed primary, which may be associated with the Tis lesion or may be a completely regressed tumor (i.e., unknown primary). The stage may be assigned by the managing physician as Tis N1-3 M0 with a stage group based on the N category as available for patient care. *Note*: Rarely, patients with a resected cancer showing only *in situ* disease (Tis) have metastatic cancer in regional lymph nodes. This mostly involves breast cancer (ductal carcinoma *in situ*), although it is still rare. The common theory is that the node metastases come from an unidentified occult invasive cancer. For clarity in registry operations and to allow study of these patients in the future, such cases should be categorized as: • Tis N1 (or N2/N3 as appropriate). • These cases cannot be assigned a stage group in the registry database. Clinicians should use careful judgment in counseling patients with this unusual finding.
Uncertainty in assigning stage group	If uncertainty exists regarding the stage group, the lower or less advanced of two possible stage groups should be assigned. *Note*: This rule does not apply to situations in which not enough information is available to allow staging, such as cases with unknown T (TX) or unknown N (NX).
Complete pathological response	If a complete pathological response has occurred and the ypTNM is ypT0 ypN0 cM0, no stage group is assigned. *Note*: This situation is not classified as Stage 0, because such a designation would denote *in situ* neoplasia. Nonetheless, the individual T, N, and M categories should be documented as T0, N0, M0

ADDITIONAL STAGING DESCRIPTORS AND GUIDELINES

N Suffixes: Sentinel Node Suffix (sn) and FNA or Core Biopsy (f)

Node category suffixes are used to indicate the method of assessment, which may have implications for the completeness of the pathological review.

Component of *N* suffix	Description
Sentinel node procedure indication (sn)	If a regional lymph node metastasis is identified by SLN biopsy only, and additional surgery in the form of a completion lymph node dissection is *not* performed, the N category is assigned with the addition of the *(sn)* suffix: for example, cN1(sn) or pN1(sn).
Time frame for cN(sn) and pN(sn)	If the sentinel node procedure is performed as: • part of the diagnostic workup and before definitive surgical treatment, in which case the proper assignment is cN1–3(sn), or • part of initial surgical management, in which case the proper assignment is pN1–3(sn). *Note*: If the patient has a completion lymph node dissection performed as a component of the initial surgical management, the suffix is not used.
(sn) suffix in clinical and pathological classifications	If a sentinel node biopsy is performed as a component of the: • diagnostic workup, it is assigned cN1(sn). • surgical resection procedure and no additional (e.g., completion) lymph node dissection is performed, it is assigned pN1(sn). • surgical resection procedure and a completion lymph node dissection is performed, it is assigned pN1. • diagnostic workup, it is assigned cN1(sn) for clinical stage, and if completion lymph node dissection is performed during surgical resection of primary site, it is assigned pN1 for pathological stage.
FNA or core biopsy indication (f)	An FNA or core needle biopsy is denoted by the *(f)* suffix, if no further resection of the nodes is performed. FNA or core biopsy meets the criterion for microscopic examination of one node for assigning the pN category.
Time frame for use of *(f)* suffix	If the FNA/biopsy procedure is performed as: • part of the diagnostic workup before treatment, it is assigned cN1–3(f). • part of primary site surgical resection, then it is assigned pN1–3(f). *Note*: If the patient subsequently undergoes a completion lymph node dissection as a component of the initial surgical management, the suffix is not used.
(f) suffix in clinical and pathological classifications	If FNA or core biopsy of regional lymph nodes is performed as a component of: • diagnostic workup, it is assigned cN1(f). • surgical resection of primary with no lymph node dissection performed, it is assigned pN1(f). • surgical resection with lymph node dissection performed, it is assigned pN1. • diagnostic workup, it is assigned cN1(f) for clinical stage; if lymph node dissection is performed as a component of the surgical resection of the primary site, it is assigned pN1 for pathological stage.

Guidelines for Primary Cancers

Multiple Primary Tumors

Multiple cancers 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.

Synchronous Primary Cancers

Component of synchronous cancers	Description
Timing for synchronous cancers	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
Multiple synchronous tumors	Multiple synchronous tumors: • are cancers of the same histology • occur in one organ
Synchronous primary tumors in a single organ	For multiple tumors in a single organ, T is assigned to the highest T category; the preferred designation is: • *m* suffix; for example, pT3(m) N0 M0. If the number of tumors is important, an acceptable alternative is: • number of tumors; for example, pT3(4) N0 M0. *Note*: The *(m)* suffix applies to multiple invasive cancers. It is not applicable to multiple foci of *in situ* cancer or to mixed invasive and *in situ* cancer.
Synchronous primary tumors in paired organs	Cancers occurring at the same time in each of paired organs are staged as separate cancers. Examples include breast, lung, and kidney. **Exception:** For tumors of the thyroid, liver, and ovary, multiplicity is a criterion of the T category and is not independently staged.

Multiple Synchronous Tumors, Suffix (m)

Component of T suffix	Description
(m) suffix for synchronous primary tumors in single organ	For multiple tumors in a single organ, T is assigned to the highest T category; the preferred designation is: • *m* suffix; for example, pT3(m) N0 M0. If the number of tumors is important, an acceptable alternative is: • number of tumors; for example, pT3(4) N0 M0. *Note*: The *(m)* suffix applies to multiple invasive cancers. It is not applicable to multiple foci of *in situ* cancer or to mixed invasive and *in situ* cancer.

Metachronous Primary Cancers

Component of metachronous cancers	Description
Timing for metachronous cancers	Cancers occurring in the same organ system that are identified with diagnosis dates >4 months from each other, except for cancers identified at the time of surgery for the first cancer occurring >4 months after the diagnosis of the first cancer if that surgery is part of the planned first course of therapy
Metachronous primaries	Metachronous primaries are primary cancers: • occurring at different times in the same or different organs.
Staging	A metachronous primary is staged as a new cancer by using the applicable TNM disease site system.
Previous treatment of the organ	Second cancers in the same organ occurring after treatment of the original cancer are staged as new cancers and are not staged using the *y* prefix.

Cancers of Unknown Primary Site

There is no evidence of a primary tumor, but the anatomic site is suspected.

Component of T0	Description
T0	T0 is assigned if there is clinical suspicion of a primary tumor, with evidence of regional or distant metastases, but there is: • no evidence of a primary tumor, or • the site of the primary tumor remains unknown. **Example**: T0 N1 M0 is assigned if: • metastatic adenocarcinoma in axillary lymph nodes is pathologically consistent with breast cancer, and there is no apparent primary breast tumor or other primary tumor site • metastatic melanoma is found in lymph nodes with no apparent primary skin lesion. *Note*: The T0 category was eliminated for head and neck squamous cell cancer, except that T0 remains a valid category for HPV- and EBV-associated oropharyngeal and nasopharyngeal cancers.
cT0 and pT0	**cT0** If physical examination, imaging, endoscopy, and other diagnostic procedures do not identify a primary tumor: • the T category is assigned as cT0. **pT0** If after surgical resection of a suspected primary tumor no evidence of tumor is identified, and it was never identified on biopsy: • the T category is assigned as pT0.
No information on primary tumor site of origin	T0 is not used for a cancer whose site of origin cannot be determined. **Example:** Poorly differentiated carcinoma with histology that is not specific for a particular primary, and for which no actual site is identified. This is designated as an unknown primary and cannot be staged.

Histologic and Specimen Descriptors

Histopathologic Type

Histopathologic type is determined by microscopic assessment whereby a tumor is categorized according to the normal tissue type or cell type it most closely resembles (e.g., hepatocellular or cholangiocarcinoma, osteosarcoma, squamous cell carcinoma).

Component of histology	Description
Resource	The *World Health Organization Classification of Tumours*, published in numerous anatomic site-specific editions, is used most commonly for histopathologic typing.
Histology codes for staging	Each chapter in the *AJCC Cancer Staging Manual* includes the applicable WHO and ICD-O-3 histology codes. If a specific histology is not listed, the case should not be staged using the AJCC classification in that chapter. Histologies appropriate for clinical use in patient care, using current preferred terminology from the WHO and ICD-O-3, are listed in each chapter. Also included are histologies requested by the surveillance community to reduce the number of unstaged cases in population-based data. These are denoted with an asterisk and italicized in the histology code table. These additional histologies represent vague or non-specific information such as carcinoma, NOS; more specific terms using features no longer part of current terminology; and other non-standard or outdated histologic terms. Caution should be used when analyzing data using these different histologies.

Component of histology	Description
Behavior	The behavior code is appended to the histology code based on the pathologist's determination of benign (/0), malignant (/3), *in situ* (/2), or uncertain malignant potential (/1).

Grade (G)

The grade of a cancer is a qualitative assessment of the degree of differentiation of the tumor. It may reflect the extent to which a tumor resembles the normal tissue at that site. Grade may provide important information on the risk of cancer metastasis and prognosis.

Component of grade	Description
Histologic grade stratification	Historically, stratification of solid tumors has sometimes included an assessment of the overall histologic differentiation of the cancer. The most common grading schema uses numeric grades from the most or well differentiated (grade 1) to the least differentiated (grade 3 or 4). This system is still used in some cancer types, although site-specific grading systems are used more commonly.
Disease site–specific histologic grade stratification	The recommended grading system for each cancer type is specified in each chapter and is the grading system to be used by the pathologist and documented in the cancer registry. For many cancer types, more precise and reproducible grading systems have been developed beyond the standard systems, and these may incorporate more specific and objective criteria based on single or multiple characteristics of the cancers. These factors include nuclear grade, number of mitoses identified microscopically (mitotic count), and measures of histologic differentiation (e.g., tubule formation in breast cancer), among others. For some cancer types, these systems have been fully validated and largely implemented worldwide. Examples include the Gleason scoring system and the grade grouping for prostate cancer and the Scarff–Bloom–Richardson (Nottingham) grading system for breast cancer.
Histologic grade if more than one grade is noted	If there is evidence of more than one grade or level of differentiation of the tumor, the highest grade is recorded, assuming that the recommended grading system was used for both biopsy and resection.
Cancer registry documentation	The cancer registry must record the grade as specified in the disease site chapter, according to the rules only in this chapter and the disease site chapter.

Lymphovascular Invasion

This descriptor indicates whether microscopic lymphovascular invasion (LVI) is identified in the cancer as recorded in the pathology report. LVI includes lymphatic invasion, vascular invasion, and lymphovascular invasion. This coding convention has been developed and implemented for use in the 8th Edition for appropriate disease sites.

Component of LVI coding	Description
0	LVI not present (absent)/not identified
1	LVI present/identified, NOS
2	Lymphatic and small vessel invasion only (L)
3	Venous (large vessel) invasion only (V)
4	BOTH lymphatic and small vessel AND venous (large vessel) invasion
9	Presence of LVI unknown/ indeterminate

The concepts regarding this staging rule continue to evolve, and further study is warranted.

Residual Tumor and Surgical Margins

The absence or presence of residual tumor after treatment is described by the symbol R (capital *R*). cTNM and pTNM describe the extent of cancer in general without consideration of treatment. cTNM and pTNM may be supplemented by the R designation to categorize the absence or presence of residual tumor status after treatment.

It is important to note that the R designation is not incorporated into TNM staging itself. However, the absence or presence of residual tumor and status of the margins may provide important information that affects subsequent treatment and prognosis and may be recorded in the medical record and cancer registry.

The absence or presence of residual tumor at the primary tumor site after treatment is denoted by the symbol R. The R categories for the primary tumor site are as follows:

R	R Definition
RX	Presence of residual tumor cannot be assessed
R0	No residual tumor
R1	Microscopic residual tumor
R2	Macroscopic residual tumor at the primary cancer site or regional nodal sites (This designation is not used to indicate metastatic disease identified but not resected at surgical exploration.)

Component of residual tumor and margins	Description
Causes of residual tumor	In some patients treated with surgery and/or neoadjuvant therapy, residual tumor may persist at the primary site and/or regional sites of disease after such treatment as a result of incomplete resection (i.e., the tumor may extend beyond the limit or ability of resection).
Indications of residual tumor	The presence of residual tumor may: • indicate the effect of therapy • influence further therapy • be a strong predictor of prognosis
Indicator of risk	The presence or absence of disease at the margin of resection may be a predictor of the risk of recurrent cancer. The presence of residual disease or positive margins may be more likely with more advanced T- or N-category tumors.
Margin status following tumor resection	Margin status after tumor resection is based on the pathology report (and correlation with the operative report if necessary) and should be recorded by using the following categories: • negative margins (tumor not present at the surgical margin) • microscopic positive margin (tumor not identified gvrossly at the margin, but present microscopically at the margin). For rare sites, definitions of margin positivity may vary, and relevant interpretation is specified in the respective chapter. • macroscopic positive margin (tumor identified grossly at the margin) • margin not assessed

Response to Neoadjuvant Therapy Assessment

Specific guidance for pathologists may assist in determining the response to neoadjuvant therapy. Additional information on reporting the response to therapy for some specific cancer types is provided in the respective disease site chapters.

Component of response to therapy	Description
Response to neoadjuvant therapy	It is important to record the response to neoadjuvant therapy. Consult disease site chapters for specific systems. For example, some disease sites include "complete," "partial," and "no response," whereas others consist of a numeric scoring system or a "regression score." If surgery is performed, it is critical to also assign the ypT and ypN for analysis of response to neoadjuvant therapy.
Mucin pools, necrosis and reactive changes not included in the assessment of residual cancer	Histologic confirmation of residual cancer requires identification of non-necrotic tumor cells. Mucin pools, necrosis, or degenerative and reactive changes without viable-appearing tumor cells are insufficient for a diagnosis of residual cancer. Mucin pools and necrotic cells currently play no role in assigning the ypT and ypN.