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and M from an element that records the presence or absence of metastases. In addition, the CS system includes "site-specific factors" used to record information beyond the anatomic extent of disease. There are two types of site-specific factors: those that are required for deriving the "Anatomic Stage/Prognostic Group" (e.g., Gleason's Score in prostate cancer) and those that are key prognostic or predictive factors for a given disease (e.g., estrogen receptor and HER2/neu status in breast cancer). Anatomic stage/prognostic groups are calculated from the T, N, and M and relevant site-specific factors. Collaborative stage does not assign a "c" or "p" to the stage grouping but only to the TNM elements. The CS system-derived groups are not necessarily purely clinical or pathologic TNM groups, but represent the best stage that combines clinical and pathologic data.

Importantly, the CS system stores the primary data in an interoperable tagged format that may be exported for other purposes including application in prognostic models and nomograms and for research into new prognostic models. The data elements that are collected in the Collaborative Stage Data Collection System are shown in Table 1.2.

The Collaborative Stage Data Collection System has been revised to accommodate this seventh edition of the *AJCC Cancer Staging Manual.* Key revisions are expansion of the site-specific factors to accommodate added prognostic factors and additional data elements necessary to record the clinical stage used for all cases, and the yp stage after neoadjuvant therapy. This will collect information on pretreatment clinical stage prior to the initiation of therapy and the posttreatment pathologic stage (yp) after completion of neoadjuvant therapy in patients who have resection. Detailed information on the CS system and current CS data element standards is available at http://www.cancerstaging.org.

TABLE 1.2. Collaborative stage data collection system data elements

Tumor	CS tumor size (primary tumor size in mm)
	CS extension (direct extension of the primary tumor)
	CS tumor size/extension eval (method of evaluating T)[a]
Nodes	CS lymph nodes (regional lymph node involvement)
	CS lymph nodes eval (method of evaluating N)[a]
	Regional nodes positive (number nodes positive)
	Regional nodes examined (number nodes examined)
Metastases	CS Mets at Dx (distant metastases present at time of diagnosis
	CS Mets Eval (method of evaluating M)[a]
Site-specific factors	CS site-specific factors (specific number defined by disease)[b]

[a] Method of evaluation fields: Define source of data – clinical (c) or pathologic (p); response to neoadjuvant therapy utilizing pathologic information (yp).

[b] Site-specific factors: Additional items necessary for (a) defining cancer stage group or (b) key prognostic factors including anatomic disease modifiers and nonanatomic factors (e.g., grade and tumor markers). Most disease sites use only a few of the available site-specific factor fields.

These tumor, node, and metastases fields for best stage are duplicated as needed for pretreatment and posttreatment stages.

For full description of Collaborative Stage Data Collection System, see http://www.cancerstaging.org/cstage/index.html.

NOMENCLATURE OF THE MORPHOLOGY OF CANCER

Cancer treatment requires assessment of the extent and behavior of the tumor and the status of the patient. The most widely used is TNM based on documentation of the anatomic extent of the cancer and selected related nonanatomic factors. 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 cancer registrars who collect the information, taking into consideration the behavior and natural history of each type of cancer.

An *accurate microscopic diagnosis* is essential to the evaluation and treatment of cancer. The histologic and morphologic characteristics of tumors are generally reported by expert pathologists. This is best accomplished 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 in classifying tumors precisely. Techniques that supplement standard histological evaluation including immunohistochemistry, cytogenetics, and genetic characterization are used to characterize tumors and their potential behavior and response to treatment.

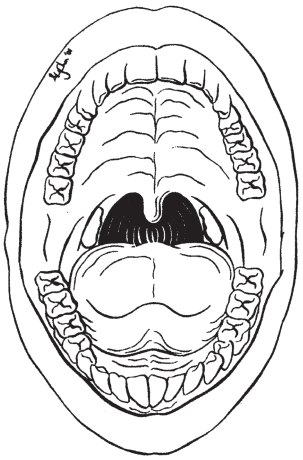
Related Classifications. In the interest of promoting international collaboration in cancer research and to facilitate comparison of data among different clinical studies, use of the *WHO International Classification of Tumours* for classification and definition of tumor types, the *International Classifications of Diseases for Oncology* (*ICD-0*) codes for storage and retrieval of data, CAP protocols for pathology reporting of cancer pathology specimens, and the Collaborative Stage Data Collection System for collecting staging data is recommended. Given here is a summary of relevant related classification and coding systems with source citations.

- *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 histological classification of tumors. The most recent edition is a ten-volume series that contains definitions, descriptions, and illustrations of tumor types and related nomenclature (WHO: World Health Organization Classification of Tumours. Various editions. Lyon, France: IARC Press, 2000–2008).
- *WHO International Classification of Diseases for Oncology* (*ICD-0*), *3rd edition.* ICD-0 is a numerical classification and coding system by topography and morphology (WHO: ICD-O-3 International Classification of Diseases for Oncology. 3rd ed. Geneva: WHO, 2000).

Illustration

Indicate on diagram primary tumor and regional nodes involved.

1.



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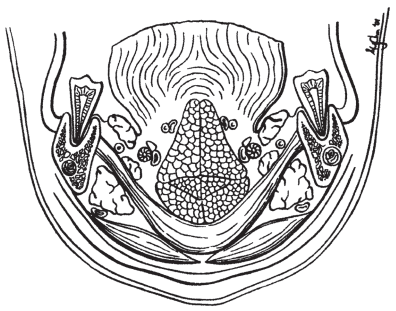

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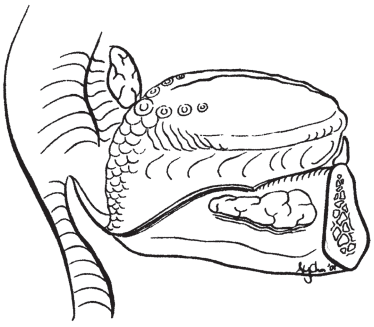

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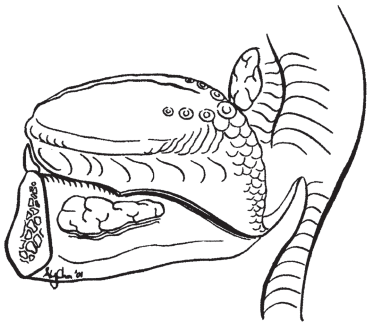

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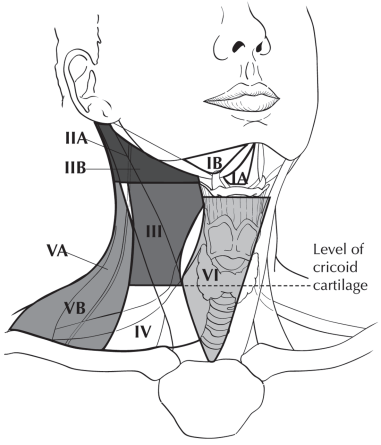

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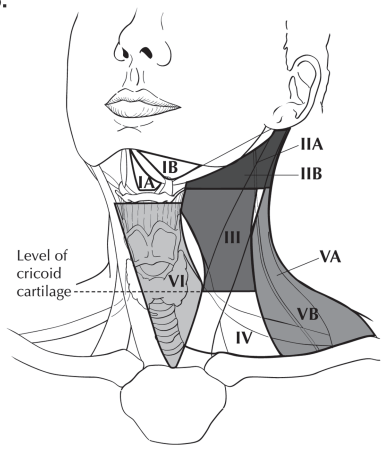

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

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Illustration

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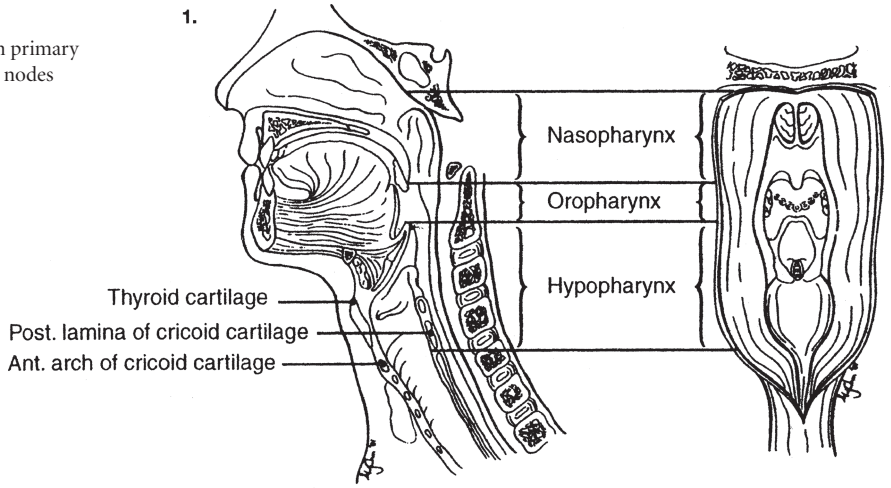

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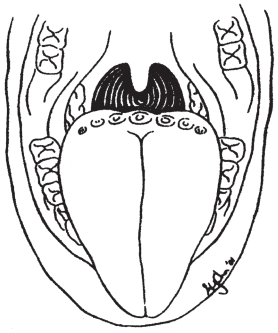

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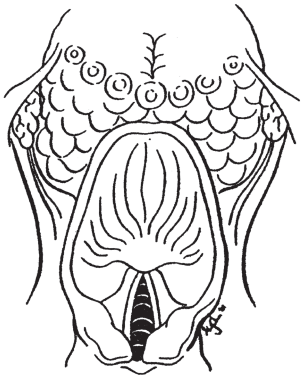

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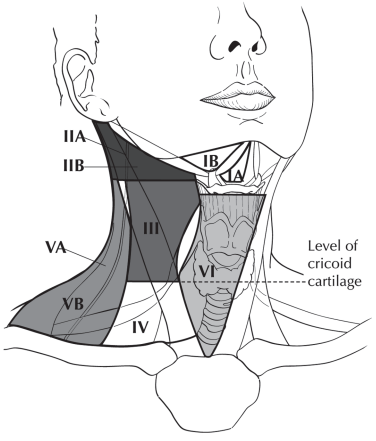

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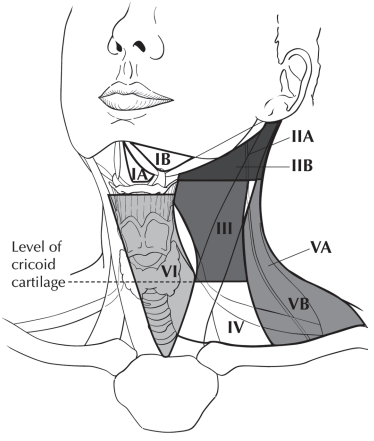

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5

Larynx

(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

At-A-Glance

SUMMARY OF CHANGES

- T4 lesions have been divided into T4a (moderately advanced local disease) and T4b (very advanced local disease), leading to the stratification of Stage IV into Stage IVA (moderately advanced local/regional disease), Stage IVB (very advanced local/regional disease), and Stage IVC (distant metastatic disease)

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

ICD-O-3 TOPOGRAPHY CODES

C10.1 Anterior (lingual) surface of epiglottis
C32.0 Glottis
C32.1 Supraglottis (laryngeal surface)
C32.2 Subglottis
C32.8* Overlapping lesion of larynx
C32.9* Larynx, NOS
*Stage by location of tumor bulk or epicenter

ICD-O-3 HISTOLOGY CODE RANGES

8000–8576, 8940–8950, 8980–8981

ANATOMY

Primary Site. The following anatomic definition of the larynx allows classification of carcinomas arising in the encompassed mucous membranes but excludes cancers arising on the lateral or posterior pharyngeal wall, pyriform fossa, postcricoid area, or base of tongue.

The anterior limit of the larynx is composed of the anterior or lingual surface of the suprahyoid epiglottis, the thyrohyoid membrane, the anterior commissure, and the anterior wall of the subglottic region, which is composed of the thyroid cartilage, the cricothyroid membrane, and the anterior arch of the cricoid cartilage.

The posterior and lateral limits include the laryngeal aspect of the aryepiglottic folds, the arytenoid region, the interarytenoid space, and the posterior surface of the subglottic space, represented by the mucous membrane covering the surface of the cricoid cartilage.

The superolateral limits are composed of the tip and the lateral borders of the epiglottis. The inferior limits are made up of the plane passing through the inferior edge of the cricoid cartilage.

LARYNX STAGING FORM

	REGIONAL LYMPH NODES (N)*	
❑ **NX**	Regional lymph nodes cannot be assessed	❑ **NX**
❑ **N0**	No regional lymph node metastasis	❑ **N0**
❑ **N1**	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension	❑ **N1**
❑ **N2**	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension	❑ **N2**
❑ **N2a**	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension	❑ **N2a**
❑ **N2b**	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension	❑ **N2b**
❑ **N2c**	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension	❑ **N2c**
❑ **N3**	Metastasis in a lymph node, more than 6 cm in greatest dimension *Note: Metastases at level VII are considered regional lymph node metastases.	❑ **N3**
	DISTANT METASTASIS (M)	
❑ **M0**	No distant metastasis (no pathologic M0; use clinical M to complete stage group)	
❑ **M1**	Distant metastasis	❑ **M1**

ANATOMIC STAGE • PROGNOSTIC GROUPS

	CLINICAL				PATHOLOGIC			
	GROUP	**T**	**N**	**M**	**GROUP**	**T**	**N**	**M**
❑	0	Tis	N0	M0	0	Tis	N0	M0
❑	I	T1	N0	M0	I	T1	N0	M0
❑	II	T2	N0	M0	II	T2	N0	M0
❑	III	T3	N0	M0	III	T3	N0	M0
		T1	N1	M0		T1	N1	M0
		T2	N1	M0		T2	N1	M0
		T3	N1	M0		T3	N1	M0
❑	IVA	T4a	N0	M0	IVA	T4a	N0	M0
		T4a	N1	M0		T4a	N1	M0
		T1	N2	M0		T1	N2	M0
		T2	N2	M0		T2	N2	M0
		T3	N2	M0		T3	N2	M0
		T4a	N2	M0		T4a	N2	M0
❑	IVB	T4b	Any N	M0	IVB	T4b	Any N	M0
		Any T	N3	M0		Any T	N3	M0
❑	IVC	Any T	Any N	M1	IVC	Any T	Any N	M1
❑	Stage unknown				Stage unknown			

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

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Illustration

Indicate on diagram primary tumor and regional nodes involved.

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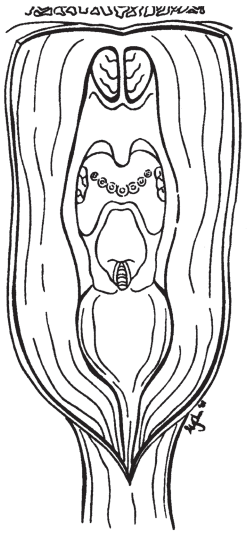

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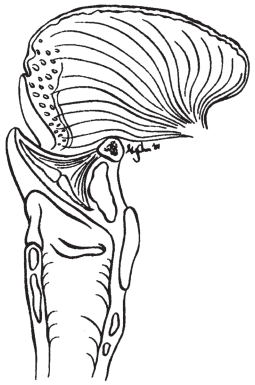

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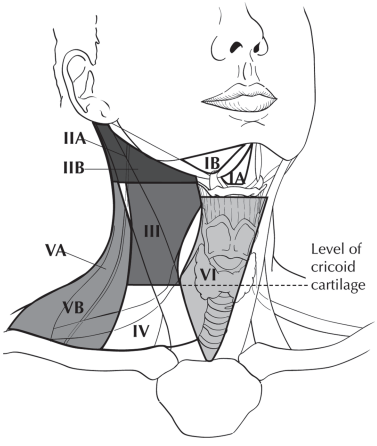

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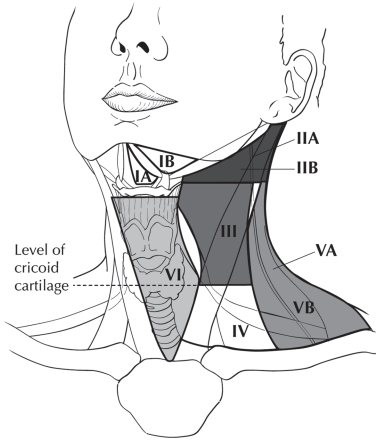

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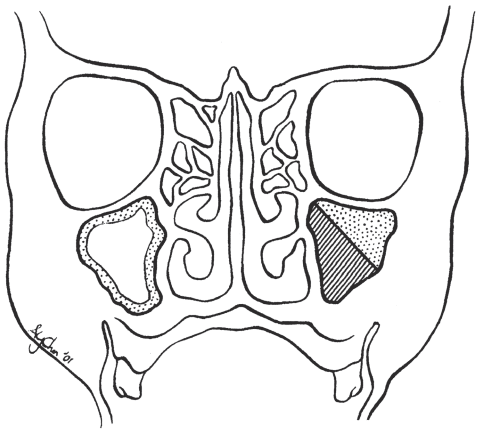

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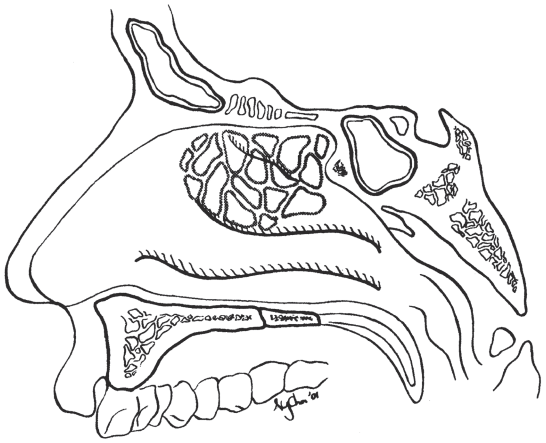

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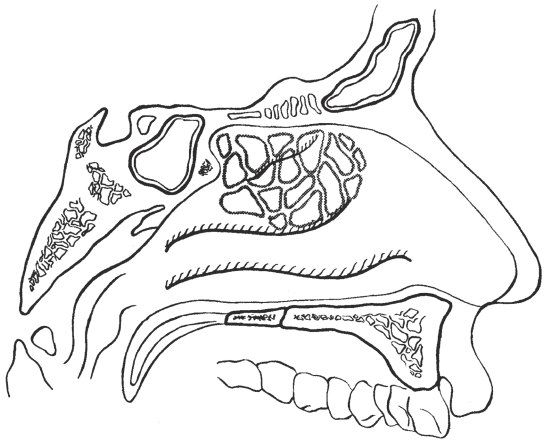

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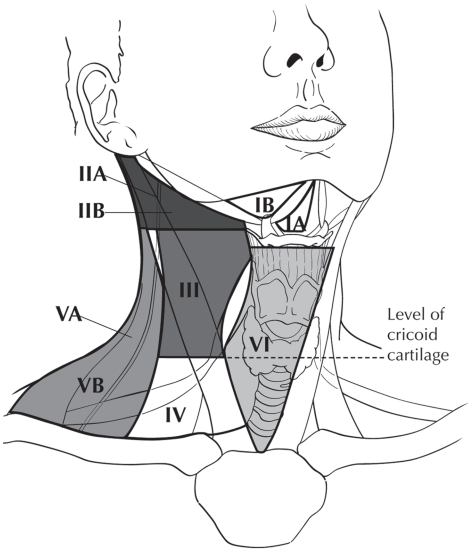

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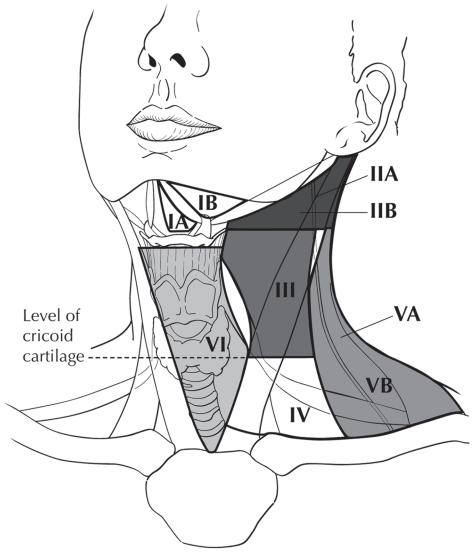

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Major Salivary Glands Staging Form

Clinical *Extent of disease before any treatment*	Stage Category Definitions		Pathologic *Extent of disease through completion of definitive surgery*
❒ y clinical – staging completed after neoadjuvant therapy but before subsequent surgery	**Tumor Size:** _____	**Laterality:** ☐ left ☐ right ☐ bilateral	❒ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	Primary Tumor (T)		
❑ TX	Primary tumor cannot be assessed		❑ TX
❑ T0	No evidence of primary tumor		❑ T0
❑ T1	Tumor 2 cm or less in greatest dimension without extraparenchymal extension*		❑ T1
❑ T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension*		❑ T2
❑ T3	Tumor more than 4 cm and/or tumor having extraparenchymal extension*		❑ T3
❑ T4a	Moderately advanced disease Tumor invades skin, mandible, ear canal, and/or facial nerve		❑ T4a
❑ T4b	Very advanced disease Tumor invades skull base and/or pterygoid plates and/or encases carotid artery		❑ T4b
	**Note:* Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.		
	Regional Lymph Nodes (N)		
❑ NX	Regional lymph nodes cannot be assessed		❑ NX
❑ N0	No regional lymph node metastasis		❑ N0
❑ N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension		❑ N1
❑ N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		❑ N2
❑ N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension		❑ N2a
❑ N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension		❑ N2b
❑ N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		❑ N2c
❑ N3	Metastasis in a lymph node, more than 6 cm in greatest dimension		❑ N3
	Distant Metastasis (M)		
❑ M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)		
❑ M1	Distant metastasis		❑ M1

Hospital Name/Address	Patient Name/Information

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Illustration

Indicate on diagram primary tumor and regional nodes involved.

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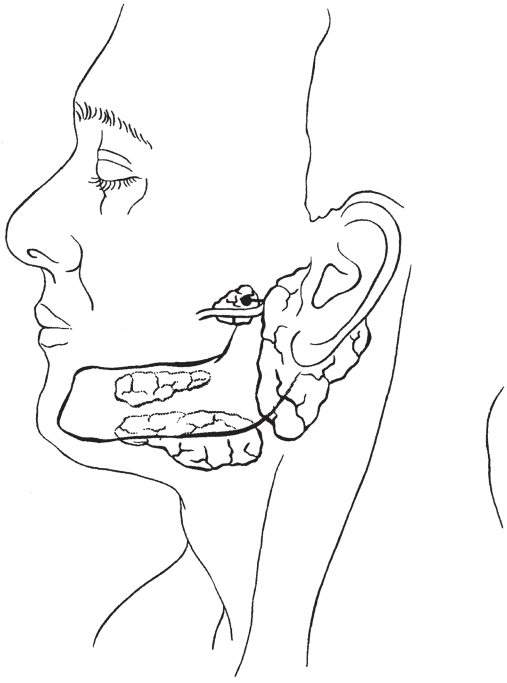

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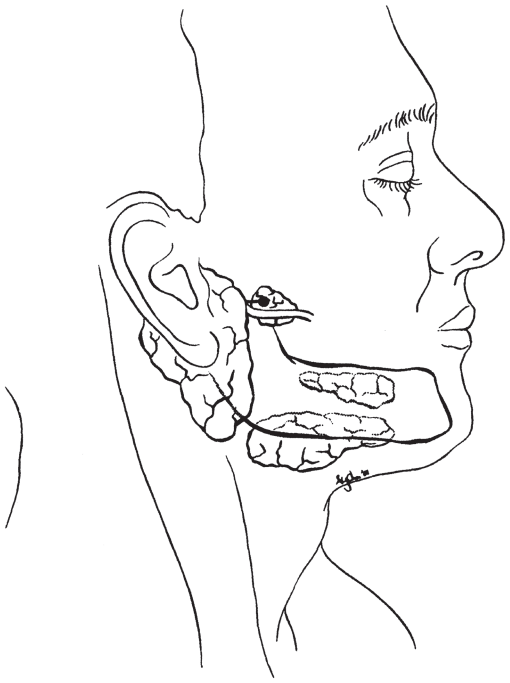

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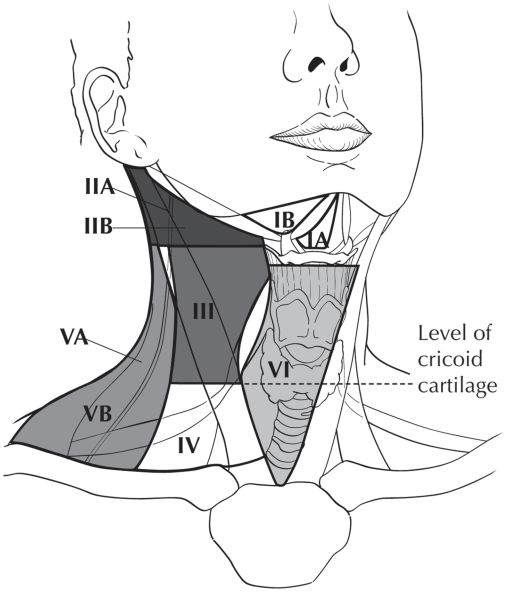

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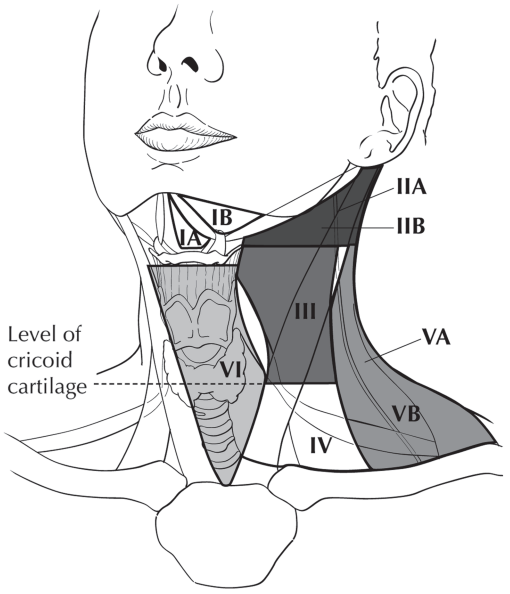

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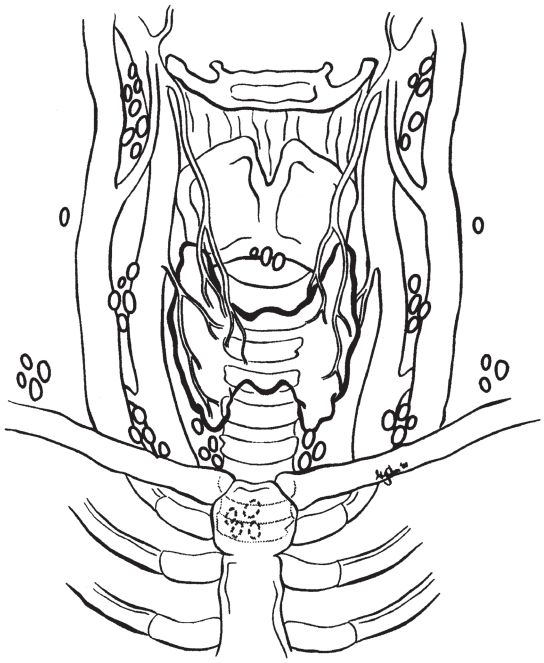

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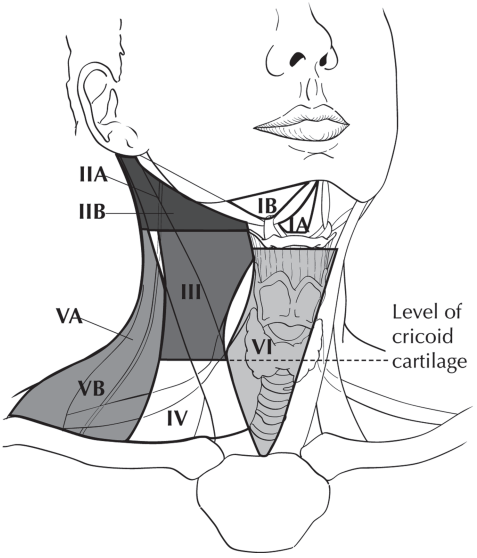

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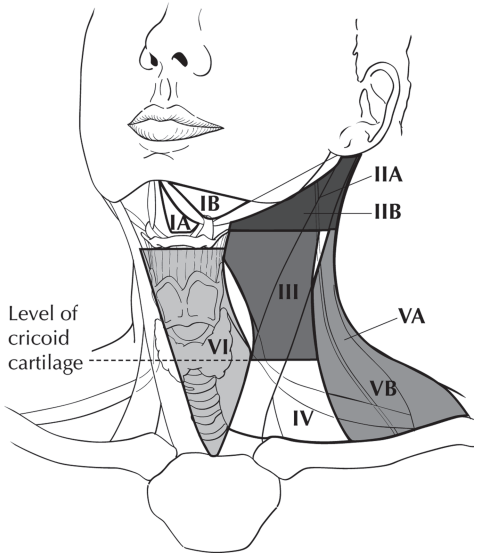

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9

Mucosal Melanoma of the Head and Neck

At-A-Glance

SUMMARY OF CHANGES

- This is a new chapter for classification of this rare tumor

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage III	T3	N0	M0
Stage IVA	T4a	N0	M0
	T3–T4a	N1	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

ICD-O-3 TOPOGRAPHY CODES

For a complete description of codes, refer to the appropriate anatomic site chapter based on the location of the mucosal melanoma (see Chapters 3–6)

Additionally, mucosal melanomas are staged for the following topography codes; however, no staging exists for nonmucosal melanoma in the same anatomic site:

C14.0 Pharynx, NOS
C14.2 Waldeyer's ring
C14.8 Overlapping lesion of lip, oral cavity and pharynx

The following topography codes are excluded:

C07.9 Parotid gland
C08.0 Submandibular gland
C08.1 Sublingual gland
C08.8 Overlapping lesion of major salivary glands
C08.9 Major salivary glands, NOS
C30.1 Middle ear
C73.9 Thyroid

ICD-O-3 HISTOLOGY CODE RANGES

8720–8790

INTRODUCTION

Mucosal melanoma is an aggressive neoplasm that warrants separate consideration. Approximately two-thirds of these lesions arise in the nasal cavity and paranasal sinuses; one quarter are found in the oral cavity and the remainder occur only sporadically in other mucosal sites of the head and neck. Even small cancers behave aggressively with high rates of recurrence and death. To reflect this aggressive behavior, primary cancers limited to the mucosa are considered T3 lesions.

ANATOMIC STAGE/PROGNOSTIC GROUPS (*CONTINUED*)

Adenocarcinoma

Stage	T	N	M	Grade
0	Tis (HGD)	N0	M0	1, X
IA	T1	N0	M0	1–2, X
IB	T1	N0	M0	3
	T2	N0	M0	1–2, X
IIA	T2	N0	M0	3
IIB	T3	N0	M0	Any
	T1–2	N1	M0	Any
IIIA	T1–2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
IIIB	T3	N2	M0	Any
IIIC	T4a	N1–2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
IV	Any	Any	M1	Any

ICD-O-3 HISTOLOGY CODE RANGES

8000–8576, 8940–8950, 8980–8981 (C15 only)
8000–8152, 8154–8231, 8243–8245, 8247–8248, 8250–8576, 8940–8950, 8980–8981 (C16 only)

INTRODUCTION

Previous stage groupings of esophageal cancer were based on a simple, orderly arrangement of increasing pathologic anatomic T, then N, and then M classifications. In contrast, this revision is data driven, based on a risk-adjusted random-survival-forest analysis of worldwide data. The previous system was neither consistent with these data nor biologically plausible. Some explanations for the discrepancy relate to the interplay among T, N, and M, histopathologic type, biologic activity of the tumor (histologic grade), and location.

The unique lymphatic anatomy of the esophagus links N to T, permitting lymph node metastases from superficial cancers (pT1); this renders prognosis similar to that of more advanced (higher pT) N0 cancers. Similarly, advanced cancers (higher pT) with a few positive nodes may have a similar prognosis to those of less advanced cancers (lower pT) with more positive nodes. Biologic activity of the cancer, reflected by histologic grade (G), modulates stage such that prognosis of well-differentiated (G1) higher-pT cancers is similar to that of less well-differentiated (G2–G4) lower-pT cancers. Previous staging recommendations ignored histopathologic type, but availability of data on a large mixture of adenocarcinoma and squamous cell carcinomas from around the world has permitted assessing the association of histopathologic type with survival.

Although at first glance these multiple trade-offs seem to create a less orderly arrangement of cancer classifications within and among stage groupings compared with previous stage groupings, when viewed from the perspective of the interplay of these important prognostic factors, the new staging system becomes biologically compelling and consistent with a number of other cancers.

A limitation of this data-driven approach is that staging is based only on pTNM from esophageal cancers treated by esophagectomy alone, without induction or postoperative chemotherapy or radiotherapy; patients not offered operation, deemed inoperable, or undergoing exploratory surgery without esophagectomy were not represented in the data. In addition, patients undergoing surgery alone with pT4 and pM1 cancers represent a select population; placing them into stage groups, therefore, required either combining some classifications or using literature as a supplement. Patients with cervical esophageal cancer, sometimes treated as a head-and-neck tumor, were also poorly represented.

ANATOMY

Primary Site. The location of the primary tumor is defined by the position of the upper end of the cancer in the esophagus. This is best expressed as the distance from the incisors to the proximal edge of the tumor and conventionally by its location within broad regions of the esophagus. ICD coding recognizes three anatomic compartments traversed by the esophagus: cervical, thoracic, and abdominal. It also arbitrarily divides the esophagus into equal thirds: upper, middle, and lower (Table 10.1). However, clinical importance of primary site of esophageal cancer is less related to its position in the esophagus than to its relation to adjacent structures (Figure 10.1).

Cervical Esophagus. Anatomically, the cervical esophagus lies in the neck, bordered superiorly by the hypopharynx and inferiorly by the thoracic inlet, which lies at the level of the sternal notch. It is subtended by the trachea, carotid sheaths,

EGJ or esophagus, are stage grouped using the gastric (non-EGJ) cancer staging system (see Chap. 11).

Esophageal Wall. The esophageal wall has three layers: mucosa, submucosa, and muscularis propria (Figure 10.2). The *mucosa* is composed of epithelium, lamina propria, and muscularis mucosae. A basement membrane isolates the mucosa from the rest of the esophageal wall. In the columnar-lined esophagus the muscularis mucosae may be a two-layered structure. The mucosal division can be classified as m1 (epithelium), m2 (lamina propria), or m3 (muscularis mucosae). The *submucosa* has no landmarks, but some divide it into inner (sm1), middle (sm2), and outer thirds (sm3). The *muscularis propria* has inner circular and outer longitudinal muscle layers. There is no serosa; rather, *adventitia* (periesophageal connective tissue) lies directly on the muscularis propria.

Adjacent Structures. In close proximity to the esophagus lie pleura-peritoneum, pericardium, and diaphragm. Cancers invading these structures may be resectable (T4a). Aorta, carotid vessels, azygos vein, trachea, left main bronchus, and vertebral body also are in close proximity, but cancers invading these structures are usually unresectable (T4b).

Lymphatics. Esophageal lymphatic drainage is intramural and longitudinal (Figure 10.2). Although a lymphatic network is concentrated in the submucosa, lymphatic channels are present in the lamina propria, an arrangement that permits lymphatic metastases early in the course of the disease from superficial cancers that are otherwise confined to the mucosa. Lymphatic drainage of the muscularis propria is more limited, but lymphatic channels pierce this layer to drain into regional lymphatic channels and lymph nodes in the periesophageal fat. Up to 43% of autopsy dissections demonstrate direct drainage from the submucosal plexus into the thoracic duct, which facilitates systemic metastases. The longitudinal nature of the submucosal lymphatic plexus permits lymphatic metastases orthogonal to the depth of tumor invasion. Implications of the longitudinal nature of lymphatic drainage are that the anatomic site of the cancer and the nodes to which lymphatics drain from that site may not be the same.

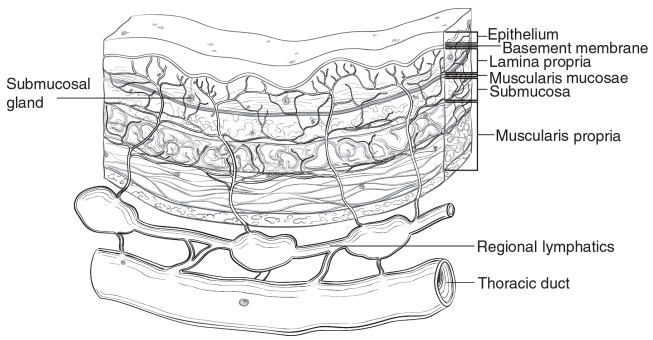


FIGURE 10.2. Esophageal wall.

Regional lymph nodes extend from periesophageal cervical nodes to celiac nodes (Figures 10.3A–D and 10.4). For radiotherapy, fields of treatment may not be constrained within this definition of regional node.

The data demonstrate that the number of regional lymph nodes containing metastases (positive nodes) is the most important prognostic factor. In classifying N, the data support convenient coarse groupings of the number of positive nodes (0, 1–2, 3–6, 7 or more). These have been designated N1 (1–2), N2 (3–6), and N3 (7 or more). Nevertheless, there are no sharp cut-points; rather, each additional positive node increases risk. Clinical determination of positive lymph node number is possible and correlated with survival. Thus, the staging recommendations apply to both clinical and pathologic staging. The data do not support lymph node ratio (number positive divided by number sampled) as a useful measure of lymph node burden. The number of sampled nodes, the denominator of the ratio, is highly variable, distorting the magnitude of lymph node burden.

Data demonstrate that in general, the more lymph nodes resected, the better the survival. This may be due to either improved N classification or a therapeutic effect of lymphadenectomy. On the basis of worldwide data, it was found that optimum lymphadenectomy depends on T classification: For pT1, approximately ten nodes must be resected to maximize survival; for pT2, 20 nodes and for pT3 or pT4, 30 nodes or more. On the basis of different data and analysis methods

FIGURE 10.3. (**A–C**) Lymph node maps for esophageal cancer. Regional lymph node stations for staging esophageal cancer, from front (**A**) and side (**B**). 1, Supraclavicular nodes; above suprasternal notch and clavicles. 2R, Right upper paratracheal nodes; between intersection of caudal margin of innominate artery with trachea and the apex of the lung. 2L, Left upper paratracheal nodes; between the top of aortic arch and apex of the lung. 3P, Posterior mediastinal nodes; upper paraesophageal nodes, above tracheal bifurcation. 4R, Right lower paratracheal nodes; between intersection of caudal margin of innominate artery with trachea and cephalic border of azygos vein. 4L, Left lower paratracheal nodes; between top of aortic arch and carina. 5, Aortopulmonary nodes; subaortic and para-aortic nodes lateral to the ligamentum arteriosum. 6, Anterior mediastinal nodes; anterior to ascending aorta or innominate artery. 7, Subcarinal nodes; caudal to the carina of the trachea. 8M, Middle paraesophageal lymph nodes; from the tracheal bifurcation to the caudal margin of the inferior pulmonary vein. 8L, Lower paraesophageal lymph nodes; from the caudal margin of the inferior pulmonary vein to the esophagogastric junction. 8R, 9, Pulmonary ligament nodes; within the inferior pulmonary ligament. 10R, Right tracheobronchial nodes; from cephalic border of azygos vein to origin of RUL bronchus. 10L, Left tracheobronchial nodes; between carina and LUL bronchus. 15, Diaphragmatic nodes; lying on the dome of the diaphragm and adjacent to or behind its crura. 16, Paracardial nodes; immediately adjacent to the gastroesophageal junction. 17, Left gastric nodes; along the course of the left gastric artery. 18, Common hepatic nodes; along the course of the common hepatic artery. 19, Splenic nodes; along the course of the splenic artery. 20, Celiac nodes; at the base of the celiac artery. (**D**) The IASLC lymph node map. (**D**, © Memorial Sloan-Kettering Cancer Center, 2009.)

ESOPHAGUS STAGING FORM

* or mixed histology including a squamous component or NOS
** Location of the primary cancer site is defined by the position of the upper (proximal) edge of the tumor in the esophagus

Adenocarcinoma

GROUP	T	N	M	Grade
❑ 0	Tis (HGD)	N0	M0	1, X
❑ IA	T1	N0	M0	1-2, X
❑ IB	T1	N0	M0	3
	T2	N0	M0	1-2, X
❑ IIA	T2	N0	M0	3
❑ IIB	T3	N0	M0	Any
	T1-2	N1	M0	Any
❑ IIIA	T1-2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
❑ IIIB	T3	N2	M0	Any
❑ IIIC	T4a	N1-2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
❑ IV	Any	Any	M1	Any
❑ Stage unknown				

* or mixed histology including a squamous component or NOS
** Location of the primary cancer site is defined by the position of the upper (proximal) edge of the tumor in the esophagus

Adenocarcinoma

GROUP	T	N	M	Grade
❑ 0	Tis (HGD)	N0	M0	1, X
❑ IA	T1	N0	M0	1-2, X
❑ IB	T1	N0	M0	3
	T2	N0	M0	1-2, X
❑ IIA	T2	N0	M0	3
❑ IIB	T3	N0	M0	Any
	T1-2	N1	M0	Any
❑ IIIA	T1-2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
❑ IIIB	T3	N2	M0	Any
❑ IIIC	T4a	N1-2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
❑ IV	Any	Any	M1	Any
❑ Stage unknown				

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)

Squamous Cell Carcinoma

REQUIRED FOR STAGING:

Location – based on the position of the upper (proximal) edge of the tumor in the esophagus (Upper or middle—cancers above lower border of inferior pulmonary vein; Lower—below inferior pulmonary vein) _____

Grade _____

CLINICALLY SIGNIFICANT:

Distance to proximal edge of tumor from incisors _____
Distance to distal edge of tumor from incisors _____
Number of regional nodes with extracapsular tumor _____

Adenocarcinoma

REQUIRED FOR STAGING:

Grade_____

CLINICALLY SIGNIFICANT:

Distance to proximal edge of tumor from incisors _____
Distance to distal edge of tumor from incisors _____
Number of regional nodes with extracapsular tumor _____

Histologic Grade (G) *(also known as overall grade)*

Grading system	*Grade*
❑ 2 grade system	❑ Grade I or 1
❑ 3 grade system	❑ Grade II or 2
❑ 4 grade system	❑ Grade III or 3
❑ No 2, 3, or 4 grade system is available	❑ Grade IV or 4

General Notes:
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

a prefix designates the stage determined at autopsy: aTNM.

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

(continued from previous page)

ANATOMIC STAGE/PROGNOSTIC GROUPS (*CONTINUED*)

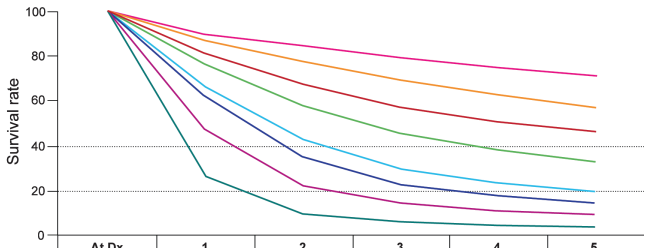
Stage IIIB	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
Stage IIIC	T4b	N2	M0
	T4b	N3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1

ICD-O-3 HISTOLOGY CODE RANGES

8000–8152, 8154–8231, 8243–8245, 8247–8248, 8250–8576, 8940–8950, 8980–8990

INTRODUCTION

Gastric cancer remains the fourth most common cancer worldwide and the second leading cause of cancer deaths (700,000 deaths annually worldwide). The highest rates of this disease continue to be in areas of Asia and Eastern Europe. Although gastric adenocarcinoma has declined significantly in the USA over the past 70 years, during the early twenty-first century an estimated 22,000 patients develop the disease each year, and of these patients, 13,000 will die, mainly because of nodal and metastatic disease present at the time of initial diagnosis. Trends in survival rates from the 1970s to the 1990s have unfortunately shown very little improvement. During the 1990s, 20% of gastric carcinoma cases were diagnosed while localized to the gastric wall, whereas 30% had evidence of regional nodal disease. Disease resulting from metastasis to other solid organs within the abdomen, as well as to extraabdominal sites, represents 35% of all cases. Although overall 5-year survival is approximately 15–20%, the 5-year survival is approximately 55% when disease is localized to the stomach (Figure 11.1).



	At Dx	1	2	3	4	5
IA	100.0	90.2	84.8	79.8	74.8	70.8
IB	100.0	87.4	77.9	69.9	62.7	57.4
IIA	100.0	82.1	67.4	57.2	50.2	45.5
IIB	100.0	76.8	58.3	46.0	38.4	32.8
IIIA	100.0	66.5	42.4	29.9	23.5	19.8
IIIB	100.0	61.6	35.4	22.9	17.8	14.0
IIIC	100.0	47.4	21.8	14.2	11.0	9.2
IV	100.0	27.0	10.0	5.6	4.5	4.0

FIGURE 11.1. Observed survival rates for 10,601 surgically resected gastric adenocarcinomas. Data from the SEER 1973–2005 Public Use File diagnosed in years 1991–2000. Stage IA includes 1,194; Stage IB, 655; Stage IIA, 1,161; Stage IIB, 1,195; Stage IIIA, 1,031; Stage IIIB, 1,660; Stage IIIC, 1,053; and Stage IV, 6,148.

The involvement of regional nodes reduces the 5-year survival to approximately 20%.

A notable shift in the site of gastric cancer reflects a proportionate increase in disease of the proximal stomach over the past several decades. Previously, there was a predominance of distal gastric cancers presenting as mass lesions or ulceration. Although other malignancies occur in the stomach, approximately 90% of all gastric neoplasms are adenocarcinomas. Tumors of the esophagogastric junction (EGJ) may be difficult to stage as either a gastric or an esophageal primary, especially in view of the increased incidence of adenocarcinoma in the esophagus that presumably results from acid reflux disease.

ANATOMY

Primary Site. The stomach is the first division of the abdominal portion of the alimentary tract, beginning at the esophagogastric junction and extending to the pylorus. The proximal stomach is located immediately below the diaphragm and is termed the cardia. The remaining portions are the fundus and body of the stomach, and the distal portion of the stomach is known as the antrum. The pylorus is a muscular ring that controls the flow of food content from the stomach into the first portion of the duodenum. The medial and lateral curvatures of the stomach are known as the lesser and greater curvatures, respectively. Histologically, the wall of the stomach has five layers: mucosal, submucosal, muscular, subserosal, and serosal.

The arbitrary 10-cm segment encompassing the distal 5 cm of the esophagus and proximal 5 cm of the stomach (cardia), with the EGJ in the middle, is an area of contention. Cancers arising in this segment have been variably staged as esophageal or gastric tumors, depending on orientation of the treating physician. In this edition, cancers whose midpoint is in the lower thoracic esophagus, EGJ, or within the proximal 5 cm of the stomach (cardia) that extend into the EGJ or esophagus (Siewert III) are staged as adenocarcinoma of the esophagus (see Chap. 10). All other cancers with a midpoint in the stomach lying more than 5 cm distal to the EGJ, or those within 5 cm of the EGJ but not extending into

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Small Intestine

(Lymphomas, carcinoid tumors, and visceral sarcomas are not included)

At-A-Glance

SUMMARY OF CHANGES

- T1 lesions have been divided into T1a (invasion of lamina propria) and T1b (invasion of submucosa) to facilitate comparison with tumors of other gastrointestinal sites
- Stage II has been subdivided into Stage IIA and Stage IIB
- The N1 category has been changed to N1 (1–3 positive lymph nodes) and N2 (four or more positive lymph nodes), leading to the division of Stage III into Stage IIIA and Stage IIIB

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4	N0	M0
Stage IIIA	Any T	N1	M0
Stage IIIB	Any T	N2	M0
Stage IV	Any T	Any N	M1

ICD-O-3 TOPOGRAPHY CODES

C17.0 Duodenum
C17.1 Jejunum
C17.2 Ileum
C17.8 Overlapping lesion of small intestine
C17.9 Small intestine, NOS

ICD-O-3 HISTOLOGY CODE RANGES

8000–8152, 8154–8231, 8243–8245, 8247–8248, 8250–8576, 8940–8950, 8980–8981

INTRODUCTION

Although the small intestine accounts for one of the largest surface areas in the human body, it is one of the least common cancer sites in the digestive system, accounting for less than 2% of all malignant tumors of the gastrointestinal tract. A variety of tumors occur in the small intestine, with approximately 25–50% of the primary malignant tumors being adenocarcinomas, depending upon the population surveyed. At the beginning of the twenty-first century, approximately 5,600 new cases of cancer involving the small intestine are seen annually in the USA. The 1,100 deaths predicted to occur from small intestinal cancer are divided almost equally between men and women. Over 60% of tumors occur in the duodenum, followed by jejunum (20%) and ileum (15%). An increased incidence of second malignancies has been noted in patients with primary small bowel adenocarcinoma, a finding related in part to the significantly increased risk for this malignancy in patients with hereditary nonpolyposis colorectal cancer. Crohn's disease and celiac disease are also associated with an increased risk for small intestinal carcinomas and lymphomas.

The patterns of local, regional, and metastatic spread for adenocarcinomas of the small intestine are comparable to those of similar histologic malignancies in other areas of the gastrointestinal tract. The classification and stage grouping described in this chapter are used for both clinical and pathologic staging of carcinomas of the small bowel and do not apply to other types of malignant small bowel tumors. Well-differentiated neuroendocrine tumors (carcinoid tumors)

APPENDIX STAGING FORM

CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS		PATHOLOGIC *Extent of disease through completion of definitive surgery*
❒ y clinical– staging completed after neoadjuvant therapy but before subsequent surgery	**TUMOR SIZE:** _____	**LATERALITY:** ☐ left ☐ right ☐ bilateral	❒ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	PRIMARY TUMOR (T)		
	Carcinoma		
❑ TX	Primary tumor cannot be assessed		❑ TX
❑ T0	No evidence of primary tumor		❑ T0
❑ Tis	Carcinoma *in situ:* intraepithelial or invasion of lamina propria*		❑ Tis
❑ T1	Tumor invades submucosa		❑ T1
❑ T2	Tumor invades muscularis propria		❑ T2
❑ T3	Tumor invades through muscularis propria into subserosa or into mesoappendix		❑ T3
❑ T4	Tumor penetrates visceral peritoneum, including mucinous peritoneal tumor within the right lower quadrant and/or directly invades other organs or structures**,***		❑ T4
❑ T4a	Tumor penetrates visceral peritoneum, including mucinous peritoneal tumor within the right lower quadrant		❑ T4a
❑ T4b	Tumor directly invades other organs or structures		❑ T4b
	* Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or lamina propria (intramucosal) with no extension through muscularis mucosae into submucosa. ** Direct invasion in T4 includes invasion of other segments of the colorectum by way of the serosa, e.g., invasion of ileum. *** Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-3 depending on the anatomical depth of wall invasion.		
	Carcinoid		
❑ TX	Primary tumor cannot be assessed		❑ TX
❑ T0	No evidence of primary tumor		❑ T0
❑ T1	Tumor 2 cm or less in greatest dimension		❑ T1
❑ T1a	Tumor 1 cm or less in greatest dimension		❑ T1a
❑ T1b	Tumor more than 1 cm but not more than 2 cm		❑ T1b
❑ T2	Tumor more than 2 cm but not more than 4 cm or with extension to the cecum		❑ T2
❑ T3	Tumor more than 4 cm or with extension to the ileum		❑ T3
❑ T4	Tumor directly invades other adjacent organs or structures, e.g., abdominal wall and skeletal muscle*		❑ T4
	Note: Tumor that is adherent to other organs or structures, grossly, is classified cT4. However, if no tumor is present in the adhesion, microscopically, the classification should be classified pT1-3 depending on the anatomical depth of wall invasion. *Penetration of the mesoappendix does not seem to be as important a prognostic factor as the size of the primary tumor and is not separately categorized.		
	REGIONAL LYMPH NODES (N)		
	Carcinoma		
❑ NX	Regional lymph nodes cannot be assessed		❑ NX
❑ N0	No regional lymph node metastasis		❑ N0
❑ N1	Metastasis in 1 to 3 regional lymph nodes		❑ N1
❑ N2	Metastasis in 4 or more regional lymph nodes		❑ N2

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

(continued on next page)

APPENDIX STAGING FORM

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)

Carcinoma

REQUIRED FOR STAGING: Grade _____

CLINICALLY SIGNIFICANT:

Preoperative/Pretreatment carcinoembryonic antigen (CEA) _____
Preoperative/Pretreatment CA 19-9 _____
Tumor Deposits (TD) _____
Microsatellite instability (MSI) _____
18q Loss of Heterozygosity (LOH) _____

Carcinoid

REQUIRED FOR STAGING: None

CLINICALLY SIGNIFICANT:

Serum Chromaganin A _____

Histologic Grade (G) *(also known as overall grade)*

Grading system	***Grade***
❑ 2 grade system	❑ Grade I or 1
❑ 3 grade system	❑ Grade II or 2
❑ 4 grade system	❑ Grade III or 3
❑ No 2, 3, or 4 grade system is available	❑ Grade IV or 4

ADDITIONAL DESCRIPTORS

Lymphatic Vessel Invasion (L) and Venous Invasion (V) have been combined into Lymph-Vascular Invasion (LVI) for collection by cancer registrars. The College of American Pathologists' (CAP) Checklist should be used as the primary source. Other sources may be used in the absence of a Checklist. Priority is given to positive results.

❑ Lymph-Vascular Invasion Not Present (absent)/Not Identified
❑ Lymph-Vascular Invasion Present/Identified
❑ Not Applicable
❑ Unknown/Indeterminate

Residual Tumor (R)

The absence or presence of residual tumor after treatment. In some cases treated with surgery and/or with neoadjuvant therapy there will be residual tumor at the primary site after treatment because of incomplete resection or local and regional disease that extends beyond the limit of ability of resection.

❑ RX Presence of residual tumor cannot be assessed
❑ R0 No residual tumor
❑ R1 Microscopic residual tumor
❑ R2 Macroscopic residual tumor

General Notes:
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

a prefix designates the stage determined at autopsy: aTNM.

surgical margins is data field recorded by registrars describing the surgical margins of the resected primary site specimen as determined only by the pathology report.

neoadjuvant treatment is radiation therapy or systemic therapy (consisting of chemotherapy, hormone therapy, or immunotherapy) administered prior to a definitive surgical procedure. If the surgical procedure is not performed, the administered therapy no longer meets the definition of neoadjuvant therapy.

❑ Clinical stage was used in treatment planning (describe): _____

❑ National guidelines were used in treatment planning ❑ NCCN ❑ Other (describe): _____

_____

_____
Physician signature Date/Time

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage	T	N	M	Dukes*	MAC*
0	Tis	N0	M0	–	–
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1–T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3–T4a	N1/N1c	M0	C	C2
	T2–T3	N2a	M0	C	C1/C2
	T1–T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3–T4a	N2b	M0	C	C2
	T4b	N1–N2	M0	C	C3
IVA	Any T	Any N	M1a	–	–
IVB	Any T	Any N	M1b	–	–

ICD-O-3 TOPOGRAPHY CODES

C18.0 Cecum
C18.2 Ascending colon
C18.3 Hepatic flexure of colon
C18.4 Transverse colon
C18.5 Splenic flexure of colon
C18.6 Descending colon
C18.7 Sigmoid colon
C18.8 Overlapping lesion of colon
C18.9 Colon, NOS
C19.9 Rectosigmoid junction
C20.9 Rectum, NOS

ICD-O-3 HISTOLOGY CODE RANGES

8000–8152, 8154–8231, 8243–8245, 8247–8248, 8250–8576, 8940–8950, 8980–8981

Note: cTNM is the clinical classification, pTNM is the pathologic classification. The y prefix is used for those cancers that are classified after neoadjuvant pretreatment (e.g., ypTNM). Patients who have a complete pathologic response are ypT0N0cM0 that may be similar to Stage Group 0 or I. The r prefix is to be used for those cancers that have recurred after a disease-free interval (rTNM).

*Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (Any TN1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.

INTRODUCTION

The TNM classification for carcinomas of the colon and rectum provides more detail than other staging systems. Compatible with the Dukes' system, the TNM adds greater precision in the identification of prognostic subgroups. TNM staging is based on the depth of tumor invasion into or beyond the wall of the colorectum (T), invasion of or adherence to adjacent organs or structures (T), the number of regional lymph nodes involved (N), and the presence or absence of distant metastasis (M). The TNM classification applies to both clinical and pathologic staging. Most cancers of the colon and many cancers of the rectum are staged after pathologic examination of a resected specimen. However, patients with high-risk rectal cancers are commonly receiving preoperative adjuvant treatment prior to surgical resection and pathological stage annotation should employ the y prefix in such cases. This staging system applies to all carcinomas arising in the colon or rectum. Adenocarcinomas of the vermiform appendix are classified according to the TNM staging system for appendix (see Chap. 13), whereas cancers that occur in the anal canal are staged according to the classification used for the anus (see Chap. 15). Well-differentiated neuroendocrine carcinomas (carcinoid tumors) of the colorectum are classified according to the TNM staging system for gastric, small bowel, and colonic and rectal carcinoid tumors (well-differentiated neuroendocrine tumors and well-differentiated neuroendocrine carcinomas) as described in Chap. 17.

ANATOMY

The divisions of the colon and rectum are as follows:

Cecum
Ascending colon
Hepatic flexure
Transverse colon
Splenic flexure
Descending colon

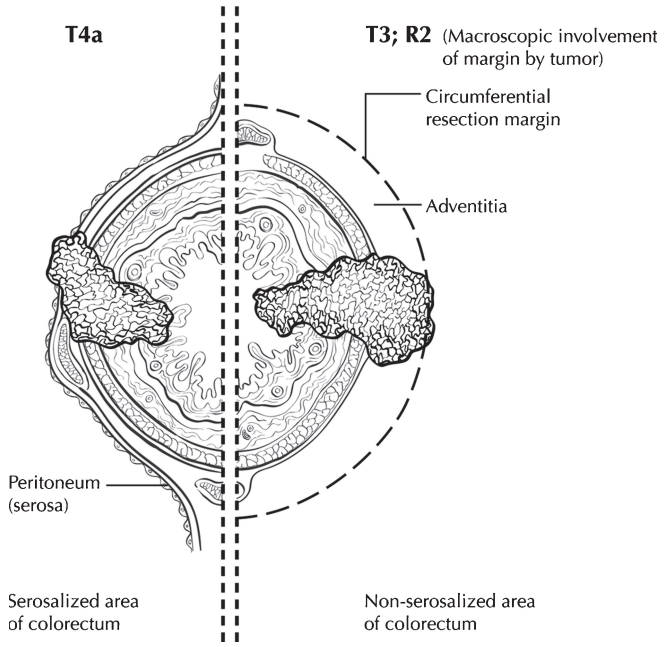


FIGURE 14.3. Circumferential resection margin.

with a significantly increased risk of local recurrence and should be classified as positive (Figure 14.3).

Residual Tumor (R) The completeness of resection is largely dependent on the status of the CRM, although the designation is global and would include the transverse margins and other disease observed but not removed at surgery. The resection (R) codes should be given for each procedure:

- R0—Complete tumor resection with all margins histologically negative
- R1—Incomplete tumor resection with microscopic surgical resection margin involvement (margins grossly uninvolved)
- R2—Incomplete tumor resection with gross residual tumor that was not resected (primary tumor, regional nodes, macroscopic margin involvement)

Isolated Tumor Cells and Molecular Node Involvement. As technology progresses and sentinel node biopsy or other procedures may become feasible in colon and rectal surgery, the issue of interpretation of very small amounts of detected tumor in regional lymph nodes will continue to be classified as pN0, and the universal terminology for these isolated tumor cells (ITC) will follow the terminology referenced in Chap. 1. The prognostic significance of ITCs, defined as single malignant cells or a few tumor cells in microclusters, identified in regional lymph nodes that otherwise would be considered to be negative is still unclear. Therefore, ITC identified the collection of data on ITC that may be generated by pathologists who use special immunohistochemical stains or molecular analysis procedures to identify ITC in nodes that might otherwise be considered negative for metastasis by standard hematoxylin and eosin (H&E). It should be noted that isolated tumor cells identified on H&E stains alone are also classified as ITC and are annotated in the same fashion as ITC seen on immunohistochemical stains (i.e., pN0(i+); "i" = "isolated tumor cells").

KRAS. Analysis of multiple recent clinical trials has shown that the presence of a mutation in either codon 12 or 13 of KRAS (abnormal or "mutated" KRAS) is strongly associated with a lack of response to treatment with anti-EGFR antibodies in patients with metastatic colorectal carcinoma. It is recommended that patients with advanced colorectal carcinoma be tested for the presence of mutations in KRAS if treatment will include an anti-EGFR antibody. Where the status of KRAS is known, it should be recorded as a site-specific factor as either Normal ("Wild Type") or Abnormal ("Mutated").

Anatomic Boundary. The boundary between the rectum and anal canal most often has been equated with the dentate line, which is identified pathologically. However, with advances in sphincter-preservation surgery, defining the boundary between the rectum and the anus as the anorectal ring, which corresponds to the proximal border of the puborectalis muscle palpable on digital rectal examination, is more appropriate.

TNM Stage of Disease. Since publication of the sixth edition, new prognostic data with regard to survival and disease relapse justifies further substaging of both Stages II and III (Tables 14.1–14.7) by anatomic criteria. Differential prognosis has been shown for patients with T4 lesions based on the extent of disease in SEER analyses for both rectal cancer (Tables 14.4 and 14.5) and colon cancer (Tables 14.6 and 14.7). Accordingly, for the seventh edition of AJCC, T4 lesions have been subdivided as T4a (tumor penetrates to the surface of the visceral peritoneum) and T4b (tumor directly invades or is adherent to other organs or structures). In addition, the number of nodes involved by metastasis has been shown to influence prognosis within both N1 and N2 groups, in separate analyses of SEER (rectal cancer, Tables 14.4–14.5, Figure 14.2; colon cancer, Tables 14.4–14.7; Figure 14.1). For the SEER analyses, both relative and observed survival are listed by TN category of disease (relative survival is survival corrected by age-related comorbidity; see Chap. 2 for more information). Also the total number of nodes examined has an important impact on survival in colon and rectal cancer (Figures 14.1 and 14.2). The impact of increased nodes examined in the resected specimen is clearly associated with better outcome in colon cancer for all combinations of T and N (Figure 14.1) whereas the association holds in T1–T3 lesions in rectal cancer but appears to be less important in T4a and T4b lesions, perhaps because of the greater use of preoperative radiation or concurrent chemoradiation of the smaller number of patients in the rectal carcinoma subgroups (Figure 14.2).

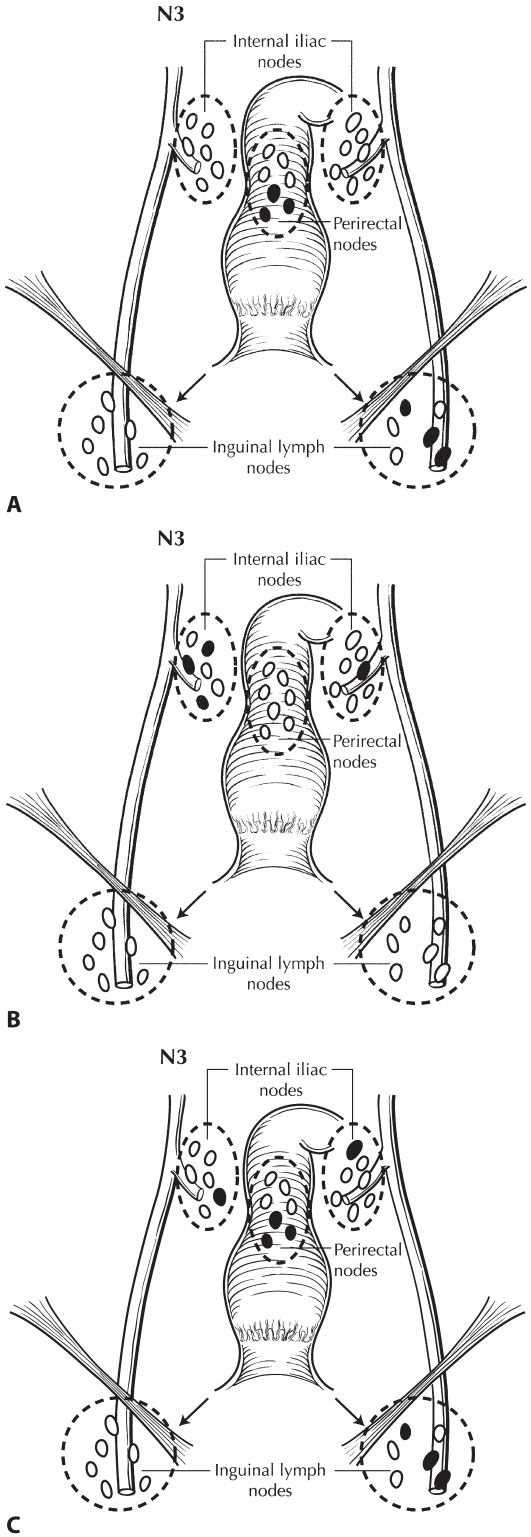


FIGURE 15.10. (**A**) N3 is defined as metastasis in perirectal and inguinal lymph nodes (as illustrated) and/or bilateral internal iliac and/or inguinal lymph nodes. (**B**) N3: metastases in bilateral internal iliac lymph nodes. (**C**) N3: metastases in bilateral internal iliac *and* inguinal lymph nodes.

ANATOMIC STAGE/PROGNOSTIC GROUPS

0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
	T3	N0	M0
IIIA	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
	T4	N0	M0
IIIB	T4	N1	M0
	Any T	N2	M0
	Any T	N3	M0
IV	Any T	Any N	M1

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)
(Recommended for Collection)

Required for staging	None
Clinically significant	HPV Status

HISTOLOGIC GRADE (G)

Grade is reported in registry systems by the grade value. A two-grade, three-grade, or four-grade system may be used. If a grading system is not specified, generally the following system is used:

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

HISTOPATHOLOGIC TYPE

The staging system applies to all carcinomas arising in the anal canal, including carcinomas that arise within anorectal fistulas. Melanomas, carcinoid tumors, and sarcomas are excluded from this staging system. Most carcinomas of the anal canal are squamous cell carcinomas. The WHO classification of the types and subtypes of carcinomas of the anal canal is shown later. The terms *transitional cell* and *cloacogenic carcinoma* have been abandoned, because these tumors are now recognized as nonkeratinizing types of squamous cell carcinoma.

16

Gastrointestinal Stromal Tumor

At-A-Glance

SUMMARY OF CHANGES

- This staging system is new for the seventh edition

ANATOMIC STAGE/PROGNOSTIC GROUPS

*Gastric GIST**

Group	T	N	M	Mitotic rate
Stage IA	T1 or T2	N0	M0	Low
Stage IB	T3	N0	M0	Low
Stage II	T1	N0	M0	High
	T2	N0	M0	High
	T4	N0	M0	Low
Stage IIIA	T3	N0	M0	High
Stage IIIB	T4	N0	M0	High
Stage IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate

*Small Intestinal GIST***

Group	T	N	M	Mitotic rate
Stage I	T1 or T2	N0	M0	Low
Stage II	T3	N0	M0	Low
Stage IIIA	T1	N0	M0	High
	T4	N0	M0	Low
Stage IIIB	T2	N0	M0	High
	T3	N0	M0	High
	T4	N0	M0	High
Stage IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate

**Note*: Also to be used for omentum.

***Note*: Also to be used for esophagus, colorectal, mesentery, and peritoneum.

ICD-O-3 TOPOGRAPHY CODES

C15.0–C15.9	Esophagus
C16.0–C16.9	Stomach
C17.0–C17.2, C17.8–C17.9	Small intestine
C18.0–C18.9	Colon
C19.9	Rectosigmoid junction
C20.9	Rectum
C48.0–C48.8	Retroperitoneum & Peritoneum

ICD-O-3 HISTOLOGY CODE RANGES

8935, 8936

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor in the gastrointestinal tract. The designation of GIST refers to a specific tumor type that is generally immunohistochemically KIT-positive and is driven by KIT or PDGFRA activating mutations.

In terms of biologic potential, GISTs encompass a continuum. They include minute or small, paucicellular, mitotically inactive, obviously benign-looking tumors previously often designated as leiomyomas. At the other end of the spectrum there are larger tumors many of which contain significant mitotic activity and are histologically sarcomatous, previously often called leiomyosarcomas. In the middle,

Liver metastasis implies the presence of tumor inside the liver parenchyma as one or more nodules. Adherence to liver capsule, even if extensive, as sometimes seen in gastric GISTs, should not be considered liver metastasis.

PROGNOSTIC FEATURES

In some cases, patients have survived for a long time after a solitary intra-abdominal GIST metastasis. Tumors with mitotic rates in the lower end of "high mitotic rate" (6–10 mitoses/50 HPFs) may behave better than those with significantly elevated mitotic rates (>10 mitoses/50 HPFs).

There may be differences in behavior between GISTs with different types of KIT and PDGFRA mutations. Because of limitations of the universal application of mutation studies (most importantly, their limited availability), mutations are not considered in this staging system. Further research is needed to examine these and other prognostic factors in detail.

Tables 16.1 and 16.2 show the disease progression of gastric and small intestinal GISTs.

DEFINITIONS OF TNM (FOR GISTS AT ALL SITES)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence for primary tumor
T1	Tumor 2 cm or less
T2	Tumor more than 2 cm but not more than 5 cm
T3	Tumor more than 5 cm but not more than 10 cm
T4	Tumor more than 10 cm in greatest dimension

Regional Lymph Nodes (N)

N0	No regional lymph node metastasis*
N1	Regional lymph node metastasis

*If regional node status is unknown, use N0, not NX

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

TABLE 16.1. Disease progression in gastric GISTs

Stage	*Tumor size (cm)*	*Mitotic rate*	*Prognostic group*[a]	*Observed rate of progressive disease*[a]
Stage IA	≤5	Low	1, 2	0–2%
Stage IB	>5–10	Low	3a	3–4%
Stage II	>5–10	High	4	Insufficient data
	>5–10	High	5	15%
	>10	Low	3b	12%
Stage IIIA	>5–10	High	6a	49%
IIIB	>10	High	6b	86%

[a]From Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic studies of 1765 cases with long-term follow-up. Am J Surg Pathol. 2005;29:52–68, with permission from Lippincott Williams & Wilkins.

TABLE 16.2. Disease progression in small intestinal GIST

Stage	*Tumor size (cm)*	*Mitotic rate*	*Prognostic group*[a]	*Observed rate of progressive disease*[a]
Stage IA	≤5	Low	1, 2	0–2%
Stage II	>5–10	Low	3a	23%
Stage III A	>10	Low	3b	49%
	≤2	High	4	50%
Stage IIIB	>2–5	High	5	73%
	>5	High	6a	72%
	>10	High	6b	89%

[a]From Miettinen M, Makhlouf HR, Sobin LH, Lasota J. Gastrointestinal stromal tumors (GISTs) of the jejunum and ileum – a clinicopathologic, immunohistochemical and molecular genetic study of 906 cases prior to imatinib with long-term follow-up. Am J Surg Pathol. 2006;30:477–89, with permission from Lippincott Williams & Wilkins.

HISTOPATHOLOGIC GRADE

Grading for GISTs is dependent on mitotic rate
Low mitotic rate: 5 or fewer per 50 HPF
High mitotic rate: over 5 per 50 HPF

ANATOMIC STAGE/PROGNOSTIC GROUPS

*Gastric GIST**

Group	**T**	**N**	**M**	**Mitotic rate**
Stage IA	T1 or T2	N0	M0	Low
Stage IB	T3	N0	M0	Low
Stage II	T1	N0	M0	High
	T2	N0	M0	High
	T4	N0	M0	Low
Stage IIIA	T3	N0	M0	High
Stage IIIB	T4	N0	M0	High
Stage IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate

*Small Intestinal GIST***

Group	**T**	**N**	**M**	**Mitotic rate**
Stage I	T1 or T2	N0	M0	Low
Stage II	T3	N0	M0	Low
Stage IIIA	T1	N0	M0	High
	T4	N0	M0	Low
Stage IIIB	T2	N0	M0	High
	T3	N0	M0	High
	T4	N0	M0	High
Stage IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate

**Note*: Also to be used for omentum.

***Note*: Also to be used for esophagus, colorectal, mesentery, and peritoneum.

Gastrointestinal Stromal Tumor Staging Form

Clinical *Extent of disease before any treatment*	Stage Category Definitions for GIST at All Sites	Pathologic *Extent of disease during and from surgery*
❒ y clinical– staging completed after neoadjuvant therapy but before subsequent surgery	**Tumor Size:** _____	❒ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	Primary Tumor (T)	
❑ TX	Primary tumor cannot be assessed	❑ TX
❑ T0	No evidence of primary tumor	❑ T0
❑ T1	Tumor 2 cm or less	❑ T1
❑ T2	Tumor more than 2 cm but not more than 5 cm	❑ T2
❑ T3	Tumor more than 5 cm but not more than 10 cm	❑ T3
❑ T4	Tumor more than 10 cm in greatest dimension	❑ T4
	Regional Lymph Nodes (N)	
❑ N0	No regional lymph node metastasis*	❑ N0
❑ N1	Regional lymph node metastasis	❑ N1
	* If regional node status is unknown, use N0, not NX	
	Distant Metastasis (M)	
❑ M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)	
❑ M1	Distant metastasis	❑ M1

Anatomic Stage • Prognostic Groups – Gastric GIST
(also to be used for omentum)

Clinical					Pathologic				
Group	**T**	**N**	**M**	**Mitotic Rate**	**Group**	**T**	**N**	**M**	**Mitotic Rate**
❑ IA	T1 or T2	N0	M0	Low	❑ IA	T1 or T2	N0	M0	Low
❑ IB	T3	N0	M0	Low	❑ IB	T3	N0	M0	Low
❑ II	T1	N0	M0	High	❑ II	T1	N0	M0	High
	T2	N0	M0	High		T2	N0	M0	High
	T4	N0	M0	Low		T4	N0	M0	Low
❑ IIIA	T3	N0	M0	High	❑ IIIA	T3	N0	M0	High
❑ IIIB	T4	N0	M0	High	❑ IIIB	T4	N0	M0	High
❑ IV	Any T	N1	M0	Any rate	❑ IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate		Any T	Any N	M1	Any rate
❑ Stage unknown					❑ Stage unknown				

Anatomic Stage • Prognostic Groups – Small Intestinal GIST
(also to be used for esophagus, colorectal, mesentery, and peritoneum)

Clinical					Pathologic				
Group	**T**	**N**	**M**	**Mitotic Rate**	**Group**	**T**	**N**	**M**	**Mitotic Rate**
❑ I	T1 or T2	N0	M0	Low	❑ I	T1 or T2	N0	M0	Low
❑ II	T3	N0	M0	Low	❑ II	T3	N0	M0	Low
❑ IIIA	T1	N0	M0	High	❑ IIIA	T1	N0	M0	High
	T4	N0	M0	Low		T4	N0	M0	Low
❑ IIIB	T2	N0	M0	High	❑ IIIB	T2	N0	M0	High
	T3	N0	M0	High		T3	N0	M0	High
	T4	N0	M0	High		T4	N0	M0	High
❑ IV	Any T	N1	M0	Any rate	❑ IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate		Any T	Any N	M1	Any rate
❑ Stage unknown					❑ Stage unknown				

Hospital Name/Address	Patient Name/Information

(continued on next page)

GASTROINTESTINAL STROMAL TUMOR STAGING FORM

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS) – FOR GIST AT ALL SITES

REQUIRED FOR STAGING: Mitotic rate _____

CLINICALLY SIGNIFICANT:

KIT Immunohistochemistry: _____

Mutational status of KIT, PDGFRA: _____

Histologic Grade (G) *(also known as overall grade)*

Histological grading, an ingredient in sarcoma staging, is not well suited to GISTs, because a majority of these tumors have low or relatively low mitotic rates below the thresholds used for grading of soft tissue tumors, and because GISTs often manifest aggressive features with mitotic rates below the thresholds used for soft tissue tumor grading (the lowest tier of mitotic rates for soft tissue sarcomas being 10 mitoses per 10 HPFs). In GIST staging, the grade is replaced by mitotic activity.

- ❑ GX Grade cannot be assessed
- ❑ G1 Low grade; mitotic rate <5/50 HPF
- ❑ G2 High grade, mitotic rate >5/50 HPF

ADDITIONAL DESCRIPTORS

Lymphatic Vessel Invasion (L) and Venous Invasion (V) have been combined into Lymph-Vascular Invasion (LVI) for collection by cancer registrars. The College of American Pathologists' (CAP) Checklist should be used as the primary source. Other sources may be used in the absence of a Checklist. Priority is given to positive results.

- ❑ Lymph-Vascular Invasion Not Present (absent)/Not Identified
- ❑ Lymph-Vascular Invasion Present/Identified
- ❑ Not Applicable
- ❑ Unknown/Indeterminate

Residual Tumor (R)

The absence or presence of residual tumor after treatment. In some cases treated with surgery and/or with neoadjuvant therapy there will be residual tumor at the primary site after treatment because of incomplete resection or local and regional disease that extends beyond the limit of ability of resection.

- ❑ RX Presence of residual tumor cannot be assessed
- ❑ R0 No residual tumor
- ❑ R1 Microscopic residual tumor
- ❑ R2 Macroscopic residual tumor

General Notes:

For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

a prefix designates the stage determined at autopsy: aTNM.

surgical margins is data field recorded by registrars describing the surgical margins of the resected primary site specimen as determined only by the pathology report.

neoadjuvant treatment is radiation therapy or systemic therapy (consisting of chemotherapy, hormone therapy, or immunotherapy) administered prior to a definitive surgical procedure. If the surgical procedure is not performed, the administered therapy no longer meets the definition of neoadjuvant therapy.

❑ Clinical stage was used in treatment planning (describe): _____

❑ National guidelines were used in treatment planning ❑ NCCN ❑ Other (describe): _____

_____

_____

Physician signature Date/Time

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

(continued from previous page)

17

Neuroendocrine Tumors

(Gastric, small bowel, colonic, rectal, and ampulla of vater carcinoid tumors [well-differentiated neuroendocrine tumors and well-differentiated neuroendocrine carcinomas]; carcinoid tumors of the appendix [see Chap. 13] and neuroendocrine tumors of the pancreas [see Chap. 24] are not included.)

At-A-Glance

SUMMARY OF CHANGES

- This staging system is new for the 7th edition

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis*	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	Any T	N1	M0
Stage IV	Any T	Any N	M1

**Note*: Tis applies only to stomach.

ICD-O-3 TOPOGRAPHY CODES

C16.0–C16.9	Stomach
C17.0–C17.9	Small intestine
C18.0, C18.2–C18.9	Colon (excludes C18.1)
C19.9	Rectosigmoid junction
C20.9	Rectum
C24.1	Ampulla of Vater

ICD-O-3 HISTOLOGY CODE RANGES

8153, 8240–8242, 8246, 8249

INTRODUCTION

Neuroendocrine tumors (NETs) arise from the diffuse neuroendocrine system, which comprises neuroendocrine cells spread as a single cell or clusters of cells throughout the entire gastrointestinal tract, the bronchopulmonary system, and the urogenital tract. These lesions are often referred to generically using the archaic term *carcinoid* in deference to the original report of 1907 by Oberndorfer. In the past the "traditional" classification of carcinoids (1963 Sandler/Williams) was based upon their presumed embryonic origin and comprised foregut (lung, thymus, stomach, pancreas, and duodenum), midgut (from duodenum beyond the Treitz ligament to the proximal transverse colon), and hindgut carcinoids (distal colon and rectum). Although this classification is used, a tumor-based classification introduced by the World Health Organization (WHO) in 2000 has far greater scientific and clinical applicability. This classification utilizes the more generic term NET, and classification of the lesions is variously based upon size, proliferative rate, localization, differentiation, and hormone production. However, the term *carcinoid* is still in widespread use in the clinical setting and in data collected by tumor registries.

Investigation of the Surveillance Epidemiology and End Results (SEER) data base, 1973–2004, demonstrates that the incidence of gastric NETs in the US population in 2004 was 0.34/100,000, and since 1973 the annual increase in incidence has been approximately 9%. For small intestinal NETs, the annual increase in incidence since 1973 is 3.51%, and the incidence in the US population for duodenal NETs is 2.06/100,000, jejunal 0.36/100,000, and ileal 4.06/100,000 in 2004. Furthermore, NETs comprised 1.25% of all malignancies in 2004 compared to only 0.75% of all malignancies in 1994. The reason for

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1

ICD-O-3 TOPOGRAPHY CODES
C22.0 Liver

ICD-O-3 HISTOLOGY CODE RANGES
8170–8175

INTRODUCTION

Primary malignancies of the liver include tumors arising from the hepatocytes (hepatocellular carcinoma), intrahepatic bile ducts (intrahepatic cholangiocarcinoma and cystadenocarcinoma), and mesenchymal elements (primary sarcoma). Only primary hepatocellular carcinoma is included in the current staging system described here. Hepatocellular carcinoma is the most common primary cancer of the liver and is a leading cause of death from cancer worldwide. Although it is uncommon in the United States, its incidence is rising. The majority of hepatocellular carcinomas arise in a background of chronic liver disease due to viral hepatitis (B or C), ethanol-related cirrhosis, and, possibly, related steatohepatitis. Cirrhosis may dominate the clinical picture and determine the prognosis. Other important indicators of outcome in hepatocellular carcinoma are resectability for cure and the extent of vascular invasion. Previously, intrahepatic bile duct cancer was staged using the system derived for hepatocellular carcinoma, but due to the markedly different incidence, epidemiology, treatment and prognosis for these diseases, staging for bile duct cancer has been removed from this chapter. A separate staging system is included for intrahepatic bile duct (see Chap. 19).

ANATOMY

Primary Site. The liver has a dual blood supply: the hepatic artery, which typically branches from the celiac artery, and the portal vein, which drains the intestine. Blood from the liver passes through the hepatic veins and enters the inferior vena cava. The liver is divided into right and left liver by a plane (Cantlie's line) projecting between the gallbladder fossa and the vena cava and defined by the middle hepatic vein. Couinaud refined knowledge about the functional anatomy of the liver and proposed division of the liver into four sectors (formerly called segments) and eight segments. In this nomenclature, the liver is divided by vertical and oblique planes or scissurae defined by the three main hepatic veins and a transverse plane or scissura that follows a line drawn through the right and left portal branches. Thus, the four traditional segments (right anterior, right posterior, left medial, and left lateral) are replaced by sectors (right anterior, right posterior, left anterior, and left posterior), and these sectors are divided into segments by the transverse scissura (Figure 18.1). The eight segments are numbered clockwise in a frontal plane. Recent advances in hepatic surgery have made possible anatomic (also called typical) resections along these planes.

Histologically, the liver is divided into lobules with central veins draining each lobule. The portal triads between the lobules contain the intrahepatic bile ducts and the blood supply, which consists of small branches of the hepatic artery and portal vein and intrahepatic lymphatic channels.

Regional Lymph Nodes. The regional lymph nodes are the hilar, hepatoduodenal ligament lymph nodes, inferior phrenic, and caval lymph nodes, among which the most prominent are the hepatic artery and portal vein lymph nodes. Nodal involvement should be coded as N1. Nodal involvement is now considered stage IV disease.

Distant Metastatic Sites. The main mode of dissemination of liver carcinomas is via the portal veins (intrahepatic) and hepatic veins. Intrahepatic venous dissemination cannot be differentiated from satellitosis or multifocal tumors and

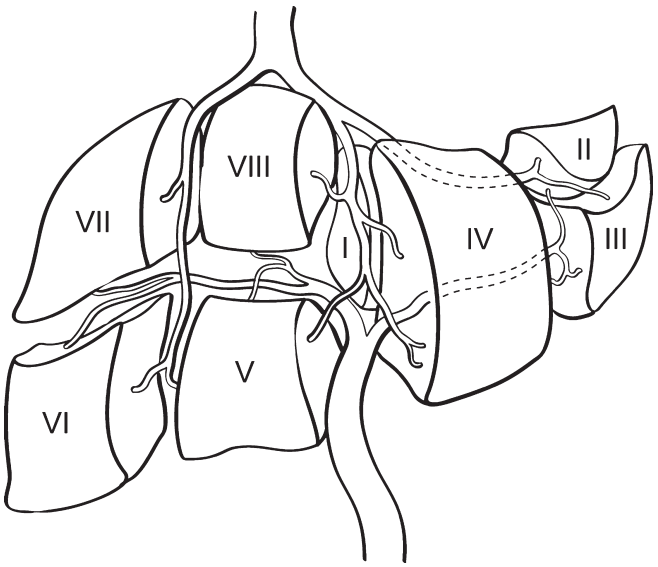


FIGURE 18.1. The eight segments of the liver are numbered clockwise in a frontal plane.

19

Intrahepatic Bile Ducts

At-A-Glance

SUMMARY OF CHANGES

- This is a novel staging system that is independent of the staging system for hepatocellular carcinoma and independent of the staging system for extrahepatic bile duct malignancy, including hilar bile duct cancers. The rare combined hepatocellular and cholangiocarcinoma (mixed hepatocholangio carcinomas) are included with the intrahepatic bile duct cancer staging classification
- The tumor category (T) is based on three major prognostic factors including tumor number, vascular invasion, and direct extrahepatic tumoral extension
- The nodal category (N) is a binary classification based on the presence or absence of regional lymph node metastasis
- The metastasis category (M) is a binary classification based on the presence or absence of distant disease
- Recommend collection of preoperative or pretreatment serum CA19–9

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IVA	T4	N0	M0
	Any T	N1	M0
Stage IVB	Any T	Any N	M1

ICD-O-3 TOPOGRAPHY CODES

C22.1 Intrahepatic bile duct

ICD-O-3 HISTOLOGY CODE RANGES

8160, 8161, 8180

INTRODUCTION

Primary hepatobiliary malignancy includes tumors of the hepatocytes (hepatocellular carcinoma), bile ducts (cholangiocarcinoma), gallbladder, and the parenchyma of the liver (sarcoma). This TNM classification applies only to cancers arising in intrahepatic bile ducts (intrahepatic cholangiocarcinoma). Hepatocellular carcinoma, tumors of the perihilar bile duct, and gallbladder carcinomas are classified separately.

Tumors of intrahepatic bile duct origin represent 15–20% of all primary liver malignancies. The tumors of the bile ducts can be anatomically subdivided into three categories including intrahepatic, perihilar, and distal cholangiocarcinoma. The proportion of cholangiocarcinoma that is accounted for by intrahepatic tumors is approximately 20%.

Clinically, these intrahepatic tumors can be difficult to differentiate from metastatic adenocarcinomas from other primary sites. The etiologic factors that predispose to the development of intrahepatic cholangiocarcinoma include primary sclerosing cholangitis, hepatobiliary parasitosis, intrahepatic lithiasis, and chronic viral hepatitis. The overall incidence rate of intrahepatic cholangiocarcinoma is 0.7 cases per 100,000 adults in the USA. The incidence of intrahepatic cholangiocarcinoma is age-dependent, with a progressive increase in cases starting in the sixth decade of life and peaking in the ninth decade. Although less common than either hepatocellular carcinoma or hilar bile duct

ANATOMY

Primary Site. The gallbladder is a pear-shaped saccular organ located under the liver situated in line with the physiologic division of the right and left lobes of the liver (Cantlie's line). It straddles Couinaud segments IVb and V. The organ can be divided into three parts: a fundus, a body, and a neck, which tapers into the cystic duct (Figure 20.1). The wall is considerably thinner than that of other hollow organs and lacks a submucosal layer. Its make up consists of a mucosa, a muscular layer, perimuscular connective tissue, and a serosa on one side (serosa is lacking on the side embedded in the liver). An important anatomic consideration is that the serosa along the liver edge is more densely adherent to the liver (cystic plate) and much of this is often left behind at the time of cholecystectomy. For this reason, partial hepatic resection incorporating portions of segments IVb and V is undertaken for some cases. Primary carcinomas of the cystic duct are included in this staging classification schema.

Regional Lymph Nodes. For accurate staging, all nodes removed at operation should be assessed for metastasis. Regional lymph nodes are limited to the hepatic hilus (including nodes along the common bile duct, hepatic artery, portal vein, and cystic duct). Celiac and superior mesenteric artery node involvement is now considered distant metastatic disease.

Metastatic Sites. Cancers of the gallbladder usually metastasize to the peritoneum and liver and occasionally to the lungs and pleura.

RULES FOR CLASSIFICATION

Gallbladder cancers are staged primarily on the basis of surgical exploration or resection, but not all patients with gallbladder cancer undergo surgical resection. Many in situ and early-stage carcinomas are not recognized grossly. They are usually staged pathologically on histologic examination of the resected specimen. The T classification depends on the depth of tumor penetration into the wall of the gallbladder, on the presence or absence of tumor invasion into the liver, hepatic artery, or portal vein, and on the presence or absence of adjacent organ involvement. Direct tumor extension into the liver is not considered distant metastasis (M). Likewise, direct invasion of other adjacent organs, including colon, duodenum, stomach, common bile duct, abdominal wall, and diaphragm, is not considered distant metastasis but is classified in the T category (T3 or T4). Tumor confined to the gallbladder is classified as either T1 or T2, depending on the depth of invasion. It must be noted that because there is no serosa on the gallbladder on the side attached to the liver, a simple cholecystectomy may not completely remove a T2 tumor, even though such tumors are considered to be confined to the gallbladder.

Validation. Validation of stage grouping is based on multivariate analyses of outcome and survival data of the National Cancer Database (totaling 10,705 patients nationwide, Figure 20.2).

Clinical Staging. Clinical evaluation usually depends on the results of ultrasonography, computed tomography, and magnetic resonance cholangiopancreatography. Clinical staging may also be based on findings from surgical exploration (laparoscopic or open) when the main tumor mass is not resected.

Pathologic Staging. Pathologic staging is based on examination of the surgical resection specimen.

The extent of resection (R0, complete resection with grossly and microscopically negative margins of resection; R1, grossly negative but microscopically positive margins of resection; R2, grossly and microscopically positive margins of resection) is a descriptor in the TNM staging system and is

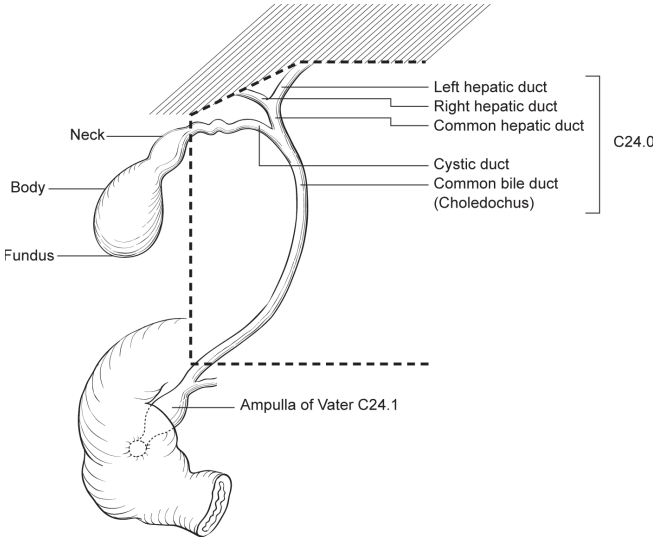


FIGURE 20.1. Schematic of the gallbladder in relation to the liver and biliary tract.

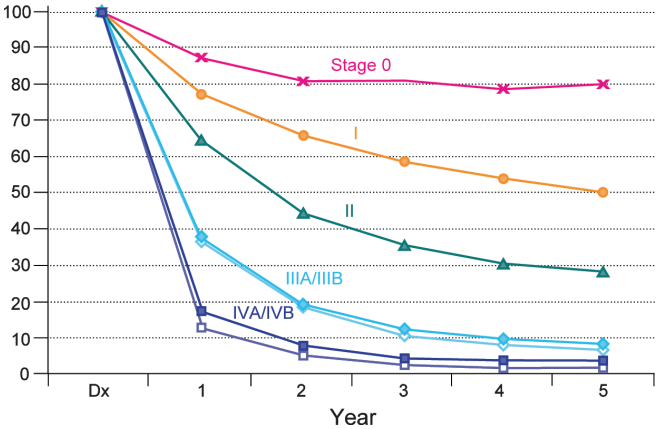


FIGURE 20.2. Observed survival rates for 10,705 gallbladder cancers. Data from the National Cancer Data Base (Commission on Cancer of the American College of Surgeons and the American Cancer Society) diagnosed in years 1989–1996.

23

Ampulla of Vater

At-A-Glance

SUMMARY OF CHANGES

- The definitions of TNM and the Stage Grouping for this chapter have not changed from the Sixth Edition

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

ICD-O-3 TOPOGRAPHY CODES

C24.1 Ampulla of Vater

ICD-O-3 HISTOLOGY CODE RANGES

8000–8152, 8154–8231, 8243–8245, 8250–8576, 8940–8950, 8980–8981

INTRODUCTION

The ampulla of Vater is strategically located at the confluence of the pancreatic and common bile ducts (Figure 23.1). Most tumors that arise in this small structure obstruct the common bile duct, causing jaundice, abdominal pain, occasionally pancreatitis, and bleeding. Clinically and pathologically, carcinomas of the ampulla may be difficult to differentiate from those arising in the head of the pancreas or in the distal segment of the common bile duct. Primary cancers of the ampulla are not common, accounting for roughly 15–25% of neoplasms arising in the periampullary region, although they constitute a high proportion of malignant tumors occurring in the duodenum. Tumors of the ampulla must be differentiated from those arising in the second part of the duodenum and invading the ampulla. Carcinomas of the ampulla and periampullary region are often associated with familial adenomatous polyposis coli.

ANATOMY

Primary Site. The ampulla is a small dilated duct less than 1.5-cm long, formed in most individuals by the union of the terminal segments of the pancreatic and common bile ducts. In 42% of individuals, however, the ampulla is the termination of the common duct only, the pancreatic duct having its own entrance into the duodenum adjacent to the ampulla. In these individuals, the ampulla may be difficult to locate or even nonexistent. The ampulla opens into the duodenum, usually on the posterior-medial wall, through a small mucosal elevation, the duodenal papilla, which is also called the papilla of Vater. Although carcinomas can arise either in the ampulla or on the papilla, they most commonly arise near the junction of the mucosa of the ampulla with that of the papilla. It may not be possible to determine the exact site of origin for large tumors. Nearly all cancers that arise in this area are well-differentiated adenocarcinomas.

Regional Lymph Nodes. A rich lymphatic network surrounds the pancreas and periampullary region, and accurate tumor staging requires that all lymph nodes that are removed be analyzed. The regional lymph nodes are the peripancreatic lymph nodes, which also include the lymph nodes along the hepatic artery and portal vein. Anatomic division of regional lymph nodes is not necessary. However, separately submitted lymph nodes should be reported as submitted. Optimal histologic examination of a pancreaticoduodenectomy specimen should include analysis of a minimum of 12 lymph nodes.

being classified as benign or malignant should be staged by this system and reported to cancer registries.

DEFINITIONS OF TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ*
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

*This also includes the "PanInIII" classification.

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)
(Recommended for Collection)

Required for staging	None
Clinically significant	Preoperative CA 19-9 Preoperative carcinoembryonic antigen (CEA) Preoperative plasma chromogranin A level (CgA) (endocrine pancreas) Mitotic count (endocrine pancreas)

HISTOLOGIC GRADE (G)

Grade is reported in registry systems by the grade value. A two-grade, three-grade, or four-grade system may be used. If a grading system is not specified, generally the following system is used:

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

HISTOPATHOLOGIC TYPE

The staging system applies to all tumors that arise in the pancreas. Neuroendocrine tumors have a distinctly different tumor biology and better long-term survival; however, the TNM system provides reasonable stage discrimination. The following tumors are included:

- Severe ductal dysplasia/carcinoma in situ (PanIn III; pancreatic intraepithelial neoplasia)
- Ductal adenocarcinoma
- Mucinous noncystic carcinoma
- Signet ring cell carcinoma
- Adenosquamous carcinoma
- Undifferentiated carcinoma
  - Spindle and giant cell types
  - Small cell types
- Mixed ductal-endocrine carcinoma
- Osteoclast-like giant cell tumor
- Serous cystadenocarcinoma
- Mucinous cystadenocarcinoma
- Intraductal papillary mucinous carcinoma with or without invasion (IPMN)
- Acinar cell carcinoma
- Acinar cell cystadenocarcinoma
- Mixed acinar-endocrine carcinoma
- Pancreaticoblastoma
- Solid pseudopapillary carcinoma
- Borderline (uncertain malignant potential) tumors
  - Mucinous cystic tumor with moderate dysplasia
  - Intraductal papillary-mucinous tumor with moderate dysplasia
  - Solid pseudopapillary tumor
- Composite carcinoid (combined with adenocarcinoma)
- Adenocarcinoid tumor
- Mixed islet cell and exocrine adenocarcinoma
- Islet cell carcinoma
- Insulinoma
- Glucagonoma
- Gastrinoma
- Vipoma
- Somatostatinoma
- Enteroglucagonoma

DEFINITIONS OF TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*
T1a	Tumor 2 cm or less in greatest dimension
T1b	Tumor more than 2 cm but 3 cm or less in greatest dimension
T2	Tumor more than 3 cm but 7 cm or less or tumor with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less); Involves main bronchus, 2 cm or more distal to the carina; Invades visceral pleura (PL1 or PL2); Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor more than 3 cm but 5 cm or less in greatest dimension
T2b	Tumor more than 5 cm but 7 cm or less in greatest dimension
T3	Tumor more than 7 cm or one that directly invades any of the following: parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (less than 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe

*The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe tumor with pleural nodules or malignant pleural (or pericardial) effusion*
M1b	Distant metastasis (in extrathoracic organs)

From Goldstraw P, Crowley J, Chansky K, et al.: The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *J Thorac Oncol* 2:706–714, 2007, with permission.

*Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.

ANATOMIC STAGE/PROGNOSTIC GROUPS

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b

LUNG STAGING FORM

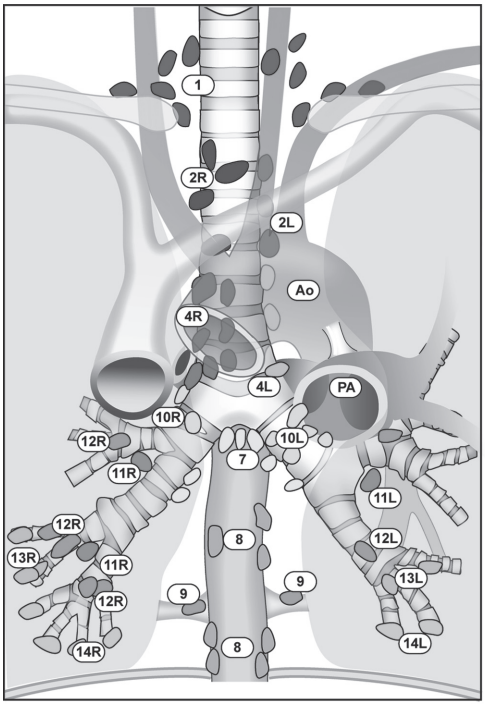
CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS		PATHOLOGIC *Extent of disease through completion of definitive surgery*
❒ y clinical – staging completed after neoadjuvant therapy but before subsequent surgery	**TUMOR SIZE:** _____	**LATERALITY:** ☐ left ☐ right ☐ bilateral	❒ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	PRIMARY TUMOR (T)		
❑ TX	Primary tumor cannot be assessed		❑ TX
❑ T0	No evidence of primary tumor		❑ T0
❑ Tis	Tis Carcinoma *in situ*		❑ Tis
❑ T1	Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*		❑ T1
❑ T1a	Tumor ≤2 cm in greatest dimension		❑ T1a
❑ T1b	Tumor > 2 cm but ≤3 cm in greatest dimension		❑ T1b
❑ T2	Tumor > 3 cm but ≤7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤ 5 cm) Involves main bronchus, ≥2 cm distal to the carina Invades visceral pleura (PL1 or PL2) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung		❑ T2
❑ T2a	Tumor > 3 cm but ≤5 cm in greatest dimension		❑ T2a
❑ T2b	Tumor > 5 cm but ≤7 cm in greatest dimension		❑ T2b
❑ T3	Tumor > 7 cm or one that directly invades any of the following: parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (< 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe		❑ T3
❑ T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe		❑ T4
	* The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.		
	REGIONAL LYMPH NODES (N)		
❑ NX	Regional lymph nodes cannot be assessed		❑ NX
❑ N0	No regional lymph node metastasis		❑ N0
❑ N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension		❑ N1
❑ N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)		❑ N2
❑ N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)		❑ N3
	DISTANT METASTASIS (M)		
❑ M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)		
❑ M1	Distant metastasis		❑ M1
❑ M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion**		❑ M1a
❑ M1b	Distant metastasis (in extrathoracic organs)		❑ M1b
	**Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where		

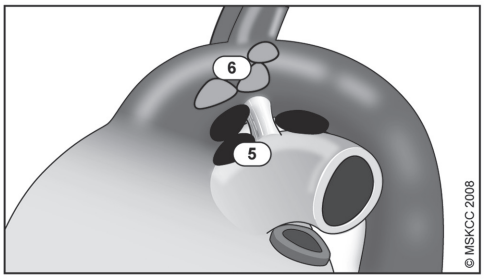
HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

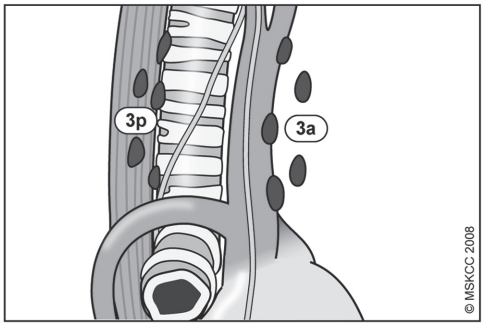
(continued on next page)

Illustration

The IASLC lymph node map shown with the proposed amalgamation of lymph node levels into zones.
(© Memorial Sloan-Kettering Cancer Center, 2009.)







Supraclavicular zone

- **1** Low cervical, supraclavicular, and sternal notch nodes

Superior Mediastinal Nodes

Upper zone

- **2R** Upper Paratracheal (right)
- **2L** Upper Paratracheal (left)
- **3a** Pre-vascular
- **3p** Retrotracheal
- **4R** Lower Paratracheal (right)
- **4L** Lower Paratracheal (left)

Aortic Nodes

AP zone

- **5** Subaortic
- **6** Para-aortic (ascending aorta or phrenic)

Inferior Mediastinal Nodes

Subcarinal zone

- **7** Subcarinal

Lower zone

- **8** Paraesophageal (below carina)
- **9** Pulmonary ligament

N_1 Nodes

Hilar/Interlobar zone

- **10** Hilar
- **11** Interlobar

Peripheral zone

- **12** Lobar
- **13** Segmental
- **14** Subsegmental

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

(continued from previous page)

INTRODUCTION

This classification is used for all primary malignant tumors of bone except primary malignant lymphoma and multiple myeloma. These tumors are relatively rare, representing less than 0.2% of all malignancies. Osteosarcoma (35%), chondrosarcoma (30%), and Ewing's sarcoma (16%) are the three most common forms of primary bone cancer. Osteosarcoma and Ewing's sarcoma develop mainly in children and young adults, whereas chondrosarcoma is usually found in middle aged and older adults. Data from these three histologies analyzed at multiple institutions, predominantly influence this staging system. Staging of bone sarcomas is the process whereby patients are evaluated with regard to histology, as well as the local and distant extent of disease. Bone sarcomas are staged based on grade, size, and the presence and location of metastases. The system is designed to help stratify patients according to known risk factors.

ANATOMY

Primary Site. All bones of the skeleton are included in this system. The current staging system does not take into account anatomic site. However, anatomic site is known to influence outcome, and therefore outcome data should be reported specifying site.

Site groups for bone sarcoma:

- Extremity
- Pelvis
- Spine

Regional Lymph Nodes. Regional lymph metastases from bone tumors are extremely rare.

Metastatic Sites. A metastatic site includes any site beyond the regional lymph nodes of the primary site. Pulmonary metastases are the most frequent site for all bone sarcomas. Extra pulmonary metastases occur infrequently, and may include secondary bone metastases, for example.

RULES FOR CLASSIFICATION

Clinical Staging. Clinical staging includes all relevant data prior to primary definitive therapy, including physical examination, imaging, and biopsy. It is dependent on the T, N, M characteristics of the identified tumor. T is divided into lesions of maximum dimension 8 cm or less (T1), and lesions greater than 8 cm (T2). T3 has been redefined to include only high-grade tumors, discontinuous, within the same bone. Metastatic disease should be evaluated for and described. In general, the minimum clinical staging workup of a bone sarcoma should include axial imaging using MRI and/or CT, CT scan of the chest, and technetium scintigraphy of the entire skeleton.

The radiograph remains the mainstay in determining whether a lesion of bone requires staging and usually is the modality that permits reliable prediction of the probable histology of a lesion of bone.

Local staging of all bone sarcomas is most accurately achieved by magnetic resonance (MR) imaging. Axial imaging, complemented by either coronal or sagittal imaging planes using T1- and T2-weighted SPIN-echo sequences, most often provides accurate depiction of intra- and extraosseous tumor. To improve conspicuity in locations such as the pelvis or vertebrae, these sequences could be augmented by fat-suppressed pulse sequences. The maximum dimension of the tumor must be measured prior to any treatment. The decision to use intravenous contrast should be based upon medical appropriateness.

Computerized tomography (CT) has a limited role in local staging of tumors. In those situations, where characterization of a lesion by radiography may be incomplete or difficult because of inadequate visualization of the matrix of a lesion, CT may be preferred to MR imaging. The role of CT in these circumstances is to characterize the lesion and determine whether it is potentially malignant or not, and the obtained CT images may suffice for local staging. CT remains the examination of choice for evaluating the presence or absence of pulmonary metastases.

Technetium scintigraphy is the examination of choice for evaluating the entire skeleton to determine whether there are multiple bony lesions. The role of positron emission tomography (PET) in the evaluation and staging of bone sarcomas remains incompletely defined. Reports indicate usefulness in detecting extrapulmonary metastases, evaluating response to chemotherapy, and determining local recurrence adjacent to prosthetic implants.

Biopsy. Biopsy of the tumor completes the staging process, and the location of the biopsy must be carefully planned to allow for eventual en bloc resection of the entire biopsy tract together with a malignant neoplasm. Staging of the lesion should precede biopsy. Imaging the tumor after biopsy may compromise the accuracy of the staging process.

Pathologic Staging. The pathologic diagnosis is based on the microscopic examination of tissue, correlated with imaging studies. Pathologic staging pTNM includes pathologic data obtained from examination of a resected specimen sufficient to evaluate the highest T category, histopathologic type and grade, regional lymph nodes as appropriate, or distant metastasis. Because regional lymph node involvement from bone tumors is rare, the pathologic stage grouping includes any of the following combinations: pT pG pN pM, or pT pG cN cM, or cT cN pM. Grade should be assigned to all bone sarcomas. Based upon published outcomes data, the current staging system accommodates a two-tiered system (low vs. high grade) for recording grade.

Restaging of Recurrent Tumors. The same staging should be used when a patient requires restaging of sarcoma recurrence. Such reports should specify whether patients have

to be associated with significantly better overall and event-free survival than patients lacking HLA class I expression in osteosarcoma. Finally, telomerase expression in osteosarcoma is associated with decreased progression free survival and overall survival.

Investigation to identify molecular markers in chondrosarcoma has progressed at a slower pace. Rozeman et al. investigated a variety of markers, none of which had prognostic importance independent of histologic grade. Decreased Indian Hedgehog signaling and loss of INK4A/p16 has been found to be important in the progression of peripheral chondrosarcoma and enchondroma, respectively.

DEFINITIONS OF TNM

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 8 cm or less in greatest dimension
T2	Tumor more than 8 cm in greatest dimension
T3	Discontinuous tumors in the primary bone site

Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Note: Because of the rarity of lymph node involvement in bone sarcomas, the designation NX may not be appropriate and cases should be considered N0 unless clinical node involvement is clearly evident.

Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Lung
M1b	Other distant sites

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage IA	T1	N0	M0	G1,2 Low grade, GX
Stage IB	T2	N0	M0	G1,2 Low grade, GX
	T3	N0	M0	G1,2 Low grade, GX
Stage IIA	T1	N0	M0	G3, 4 High grade
Stage IIB	T2	N0	M0	G3, 4 High grade
Stage III	T3	N0	M0	G3, 4 High grade
Stage IVA	Any T	N0	M1a	Any G
Stage IVB	Any T	N1	Any M	Any G
	Any T	Any N	M1b	Any G

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)
(Recommended for Collection)

Required for staging	Grade
Clinically significant	Three dimensions of tumor size
	Percentage necrosis post neoadjuvant systemic therapy from pathology report
	Number of resected pulmonary metastases from pathology report

HISTOLOGIC GRADE (G)

Grade is reported in registry systems by the grade value. A two-grade, three-grade, or four-grade system may be used. If a grading system is not specified, generally the following system is used:

GX	Grade cannot be assessed
G1	Well differentiated – low grade
G2	Moderately differentiated – low grade
G3	Poorly differentiated
G4	Undifferentiated

Note: Ewing's sarcoma is classified as G4.

HISTOPATHOLOGIC TYPE

Classification of Primary Malignant Bone Tumors

1. Osteosarcoma
   a. Intramedullary high grade
      - Osteoblastic
      - Chondroblastic
      - Fibroblastic
      - Mixed
      - Small cell
      - Other (telangiectatic, epithelioid, chondromyxoid fibroma-like, chondroblastoma-like, osteoblastoma-like, giant cell rich)

   b. Intramedullary low grade
   c. Juxtacortical high grade (high grade surface osteosarcoma)
   d. Juxtacortical intermediate grade chondroblastic (periosteal osteosarcoma)
   e. Juxtacortical low grade (parosteal osteosarcoma)
2. Chondrosarcoma
   a. Intramedullary
      - Conventional (hyaline/myxoid)
      - Clear cell
      - Dedifferentiated
      - Mesenchymal

   b. Juxtacortical
3. Primitive neuroectodermal tumor/Ewing's sarcoma
4. Angiosarcoma
   a. Conventional
   b. Epithelioid hemangioendothelioma

BONE STAGING FORM

CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS		PATHOLOGIC *Extent of disease during and from surgery*
❒ y clinical – staging completed after neoadjuvant therapy but before subsequent surgery	**TUMOR SIZE:** _____	**LATERALITY:** ☐ left ☐ right ☐ bilateral	❒ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	PRIMARY TUMOR (T)		
❑ TX	Primary tumor cannot be assessed		❑ TX
❑ T0	No evidence of primary tumor		❑ T0
❑ T1	Tumor 8 cm or less in greatest dimension		❑ T1
❑ T2	Tumor more than 8 cm in greatest dimension		❑ T2
❑ T3	Discontinuous tumors in the primary bone site		❑ T3
	REGIONAL LYMPH NODES (N)		
❑ NX	Regional lymph nodes cannot be assessed		❑ NX
❑ N0	No regional lymph node metastasis		❑ N0
❑ N1	Regional lymph node metastasis		❑ N1
	DISTANT METASTASIS (M)		
❑ M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)		
❑ M1	Distant metastasis		❑ M1
❑ M1a	Lung		❑ M1a
❑ M1b	Other distant sites		❑ M1b

ANATOMIC STAGE • PROGNOSTIC GROUPS

CLINICAL

GROUP	T	N	M			
❑ IA	T1	N0	M0	G1,2	Low grade	GX
❑ IB	T2	N0	M0	G1,2	Low grade	GX
❑ IB	T3	N0	M0	G1,2	Low grade	GX
❑ IIA	T1	N0	M0	G3,4	High grade	
❑ IIB	T2	N0	M0	G3,4	High grade	
❑ III	T3	N0	M0	G3,4*	High grade	
❑ IVA	Any T	N0	M1a	Any G		
❑ IVB	Any T	N1	Any M	Any G		
	Any T	Any N	M1b	Any G		

* Ewing's sarcoma is classified as G4.
❑ Stage unknown

PATHOLOGIC

GROUP	T	N	M			
❑ IA	T1	N0	M0	G1,2	Low grade	GX
❑ IB	T2	N0	M0	G1,2	Low grade	GX
❑ IB	T3	N0	M0	G1,2	Low grade	GX
❑ IIA	T1	N0	M0	G3,4	High grade	
❑ IIB	T2	N0	M0	G3,4	High grade	
❑ III	T3	N0	M0	G3,4*	High grade	
❑ IVA	Any T	N0	M1a	Any G		
❑ IVB	Any T	N1	Any M	Any G		
	Any T	Any N	M1b	Any G		

* Ewing's sarcoma is classified as G4.
❑ Stage unknown

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)

REQUIRED FOR STAGING: Grade _____

CLINICALLY SIGNIFICANT:

Three dimensions of tumor size _____ x _____ x _____

Percentage necrosis post neoadjuvant systemic therapy from pathology report: _____

Number of resected pulmonary metastases from pathology report: _____

General Notes:
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

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Soft Tissue Sarcoma

(Kaposi's sarcoma, fibromatosis [desmoid tumor], and sarcoma arising from the dura mater, brain, parenchymatous organs, or hollow viscera are not included.)

At-A-Glance

SUMMARY OF CHANGES

- Gastrointestinal stromal tumor (GIST) is now included in Chap. 16; fibromatosis (desmoid tumor), Kaposi's sarcoma, and infantile fibrosarcoma are no longer included in the histological types for this site
- Angiosarcoma, extraskeletal Ewing's sarcoma, and dermatofibrosarcoma protuberans have been added to the list of histologic types for this site
- N1 disease has been reclassified as Stage III rather than Stage IV disease
- Grading has been reformatted from a four grade to a three-grade system as per the criteria recommended by the College of American Pathologists

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage IA	T1a	N0	M0	G1, GX
	T1b	N0	M0	G1, GX
Stage IB	T2a	N0	M0	G1, GX
	T2b	N0	M0	G1, GX
Stage IIA	T1a	N0	M0	G2, G3
	T1b	N0	M0	G2, G3
Stage IIB	T2a	N0	M0	G2
	T2b	N0	M0	G2
Stage III	T2a, T2b	N0	M0	G3
	Any T	N1	M0	Any G
Stage IV	Any T	Any N	M1	Any G

ICD-O-3 TOPOGRAPHY CODES

C38.0	Heart
C38.1	Anterior mediastinum
C38.2	Posterior mediastinum
C38.3	Mediastinum, NOS
C38.8	Overlapping lesion of heart, mediastinum, and pleura
C47.0	Peripheral nerves and autonomic nervous system of head, face, and neck
C47.1	Peripheral nerves and autonomic nervous system of upper limb and shoulder
C47.2	Peripheral nerves and autonomic nervous system of lower limb and hip
C47.3	Peripheral nerves and autonomic nervous system of thorax
C47.4	Peripheral nerves and autonomic nervous system of abdomen
C47.5	Peripheral nerves and autonomic nervous system of pelvis
C47.6	Peripheral nerves and autonomic nervous system of trunk, NOS
C47.8	Overlapping lesion of peripheral nerves and autonomic nervous system
C47.9	Autonomic nervous system, NOS
C48.0	Retroperitoneum
C48.1	Specified parts of peritoneum
C48.2	Peritoneum, NOS

Soft Tissue Sarcoma Staging Form

Clinical *Extent of disease before any treatment*	Stage Category Definitions		Pathologic *Extent of disease during and from surgery*
❒ y clinical–staging completed after neoadjuvant therapy but before subsequent surgery	**Tumor Size:** _____	**Laterality:** ☐ left ☐ right ☐ bilateral	❒ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	Primary Tumor (T) Primary tumor cannot be assessed No evidence of primary tumor Tumor 5 cm or less in greatest dimension Superficial tumor Deep tumor Tumor more than 5 cm in greatest dimension Superficial tumor Deep tumor Note: Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located either exclusively beneath the superficial fascia, superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia.		❑ TX ❑ T0 ❑ T1 ❑ T1a ❑ T1b ❑ T2 ❑ T2a ❑ T2b
❑ NX ❑ N0 ❑ N1*	**Regional Lymph Nodes (N)** Regional lymph nodes cannot be assessed No regional lymph node metastasis Regional lymph node metastasis *Note: Presence of positive nodes (N1) in M0 tumors is considered Stage III		❑ NX ❑ N0 ❑ N1
❑ M0 ❑ M1	**Distant Metastasis (M)** No distant metastasis (no pathologic M0; use clinical M to complete stage group) Distant metastasis		❑ M1

Anatomic Stage • Prognostic Groups

Clinical

Group	T	N	M	Grade
❑ IA	T1a	N0	M0	G1, GX
	T1b	N0	M0	G1, GX
❑ IB	T2a	N0	M0	G1, GX
	T2b	N0	M0	G1, GX
❑ IIA	T1a	N0	M0	G2, G3
	T1b	N0	M0	G2, G3
❑ IIB	T2a	N0	M0	G2
	T2b	N0	M0	G2
❑ III	T2a, T2b	N0	M0	G3
	Any T	N1	M0	Any G
❑ IV	Any T	Any N	M1	Any G

❑ Stage unknown

Pathologic

Group	T	N	M	Grade
❑ IA	T1a	N0	M0	G1, GX
	T1b	N0	M0	G1, GX
❑ IB	T2a	N0	M0	G1, GX
	T2b	N0	M0	G1, GX
❑ IIA	T1a	N0	M0	G2, G3
	T1b	N0	M0	G2, G3
❑ IIB	T2a	N0	M0	G2
	T2b	N0	M0	G2
❑ III	T2b	N0	M0	G3
	Any T	N1	M0	Any G
❑ IV	Any T	Any N	M1	Any G

❑ Stage unknown

Hospital Name/Address	Patient Name/Information

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SOFT TISSUE SARCOMA STAGING FORM

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)

REQUIRED FOR STAGING: Grade _____

CLINICALLY SIGNIFICANT:

Neurovascular invasion as determined by pathology: _____

Bone invasion as determined by imaging: _____

If pM1, source of pathologic metastatic specimen: _____

Histologic Grade (G) *(also known as overall grade)*

Grading system	***Grade***
❑ 2 grade system	❑ Grade I or 1
❑ 3 grade system	❑ Grade II or 2
❑ 4 grade system	❑ Grade III or 3
❑ No 2, 3, or 4 grade system is available	❑ Grade IV or 4

ADDITIONAL DESCRIPTORS

Lymphatic Vessel Invasion (L) and Venous Invasion (V) have been combined into Lymph-Vascular Invasion (LVI) for collection by cancer registrars. The College of American Pathologists' (CAP) Checklist should be used as the primary source. Other sources may be used in the absence of a Checklist. Priority is given to positive results.

- ❑ Lymph-Vascular Invasion Not Present (absent)/Not Identified
- ❑ Lymph-Vascular Invasion Present/Identified
- ❑ Not Applicable
- ❑ Unknown/Indeterminate

Residual Tumor (R)

The absence or presence of residual tumor after treatment. In some cases treated with surgery and/or with neoadjuvant therapy there will be residual tumor at the primary site after treatment because of incomplete resection or local and regional disease that extends beyond the limit of ability of resection.

- ❑ RX Presence of residual tumor cannot be assessed
- ❑ R0 No residual tumor
- ❑ R1 Microscopic residual tumor
- ❑ R2 Macroscopic residual tumor

General Notes:
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

a prefix designates the stage determined at autopsy: aTNM.

surgical margins is data field recorded by registrars describing the surgical margins of the resected primary site specimen as determined only by the pathology report.

neoadjuvant treatment is radiation therapy or systemic therapy (consisting of chemotherapy, hormone therapy, or immunotherapy) administered prior to a definitive surgical procedure. If the surgical procedure is not performed, the administered therapy no longer meets the definition of neoadjuvant therapy.

❑ Clinical stage was used in treatment planning (describe): _____

❑ National guidelines were used in treatment planning ❑ NCCN ❑ Other (describe): _____

_____

Physician signature Date/Time

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

(continued from previous page)

however, Lindelof and colleagues[45] report that most lethal cSCCs in their study were 5–19 mm in diameter. They also point out that focusing on tumor size may be misleading in immunocompromised populations because small tumors can behave very aggressively. For centers prospectively studying cSCC, recording of presence and type of immunosuppression is recommended.

CONCLUSIONS

The seventh edition of the AJCC Staging Manual features MCC as a separate chapter and cSCC is staged in this chapter entitled "Cutaneous Squamous cell and Other Carcinomas." The remainder of NMSC tumors (such as appendageal tumors and BCC) will also be included within the cSCC chapter since those tumors can rarely be advanced and are occasionally described to undergo metastasis. As the first published staging system devoted specifically to cSCC prognosis, this represents an important step for better understanding and studying the prognosis of this potentially metastatic tumor. Additionally, since many cSCC tumors occur on the head and neck, the seventh edition cSCC staging system is congruent with Head and Neck Cancer staging system. Furthermore, the new T staging definitions for the seventh edition for cSCC now capture additional features believed to correlate with high-risk cSCC in order to more meaningfully stratify patients based on prospective systematic data. Certainly there is still a need for multivariate data analysis, particularly to determine the relative contributions of the various described T factors influencing cSCC prognosis. Finally, the new N staging definitions are congruent with Head and Neck staging and reflect recent data that suggests that prognosis is inversely correlated with increasing nodal disease.

DEFINITIONS OF TNM

Definitions for clinical (cTNM) and pathologic (pTNM) classifications are the same. Patients with cSCC in situ are categorized as Tis. Carcinomas that are indeterminate or cannot be staged should be category TX. Carcinomas 2 cm or less in diameter are T1, if they have fewer than two high-risk features. Clinical high-risk features include primary site on ear or hair-bearing lip. Histologic high-risk features include depth >2 mm, Clark level ≥IV/V, poor differentiation, and the presence of perineural invasion. Tumors greater than 2 cm in diameter are classified as T2. Tumors 2 cm or less in diameter are classified as T2 if the tumor has two or more high-risk features. Invasion into facial bones is classified as T3, while invasion to base of skull or axial skeleton is classified as T4.

Local and regional metastases most commonly present in the regional lymph nodes. The actual status of nodal metastases identified by clinical inspection or imaging and the status and number of positive and total nodes by pathologic analysis must be reported for staging purposes. In instances where lymph node status is not recorded, a designation of NX is used. A solitary parotid or regional lymph node metastasis measuring 3 cm or less in size is given a N1 designation. Several different lymph node states are classified as N2: N2a represents a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; N2b is defined by multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; N2c includes bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension. Nodal metastases more than 6 cm in greatest dimension are classified as N3.

Distant metastases are staged primarily by the presence (M1) or absence (M0) of metastases in distant organs or sites outside of the regional lymph nodes.

Primary Tumor (T)*	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension with less than two high-risk features**
T2	Tumor greater than 2 cm in greatest dimension *or* Tumor any size with two or more high-risk features**
T3	Tumor with invasion of maxilla, mandible, orbit, or temporal bone
T4	Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base

*Excludes cSCC of the eyelid (see Chap. 48).

**High-risk features for the primary tumor (T) staging

Depth/invasion	>2 mm thickness
	Clark level ≥IV
	Perineural invasion
Anatomic location	Primary site ear
	Primary site hair-bearing lip
Differentiation	Poorly differentiated or undifferentiated

Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension

CUTANEOUS SQUAMOUS CELL/OTHER CUTANEOUS CARCINOMA STAGING FORM

CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS		PATHOLOGIC *Extent of disease through completion of definitive surgery*
❒ y clinical–staging completed after neoadjuvant therapy but before subsequent surgery	**TUMOR SIZE:** _____	**LATERALITY:** ☐ midline ☐ left ☐ right ☐ bilateral	❒ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	PRIMARY TUMOR (T)*		
❑ TX	Primary tumor cannot be assessed		❑ TX
❑ T0	No evidence of primary tumor		❑ T0
❑ Tis	Tis Carcinoma *in situ*		❑ Tis
❑ T1	Tumor 2 cm or less in greatest dimension with less than two high risk features**		❑ T1
❑ T2	Tumor greater than 2 cm in greatest dimension *or* Tumor any size with two or more high risk features**		❑ T2
❑ T3	Tumor with invasion of maxilla, orbit, or temporal bone		❑ T3
❑ T4	Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base		❑ T4
	* Excludes cSCC of the eyelid – See Chapter 48.		
	**High Risk Features for the Primary Tumor (T) Staging: Depth/Invasion: >2 mm thickness, Clark level ≥ IV, Perineural invasion; Anatomic Location: Primary site ear, Primary site hair-bearing lip; Differentiation: Poorly differentiated or undifferentiated		
	REGIONAL LYMPH NODES (N)		
❑ NX	Regional lymph nodes cannot be assessed		❑ NX
❑ N0	No regional lymph node metastasis		❑ N0
❑ N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension		❑ N1
❑ N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		❑ N2
❑ N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension		❑ N2a
❑ N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension		❑ N2b
❑ N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		❑ N2c
❑ N3	Metastasis in a lymph node, more than 6 cm in greatest dimension		❑ N3
	DISTANT METASTASIS (M)		
❑ M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)		
❑ M1	Distant metastasis		❑ M1

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

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Merkel Cell Carcinoma

(Staging for Merkel Cell of the eyelid [C44.1] is not included in this chapter – see Chap. 48, "Carcinoma of the Eyelid")

At-A-Glance

SUMMARY OF CHANGES

- This is the first staging chapter specific for Merkel cell carcinoma. Merkel cell carcinoma was previously included in the "Carcinoma of the Skin" chapter

ANATOMIC STAGE/PROGNOSTIC GROUPS

Patients with primary Merkel cell carcinoma with no evidence of regional or distant metastases (either clinically or pathologically) are divided into two stages: Stage I for primary tumors ≤2 cm in size and Stage II for primary tumors >2 cm in size. Stages I and II are further divided into A and B substages based on method of nodal evaluation. Patients who have pathologically proven node negative disease (by microscopic evaluation of their draining lymph nodes) have improved survival (substaged as A) compared with those who are only evaluated clinically (substaged as B). Stage II has an additional substage (IIC) for tumors with extracutaneous invasion (T4) and negative node status regardless of whether the negative node status was established microscopically or clinically. Stage III is also divided into A and B categories for patients with microscopically positive and clinically occult nodes (IIIA) and macroscopic nodes (IIIB). There are no subgroups of Stage IV Merkel cell carcinoma.

Stage 0	Tis	N0	M0
Stage IA	T1	pN0	M0
Stage IB	T1	cN0	M0
Stage IIA	T2/T3	pN0	M0
Stage IIB	T2/T3	cN0	M0
Stage IIC	T4	N0	M0
Stage IIIA	Any T	N1a	M0
Stage IIIB	Any T	cN1/N1b/N2	M0
Stage IV	Any T	Any N	M1

Note: Isolated tumor cells should be considered positive nodes, similar to melanoma (see Chapter 31).

ICD-O-3 TOPOGRAPHY CODES

C44.0 Skin of lip, NOS
C44.2 External ear
C44.3 Skin of other and unspecified parts of face
C44.4 Skin of scalp and neck
C44.5 Skin of trunk
C44.6 Skin of upper limb and shoulder
C44.7 Skin of lower limb and hip
C44.8 Overlapping lesion of skin
C44.9 Skin, NOS
C51.0 Labium majus
C51.1 Labium minus
C51.2 Clitoris
C51.8 Overlapping lesion of vulva
C51.9 Vulva, NOS
C60.0 Prepuce
C60.1 Glans penis
C60.2 Body of penis
C60.8 Overlapping lesion of penis
C60.9 Penis, NOS
C63.2 Scrotum, NOS

ICD-O-3 HISTOLOGY CODE RANGES

8247

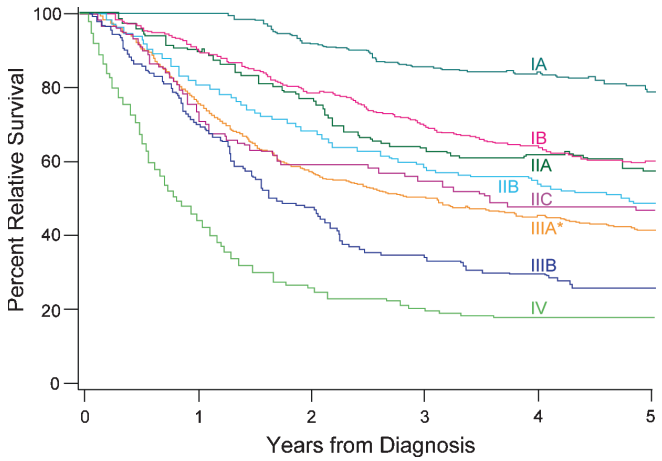


FIGURE 30.4. Relative survival for 2,856 Merkel cell carcinoma patients by stage. Percent relative survival was calculated for cases in the National Cancer Database using age- and sex-matched control data from the Centers for Disease Control and Prevention. Stages are as indicated in the figure except for Stage IIIA which could not be derived using this dataset. The *curve* marked "IIIA*" represents pathologically node positive patients, with the clinical node status unknown or negative. It is anticipated that true Stage IIIA patients (clinical node status negative) have better survival than the line marked with "IIIA*." Total number of patients was 2,856, and individual substages were as follows: IA = 266, IB = 754, IIA = 124, IIB = 414, IIC = 84, IIIA* = 794, IIIB = 143, IV = 277.

than 5 cm (T3). Extracutaneous invasion by the primary tumor into bone, muscle, fascia, or cartilage is classified as T4. Inclusion of 2 cm MCC tumors as T1 is consistent with the prior AJCC staging system but differs from other frequently used MCC staging systems[12,14] that categorize 2 cm tumors as T2. The breakdown of T category is conserved from the prior version of AJCC staging for "Carcinoma of the Skin."

Regional metastases most commonly present in the regional lymph nodes. A second staging definition is related to nodal tumor burden: microscopic vs. macroscopic. Therefore, patients without clinical or radiologic evidence of lymph node metastases but who have pathologically documented nodal metastases are defined by convention as exhibiting "microscopic" or "clinically occult" nodal metastases. In contrast, MCC patients with both clinical evidence of nodal metastases *and* pathologic examination confirming nodal metastases are defined by convention as having "macroscopic" or "clinically apparent" nodal metastases. Nodes clinically positive by exam and negative by pathology would be classified as pN0. Clinically positive nodes in the draining nodal basin that are assumed to be involved with Merkel cell carcinoma but are without pathologic confirmation (no pathology performed) should be classified as N1b and the pathologic classification would be NX. Then in determining the stage grouping, it would be Stage IIIB defaulting to the higher N category.

Distant metastases are defined as metastases that have spread beyond the draining lymph node basin, including cutaneous, nodal, and visceral sites.

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor (e.g., nodal/metastatic presentation without associated primary)
Tis	In situ primary tumor
T1	Less than or equal to 2 cm maximum tumor dimension
T2	Greater than 2 cm but not more than 5 cm maximum tumor dimension
T3	Over 5 cm maximum tumor dimension
T4	Primary tumor invades bone, muscle, fascia, or cartilage

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
cN0	Nodes negative by clinical exam* (no pathologic node exam performed)
pN0	Nodes negative by pathologic exam
N1	Metastasis in regional lymph node(s)
N1a	Micrometastasis**
N1b	Macrometastasis***
N2	In transit metastasis****

*Clinical detection of nodal disease may be via inspection, palpation, and/or imaging.

**Isolated tumor cells in a lymph node are classified as micrometastases (N1a) and the presence of isolated tumor cells recorded using the prognostic factor. Micrometastases are diagnosed after sentinel or elective lymphadenectomy.

***Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or needle biopsy.

****In transit metastasis: a tumor distinct from the primary lesion and located either (1) between the primary lesion and the draining regional lymph nodes or (2) distal to the primary lesion.

Distant Metastasis (M)

M0	No distant metastasis
M1	Metastasis beyond regional lymph nodes
M1a	Metastasis to skin, subcutaneous tissues or distant lymph nodes
M1b	Metastasis to lung
M1c	Metastasis to all other visceral sites

ANATOMIC STAGE/PROGNOSTIC GROUPS

Patients with primary Merkel cell carcinoma with no evidence of regional or distant metastases (either clinically or pathologically) are divided into two stages: Stage I for primary tumors ≤2 cm in size and Stage II for primary tumors >2 cm in size. Stages I and II are further divided into A and B substages based on method of nodal evaluation. Patients who have pathologically proven node

negative disease (by microscopic evaluation of their draining lymph nodes) have improved survival (substaged as A) compared to those who are only evaluated clinically (substaged as B). Stage II has an additional substage (IIC) for tumors with extracutaneous invasion (T4) and negative node status regardless of whether the negative node status was established microscopically or clinically. Stage III is also divided into A and B categories for patients with microscopically positive and clinically occult nodes (IIIA) and macroscopic nodes (IIIB). There are no subgroups of Stage IV Merkel cell carcinoma.

Stage 0	Tis	N0	M0
Stage IA	T1	pN0	M0
Stage IB	T1	cN0	M0
Stage IIA	T2/T3	pN0	M0
Stage IIB	T2/T3	cN0	M0
Stage IIC	T4	N0	M0
Stage IIIA	Any T	N1a	M0
Stage IIIB	Any T	cN1/N1b/N2	M0
Stage IV	Any T	Any N	M1

Note: Isolated tumor cells should be considered positive nodes, similar to melanoma (see Chapter 31).

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS) (Recommended for Collection)

Required for staging	None
Clinically significant	Measured thickness (depth) Tumor base transection status Profound immune suppression Tumor infiltrating lymphocytes in the primary tumor (TIL) Growth pattern of primary tumor Size of tumor nests in regional lymph nodes Clinical status of regional lymph nodes Regional lymph nodes pathological extracapsular extension Isolated tumor cells in regional lymph node(s)

HISTOLOGIC GRADE (G)

Histologic grade is not used in the staging of Merkel cell carcinoma.

HISTOPATHOLOGIC TYPE

While several distinct morphologic patterns have been described for MCC, these have not been reproducibly found to be of prognostic significance. These histologic subtypes include: intermediate type (most common), small cell type (second most common), and trabecular type (least common but most characteristic pattern of MCC).

REFERENCES

1. Tang CK, Toker C. Trabecular carcinoma of the skin: an ultrastructural study. Cancer. 1978;42(5):2311–21.
2. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human merkel cell carcinoma. Science. 2008;319:1096–100.
3. Agelli M, Clegg LX. Epidemiology of primary Merkel cell carcinoma in the United States. J Am Acad Dermatol. 2003;49(5):832–41.
4. Heath ML, Jaimes N, Lemos B, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. J Am Acad Dermatol. 2008;58(3):375–81.
5. Kanitakis J, Euvrard S, Chouvet B, Butnaru AC, Claudy A. Merkel cell carcinoma in organ-transplant recipients: report of two cases with unusual histological features and literature review. J Cutan Pathol. 2006;33(10):686–94.
6. Penn I, First MR. Merkel's cell carcinoma in organ recipients: report of 41 cases. Transplantation. 1999;68(11):1717–21.
7. Hodgson NC. Merkel cell carcinoma: changing incidence trends. J Surg Oncol. 2005;89(1):1–4.
8. Lemos B, Nghiem P. Merkel cell carcinoma: more deaths but still no pathway to blame. J Invest Dermatol. 2007;127(9):2100–3.
9. Medina-Franco H, Urist MM, Fiveash J, Heslin MJ, Bland KI, Beenken SW. Multimodality treatment of Merkel cell carcinoma: case series and literature review of 1024 cases. Ann Surg Oncol. 2001;8(3):204–8.
10. Allen PJ, Zhang ZF, Coit DG. Surgical management of Merkel cell carcinoma. Ann Surg. 1999;229(1):97–105.
11. AJCC cancer staging manual. 6th ed. Chicago, IL: Springer; 2002.
12. Allen PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, Coit DG. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. J Clin Oncol. 2005;23(10):2300–9.
13. Clark JR, Veness MJ, Gilbert R, O'Brien C J, Gullane PJ. Merkel cell carcinoma of the head and neck: Is adjuvant radiotherapy necessary? Head Neck. 2007;29(3):249–57.
14. Yiengpruksawan A, Coit DG, Thaler HT, Urmacher C, Knapper WK. Merkel cell carcinoma. Prognosis and management. Arch Surg. 1991;126(12):1514–9.
15. Gupta SG, Wang LC, Penas PF, Gellenthin M, Lee SJ, Nghiem P. Sentinel lymph node biopsy for evaluation and treatment of patients with Merkel cell carcinoma: the Dana-Farber experience and meta-analysis of the literature. Arch Dermatol. 2006;142(6):685–90.
16. Voog E, Biron P, Martin JP, Blay JY. Chemotherapy for patients with locally advanced or metastatic Merkel cell carcinoma. Cancer. 1999;85(12):2589–95.
17. Buell JF, Trofe J, Hanaway MJ, et al. Immunosuppression and Merkel cell cancer. Transplant Proc. 2002;34(5):1780–1.

MERKEL CELL CARCINOMA STAGING FORM

CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS	PATHOLOGIC *Extent of disease through completion of definitive surgery*
❒ y clinical–staging completed after neoadjuvant therapy but before subsequent surgery	**TUMOR SIZE:** _____ **LATERALITY:** ☐ midline ☐ left ☐ right ☐ bilateral	❒ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	PRIMARY TUMOR (T)	
❑ **TX**	Primary tumor cannot be assessed	❑ **TX**
❑ **T0**	No evidence of primary tumor	❑ **T0**
❑ **Tis**	*In situ* primary tumor	❑ **Tis**
❑ **T1**	Less than or equal to 2 cm maximum tumor dimension	❑ **T1**
❑ **T2**	Greater than 2 cm but not more than 5 cm maximum tumor dimension	❑ **T2**
❑ **T3**	Over 5 cm maximum tumor dimension	❑ **T3**
❑ **T4**	Primary tumor invades bone, muscle, fascia, or cartilage	❑ **T4**
	REGIONAL LYMPH NODES (N)	
❑ **NX**	Regional lymph nodes cannot be assessed	❑ **NX**
❑ **N0**	No regional lymph node metastasis	❑ **N0**
❑ **cN0**	Nodes negative by clinical exam* (no pathologic node exam performed)	
	Nodes negative by pathologic exam	❑ **pN0**
❑ **N1**	Metastasis in regional lymph node(s)	❑ **N1**
	Micrometastasis**	❑ **N1a**
	Macrometastasis***	❑ **N1b**
❑ **N2**	In transit metastasis ****	❑ **N2**
	*Clinical detection of nodal disease may be via inspection, palpation and/or imaging	
	**Isolated tumor cells in a lymph node are classified as micrometastases (N1a) and the presence of isolated tumor cells recorded using the prognostic factor. Micrometastases are diagnosed after sentinel or elective lymphadenectomy	
	***Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or needle biopsy	
	****In transit metastasis: a tumor distinct from the primary lesion and located either 1) between the primary lesion and the draining regional lymph nodes or 2) distal to the primary lesion	
	DISTANT METASTASIS (M)	
❑ **M0**	No distant metastasis (no pathologic M0; use clinical M to complete stage group)	
❑ **M1**	Metastasis beyond regional lymph nodes	❑ **M1**
❑ **M1a**	Metastasis to skin, subcutaneous tissues or distant lymph nodes	❑ **M1a**
❑ **M1b**	Metastasis to lung	❑ **M1b**
❑ **M1c**	Metastasis to all other visceral sites	❑ **M1c**

ANATOMIC STAGE • PROGNOSTIC GROUPS

CLINICAL

GROUP	T	N	M
❑ 0	Tis	N0	M0
❑ IB	T1	N0	M0
❑ IIB	T2/T3	N0	M0
❑ IIC	T4	N0	M0
❑ IIIB	Any T	cN1/N1b/N2	M0
❑ IV	Any T	Any N	M1

❑ Stage unknown

Note: Isolated tumor nodes should be considered positive nodes.

PATHOLOGIC

GROUP	T	N	M
❑ 0	Tis	N0	M0
❑ IA	T1	pN0	M0
❑ IIA	T2/T3	pN0	M0
❑ IIC	T4	N0	M0
❑ IIIA	Any T	N1a	M0
❑ IIIB	Any T	N1b/N2	M0
❑ IV	Any T	Any N	M1

❑ Stage unknown

Note: Isolated tumor nodes should be considered positive nodes.

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

(continued on next page)

MELANOMA OF THE SKIN STAGING FORM

ANATOMIC STAGE • PROGNOSTIC GROUPS

CLINICAL*

GROUP	T	N	M
❑ 0	Tis	N0	M0
❑ IA	T1a	N0	M0
❑ IB	T1b	N0	M0
	T2a	N0	M0
❑ IIA	T2b	N0	M0
	T3a	N0	M0
❑ IIB	T3b	N0	M0
	T4a	N0	M0
❑ IIC	T4b	N0	M0
❑ III	Any T	≥N1	M0
❑ IV	Any T	Any N	M1

* Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

❑ Stage unknown

PATHOLOGIC+

GROUP	T	N	M
❑ 0	Tis	N0	M0
❑ IA	T1a	N0	M0
❑ IB	T1b	N0	M0
	T2a	N0	M0
❑ IIA	T2b	N0	M0
	T3a	N0	M0
❑ IIB	T3b	N0	M0
	T4a	N0	M0
❑ IIC	T4b	N0	M0
❑ IIIA	T1 – 4a	N1a	M0
	T1 – 4a	N2a	M0
❑ IIIB	T1 – 4b	N1a	M0
	T1 – 4b	N2a	M0
	T1 – 4a	N1b	M0
	T1 – 4a	N2b	M0
	T1 – 4a	N2c	M0
❑ IIIC	T1 – 4b	N1b	M0
	T1 – 4b	N2b	M0
	T1 – 4b	N2c	M0
	Any T	N3	M0
❑ IV	Any T	Any N	M1

+ Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 or Stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

❑ Stage unknown

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)

REQUIRED FOR STAGING: None

CLINICALLY SIGNIFICANT:

Measured thickness (depth) _____
Ulceration _____
Serum lactate dehydrogenase (LDH) _____
Mitotic rate _____
Tumor infiltrating lymphocytes (TIL) _____
Level of invasion _____
Vertical growth plate _____
Regression _____

Histologic Grade (G) *(also known as overall grade)*

Histologic grading is not used in the staging of Melanoma.

General Notes:
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

(continued from previous page)

Posttreatment ypT. Clinical (pretreatment) T will be defined by clinical and radiographic findings, while y pathologic (posttreatment) T will be determined by pathologic size and extension. The ypT will be measured as the largest single focus of invasive tumor, with the modifier "m" indicating multiple foci. The measurement of the largest tumor focus should not include areas of fibrosis within the tumor bed. The inclusion of additional information in the pathology report such as the distance over which tumor foci extend, the number of tumor foci present, or the number of slides/blocks in which tumor appears may assist the clinician in estimating the extent of disease. A comparison of the cellularity in the initial biopsy to that in the posttreatment specimen may also aid in the assessment of response.

Note: If a cancer was designated as inflammatory before neoadjuvant chemotherapy, the patient will be designated to have inflammatory breast cancer throughout, even if the patient has complete resolution of inflammatory findings.

Regional Lymph Nodes (N)

Clinical

NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastases
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastases
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected* ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)

**Note*: *Clinically detected* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, for example, cN1. Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.

Pathologic (pN)*

pNX	Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis identified histologically

Note: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.

pN0(i−)	No regional lymph node metastases histologically, negative IHC
pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)
pN0 (mol−)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
pN0 (mol+)	Positive molecular findings (RT-PCR),** but no regional lymph node metastases detected by histology or IHC
pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected***
pN1mi	Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
pN1c	Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected

Pathologic (pN) (Continued)*	
pN2	Metastases in 4–9 axillary lymph nodes; or in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastases in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN3	Metastases in ten or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected**** ipsilateral internal mammary lymph nodes in the *presence* of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in ten or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected**** ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes andin internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Notes:
*Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," for example, pN0(sn).

**RT-PCR: reverse transcriptase/polymerase chain reaction.

***"Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

****"Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.

Posttreatment ypN

- Post-treatment yp "N" should be evaluated as for clinical (pretreatment) "N" methods above. The modifier "sn" is used only if a sentinel node evaluation was performed after treatment. If no subscript is attached, it is assumed that the axillary nodal evaluation was by axillary node dissection (AND).
- The X classification will be used (ypNX) if no yp posttreatment SN or AND was performed
- N categories are the same as those used for pN.

Distant Metastases (M)	
M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Posttreatment yp M classification. The M category for patients treated with neoadjuvant therapy is the category assigned in the clinical stage, prior to initiation of neoadjuvant therapy. Identification of distant metastases after the start of therapy in cases where pretherapy evaluation showed no metastases is considered progression of disease. If a patient was designated to have detectable distant metastases (M1) before chemotherapy, the patient will be designated as M1 throughout.

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Notes:
*T1 includes T1mi.

**T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

- M0 includes M0(i+).
- The designation pM0 is not valid; any M0 should be clinical.
- If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
- Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.
- Postneoadjuvant therapy is designated with "yc" or "yp" prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)
(Recommended for Collection)

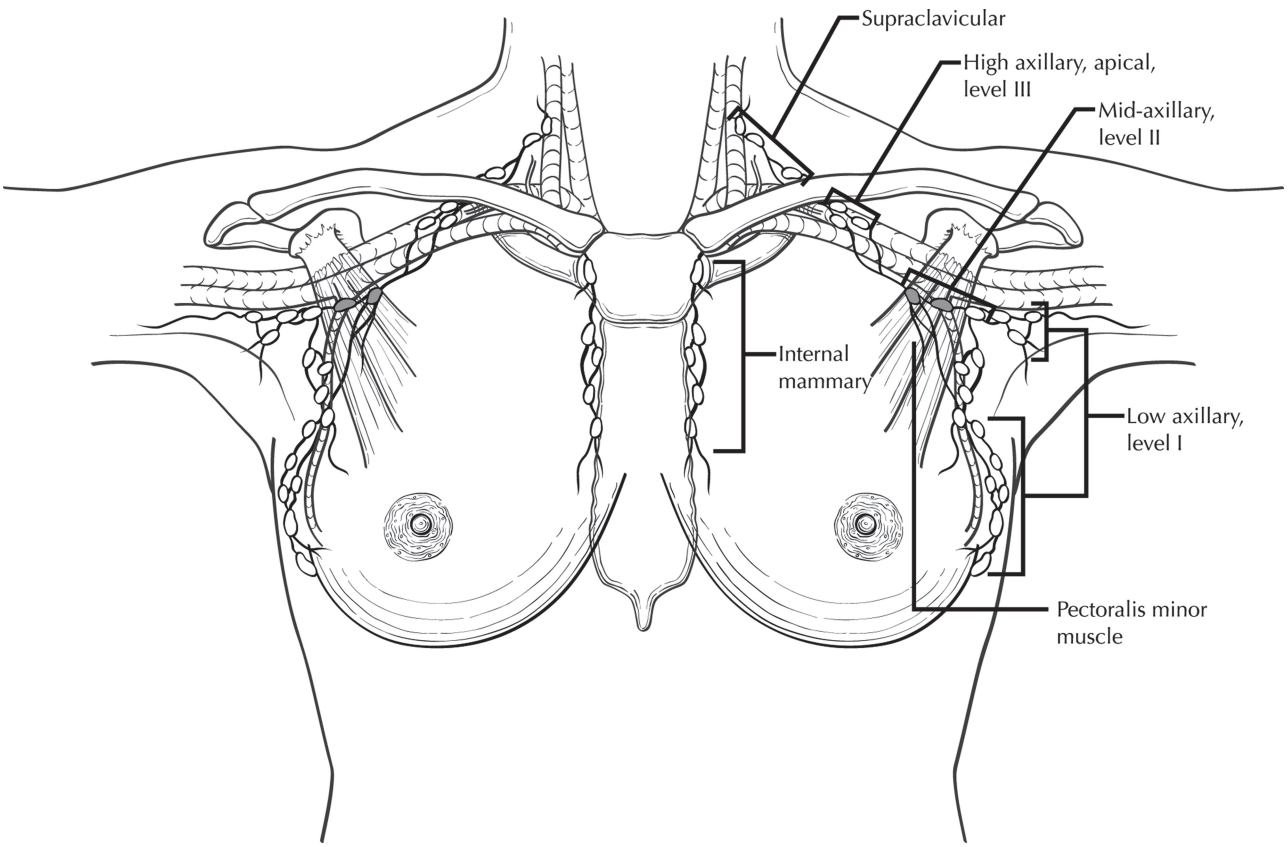
Required for staging	None
Clinically significant	Paget's disease Tumor grade (Scarff–Bloom–Richardson system) Estrogen receptor and test method (IHC, RT-PCR, other) Progesterone receptor and test method (IHC, RT-PCR, other) HER2 status and test method (IHC, FISH, CISH, RT-PCR, other) Method of lymph node assessment (e.g., clinical, fine needle aspiration; core biopsy; sentinel lymph node biopsy) IHC of regional lymph nodes Molecular studies regional lymph nodes Distant metastases method of detection (clinical, radiographic, biopsy) Circulating tumor cells (CTC) and method of detection (RT-PCR, immunomagnetic separation, other) Disseminated tumor cells (DTC; bone marrow micrometastases) and method of detection (RT-PCR, immunohistochemical, other) Multigene signature score
Response to neoadjuvant therapy	Will be collected in the registry but does not affect the postneoadjuvant stage
Complete response (CR)	Pathologic complete response can only be determined by histopathologic evaluation and is defined by the absence of invasive carcinoma in the breast and lymph nodes. Residual in situ cancer, in the absence of invasive disease, constitutes a pCR. Patients with isolated tumor foci in lymph nodes are not classified as having a CR. The presence of axillary nodal tumor deposits of any size, including cell clusters less than or equal to 0.2 mm, excludes a complete response. These patients will be categorized as ypN0(i+).
Partial response (PR)	A decrease in either or both the T or N category compared to the pretreatment T or N, and no increase in either T or N. After chemotherapy, one should use the method that most clearly defined tumor dimensions at baseline for this comparison, although prechemotherapy pT cannot be measured. Clinical (pretreatment) T will be defined by clinical and radiographic findings. y pathologic (posttreatment) T will be determined by pathologic size and extension. Nodal response should be determined by physical examination or radiologic evaluation, if the nodes are palpable or visible before chemotherapy. If prechemotherapy pathologic lymph node involvement is demonstrated by fine needle aspiration, core biopsy, or sentinel node biopsy, it should be recorded as such. Absence of posttreatment pathologic nodal involvement should be used to document pathologic complete response, and should be recorded, but does not necessarily represent a true "response" since one does not know whether lymph nodes removed surgically postchemotherapy were involved prior to chemotherapy.
No response (NR)	No apparent change in either the T or N categories compared to the clinical (pretreatment) assignment or an increase in the T or N category at the time of y pathologic evaluation. Clinical (pretreatment) T will be defined by clinical and radiographic findings. yp (posttreatment) T will be determined by pathologic size. The response category will be appended to the y stage description. For example: • ypTisypN0cM0CR; ypT1ypN0cM0PR; ypT2ypN1cM0NR

HISTOLOGIC GRADE (G)

All invasive breast carcinomas should be graded. The Nottingham combined histologic grade (Elston-Ellis modification of Scarff–Bloom–Richardson grading system) is recommended.[2,23] The grade for a tumor is determined by assessing morphologic features (tubule formation, nuclear pleomorphism,

Illustration

Indicate on diagram primary tumor and regional nodes involved.



HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

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Vulva

(Mucosal malignant melanoma is not included)

At-A-Glance

SUMMARY OF CHANGES

- The definition of TNM and the Stage Grouping for this chapter have changed from the Sixth Edition and reflect new staging adopted by the International Federation of Gynecology and Obstetrics (FIGO) (2008)

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0*	Tis	N0	M0
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T1, T2	N1a, N1b	M0
Stage IIIB	T1, T2	N2a, N2b	M0
Stage IIIC	T1, T2	N2c	M0
Stage IVA	T1, T2	N3	M0
	T3	Any N	M0
Stage IVB	Any T	Any N	M1

**Note*: FIGO no longer includes Stage 0 (Tis).

ICD-O-3 TOPOGRAPHY CODES

C51.0 Labium majus
C51.1 Labium minus
C51.2 Clitoris
C51.8 Overlapping lesion of vulva
C51.9 Vulva, NOS

ICD-O-3 HISTOLOGY CODE RANGES

8000–8246, 8248–8576, 8940–8950, 8980–8981

ANATOMY

Primary Site. The vulva is the anatomic area immediately external to the vagina. It includes the labia and the perineum. The tumor may extend to involve the vagina, urethra, or anus. It may be fixed to the pubic bone. Changes to the staging classification reflect a belief that tumor size independent of other factors (spread to adjacent structures, nodal metastases) is less important in predicting survival.

Regional Lymph Nodes. The femoral and inguinal nodes are the sites of regional spread. For pN, histologic examination of regional lymphadenectomy specimens will ordinarily include six or more lymph nodes. For TNM staging, cases with fewer than six resected nodes should be classified using the TNM pathologic classification according to the status of those nodes (e.g., pN0; pN1) as per the general rules of TNM. The number of resected and positive nodes should be recorded (note that FIGO classifies cases with less than six nodes resected as pNX). The concept of sentinel lymph node mapping where only one or two key nodes are removed is currently being investigated. In most cases, a surgical assessment of regional lymph nodes (inguinal-femoral lymphadenectomy) is performed. Rarely, assessment of lymph nodes will be made by radiologic guided fine-needle aspiration or use of imaging techniques [computerized tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET)]. The current revisions to staging adopted reflect a recognition that the number and size of lymph node metastases more accurately reflect prognosis.

Metastatic Sites. The metastatic sites include any site beyond the area of the regional lymph nodes. Tumor involvement of pelvic lymph nodes, including internal iliac, external iliac, and common iliac lymph nodes, is considered distant metastasis.

RULES FOR CLASSIFICATION

Clinical Staging. Cases should be classified as carcinoma of the vulva when the primary site of the growth is in the vulva. Tumors present on the vulva as secondary growths from either a genital or an extragenital site should be excluded. This classification does not apply to mucosal malignant melanoma. There should be histologic confirmation of the tumor.

Pathologic Staging. FIGO uses surgical/pathologic staging for vulvar cancer. Stage should be assigned at the time of definitive surgical treatment or prior to radiation or chemotherapy if either of these is the initial mode of therapy. The stage cannot be changed on the basis of disease progression or recurrence or on the basis of response to initial radiation or chemotherapy that precedes primary tumor resection.

PROGNOSTIC FEATURES

Vulvar cancer is a surgically staged malignancy. Surgical-pathologic staging provides specific information about primary tumor size and lymph node status, which are the most important prognostic factors in vulvar cancer. Other commonly evaluated items, such as histologic type, differentiation, DNA ploidy, and S-phase fraction analysis, as well as age, are not uniformly identified as important prognostic factors in vulvar cancer.

DEFINITIONS OF TNM

The definitions of the T categories correspond to the stages accepted by the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO). Both systems are included for comparison.

Primary Tumor (T)

TNM Categories	*FIGO Stages*	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis*		Carcinoma in situ (preinvasive carcinoma)
T1a	IA	Lesions 2 cm or less in size, confined to the vulva or perineum and with stromal invasion 1.0 mm or less**
T1b	IB	Lesions more than 2 cm in size *or* any size with stromal invasion more than 1.0 mm, confined to the vulva or perineum
T2***	II	Tumor of any size with extension to adjacent perineal structures (lower/distal 1/3 urethra, lower/distal 1/3 vagina, anal involvement)
T3****	IVA	Tumor of any size with extension to any of the following: upper/proximal 2/3 of urethra, upper/proximal 2/3 vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone

**Note*: FIGO no longer includes Stage 0 (Tis).

***Note*: The depth of invasion is defined as the measurement of the tumor from the epithelial–stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

***FIGO uses the classification T2/T3. This is defined as T2 in TNM.

****FIGO uses the classification T4. This is defined as T3 in TNM.

Regional Lymph Nodes (N)

TNM Categories	*FIGO Stages*	
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		One or two regional lymph nodes with the following features
N1a	IIIA	1 or 2 lymph node metastases each 5 mm or less
N1b	IIIA	One lymph node metastasis 5 mm or greater
N2	IIIB	Regional lymph node metastasis with the following features
N2a	IIIB	Three or more lymph node metastases each less than 5 mm
N2b	IIIB	Two or more lymph node metastases 5 mm or greater
N2c	IIIC	Lymph node metastasis with extracapsular spread
N3	IVA	Fixed or ulcerated regional lymph node metastasis

An effort should be made to describe the site and laterality of lymph node metastases.

Distant Metastasis (M)

TNM Categories	*FIGO Stages*	
M0		No distant metastasis
M1	IVB	Distant metastasis (including pelvic lymph node metastasis)

VULVA STAGING FORM

CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS		PATHOLOGIC *Extent of disease during and from surgery*
❒ y clinical– staging completed after neoadjuvant therapy but before subsequent surgery	**TUMOR SIZE:** _____	**LATERALITY:** ☐ left ☐ right ☐ bilateral	❒ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery

TNM CATEGORY	FIGO STAGE	PRIMARY TUMOR (T)	TNM CATEGORY	FIGO STAGE
❑ TX		Primary tumor cannot be assessed	❑ TX	
❑ T0		No evidence of primary tumor	❑ T0	
❑ Tis	*	Carcinoma *in situ* (preinvasive carcinoma)	❑ Tis	*
❑ T1a	IA	Lesions ? 2 cm in size, confined to the vulva or perineum and with stromal invasion ? 1.0 mm**	❑ T1a	IA
❑ T1b	IB	Lesions >2 cm in size **or** any size with stromal invasion >1.0 mm, confined to the vulva or perineum	❑ T1b	IB
❑ T2***	II	Tumor of any size with extension to adjacent perineal structures (Lower/distal 1/3 urethra, lower/distal 1/3 vagina, anal involvement)	❑ T2***	II
❑ T3****	IVA	Tumor of any size with extension to any of the following: upper/proximal 2/3 of urethra, upper/proximal 2/3 vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone,	❑ T3****	IVA

* FIGO staging no longer includes Stage 0 (Tis).

** The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

*** FIGO uses the classification T2/T3. This is defined as T2 in TNM.

**** FIGO uses the classification T4. This is defined as T3 in TNM.

TNM CATEGORY	FIGO STAGE	REGIONAL LYMPH NODES (N)	TNM CATEGORY	FIGO STAGE
❑ NX		Regional lymph nodes cannot be assessed	❑ NX	
❑ N0		No regional lymph node metastasis	❑ N0	
❑ N1		One or two regional lymph node with the following features	❑ N1	
❑ N1a	IIIA	One or two lymph node metastasis each 5 mm or less	❑ N1a	IIIA
❑ N1b	IIIA	One lymph node metastases 5 mm or greater	❑ N1b	IIIA
❑ N2	IIIB	Regional lymph node metastasis with the following features:	❑ N2	IIIB
❑ N2a	IIIB	Three or more lymph node metastases each less than 5 mm	❑ N2a	IIIB
❑ N2b	IIIB	Two or more lymph node metastases 5 mm or greater	❑ N2b	IIIB
❑ N2c	IIIC	Lymph node metastasis with extracapsular spread	❑ N2c	IIIC
❑ N3	IVA	Fixed or ulcerated regional lymph node metastasis	❑ N3	IVA

An effort should be made to describe the site and laterality of lymph node metastases.

TNM CATEGORY	FIGO STAGE	DISTANT METASTASIS (M)	TNM CATEGORY	FIGO STAGE
❑ M0		No distant metastasis (no pathologic M0; use clinical M to complete stage group)		
❑ M1	IVB	Distant metastasis (including pelvic lymph node metastasis)	❑ M1	IVB

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

(continued on next page)

VAGINA STAGING FORM

CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS		PATHOLOGIC *Extent of disease during and from surgery*
❒ y clinical – staging completed after neoadjuvant therapy but before subsequent surgery	**TUMOR SIZE:** _____	**LATERALITY:** ☐ left ☐ right ☐ bilateral	❒ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery

TNM CATEGORY	FIGO STAGE	PRIMARY TUMOR (T)	TNM CATEGORY	FIGO STAGE
❑ TX		Primary tumor cannot be assessed	❑ TX	
❑ T0		No evidence of primary tumor	❑ T0	
❑ Tis	*	Carcinoma *in situ*	❑ Tis	*
❑ T1	I	Tumor confined to vagina	❑ T1	I
❑ T2	II	Tumor invades paravaginal tissues but not to pelvic wall	❑ T2	II
❑ T3	III	Tumor extends to pelvic wall**	❑ T3	III
❑ T4	IVA	Tumor invades mucosa of the bladder or rectum and/or extends beyond the true pelvis (bullous edema is not sufficient evidence to classify a tumor as T4)	❑ T4	IVA

*FIGO staging no longer includes Stage 0 (Tis).

**Pelvic wall is defined as muscle, fascia, neurovascular structures, or skeletal portions of the bony pelvis.

TNM CATEGORY	FIGO STAGE	REGIONAL LYMPH NODES (N)	TNM CATEGORY	FIGO STAGE
❑ NX		Regional lymph nodes cannot be assessed	❑ NX	
❑ N0		No regional lymph node metastasis	❑ N0	
❑ N1	III	Pelvic or inguinal lymph node metastasis	❑ N1	III

TNM CATEGORY	FIGO STAGE	DISTANT METASTASIS (M)	TNM CATEGORY	FIGO STAGE
❑ M0		No distant metastasis (no pathologic M0; use clinical M to complete stage group)		
❑ M1	IVB	Distant metastasis	❑ M1	IVB

ANATOMIC STAGE • PROGNOSTIC GROUP

CLINICAL

GROUP	T	N	M
❑ 0	Tis	N0	M0
❑ I	T1	N0	M0
❑ II	T2	N0	M0
❑ III	T1–T3	N1	M0
	T3	N0	M0
❑ IVA	T4	Any N	M0
❑ IVB	Any T	Any N	M1

*FIGO no longer includes Stage 0 (Tis).

❑ Stage unknown

PATHOLOGIC

GROUP	T	N	M
❑ 0	Tis	N0	M0
❑ I	T1	N0	M0
❑ II	T2	N0	M0
❑ III	T1–T3	N1	M0
	T3	N0	M0
❑ IVA	T4	Any N	M0
❑ IVB	Any T	Any N	M1

*FIGO no longer includes Stage 0 (Tis).

❑ Stage unknown

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

(continued on next page)

CERVIX UTERI STAGING FORM

TNM CATEGORY	FIGO STAGE	DISTANT METASTASIS (M)	TNM CATEGORY	FIGO STAGE
❑ M0		No distant metastasis (no pathologic M0; use clinical M to complete stage group)		
❑ M1	IVB	Distant metastasis (including peritoneal spread, involvement of supraclavicular, mediastinal, or paraaortic lymph nodes, lung, liver, or bone)	❑ M1	IVB

ANATOMIC STAGE • PROGNOSTIC GROUPS (FIGO 2008)

CLINICAL

GROUP	T	N	M
❑ Stage 0*	Tis	N0	M0
❑ Stage I	T1	N0	M0
❑ Stage IA	T1a	N0	M0
❑ Stage IA1	T1a1	N0	M0
❑ Stage IA2	T1a2	N0	M0
❑ Stage IB	T1b	N0	M0
❑ Stage IB1	T1b1	N0	M0
❑ Stage IB2	T1b2	N0	M0
❑ Stage II	T2	N0	M0
❑ Stage IIA	T2a	N0	M0
❑ Stage IIA1	T2a1	N0	M0
❑ Stage IIA2	T2a2	N0	M0
❑ Stage IIB	T2b	N0	M0
❑ Stage III	T3	N0	M0
❑ Stage IIIA	T3a	N0	M0
❑ Stage IIIB	T3b	Any N	M0
	T1-3	N1	M0
❑ Stage IVA	T4	Any N	M0
❑ Stage IVB	Any T	Any N	M1

*FIGO no longer includes Stage 0 (Tis)

❑ Stage unknown

PATHOLOGIC

GROUP	T	N	M
❑ Stage 0*	Tis	N0	M0
❑ Stage I	T1	N0	M0
❑ Stage IA	T1a	N0	M0
❑ Stage IA1	T1a1	N0	M0
❑ Stage IA2	T1a2	N0	M0
❑ Stage IB	T1b	N0	M0
❑ Stage IB1	T1b1	N0	M0
❑ Stage IB2	T1b2	N0	M0
❑ Stage II	T2	N0	M0
❑ Stage IIA	T2a	N0	M0
❑ Stage IIA1	T2a1	N0	M0
❑ Stage IIA1	T2a2	N0	M0
❑ Stage IIB	T2b	N0	M0
❑ Stage III	T3	N0	M0
❑ Stage IIIA	T3a	N0	M0
❑ Stage IIIB	T3b	Any N	M0
	T1-3	N1	M0
❑ Stage IVA	T4	Any N	M0
❑ Stage IVB	Any T	Any N	M1

*FIGO no longer includes Stage 0 (Tis)

❑ Stage unknown

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)

REQUIRED FOR STAGING: None

CLINICALLY SIGNIFICANT:

FIGO Stage: _____

Pelvic nodal status and method of assessment: _____

Paraaortic nodal status and method of assessment: _____

Distant (mediastinal, scalene) nodal status and method of assessment: _____

Histologic Grade (G) *(also known as overall grade)*

Grading system	*Grade*
❑ 2 grade system	❑ Grade I or 1
❑ 3 grade system	❑ Grade II or 2
❑ 4 grade system	❑ Grade III or 3
❑ No 2, 3, or 4 grade system is available	❑ Grade IV or 4

General Notes:
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

(continued from previous page)

ANATOMIC STAGE/PROGNOSTIC GROUPS (*CONTINUED*)

Sarcomas

Stage I	T1	N0	M0
Stage IA*	T1a	N0	M0
Stage IB*	T1b	N0	M0
Stage IC**	T1c	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T1, T2, T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

**Note*: Stage IA and IB differ from those applied for leiomyosarcoma and endometrial stromal sarcoma.

***Note*: Stage IC does not apply for leiomyosarcoma and endometrial stromal sarcoma.

ICD-O-3 HISTOLOGY CODE RANGES

8000–8576, 8890–8898, 8930–8933, 8940–8950, 8980–8981

INTRODUCTION

The classification for uterine cancers has been subdivided for the seventh edition of TNM in accordance with changes adopted by the International Federation of Gynecology and Obstetrics (FIGO) to have separate systems for endometrial adenocarcinomas and uterine sarcomas. The new schemas for sarcomas are fully described in publications by FIGO.

ANATOMY

Primary Site. The upper two-thirds of the uterus above the level of the internal cervical os is referred to as the uterine corpus. The oviducts (fallopian tubes) and the round ligaments enter the uterus at the upper and outer corners (cornu) of the pear-shaped organ. The portion of the uterus that is above a line connecting the tubo-uterine orifices is referred to as the uterine fundus. The lower third of the uterus is called the cervix and lower uterine segment. Tumor involvement of the cervical stroma is prognostically important and affects staging (T2). The new staging system no longer distinguishes endocervical mucosal/glandular involvement (formerly stage IIA). The location of the tumor must be carefully evaluated and recorded by the pathologist. The depth of tumor invasion into the myometrium is also of prognostic significance and should be included in the pathology report. Involvement of the ovaries by direct extension or metastases, or penetration of tumor to the uterine serosa is important to identify and classify the tumor as T3a.

Malignant cells in peritoneal cytology samples have been documented in approximately 10% of cases of presumed uterine confined endometrial cancer cases. The prognostic importance of positive cytology has been debated. Depth of myometrial invasion, tumor grade, and presence of extrauterine disease are felt to be more prognositically significant, and as such the 2008 FIGO staging system will no longer use peritoneal cytology for the purposes of staging (formerly T3a, FIGO stage IIIA). T3b lesions reflect regional extension of disease and include extension of the tumor through the myometrial wall of the uterus into the parametrium and/or extension/metastatic involvement of the vagina.

Regional Lymph Nodes. The regional lymph nodes are paired and each of the paired sites should be examined. The regional nodes are as follows:

Obturator
Internal iliac (hypogastric)
External iliac
Common iliac
Para-aortic
Presacral
Parametrial

For adequate evaluation of the regional lymph nodes, a representative evaluation of bilateral para-aortic and pelvic lymph nodes (including external iliac, internal iliac, and obturator nodes) should be documented in the operative and surgical pathology reports. Parametrial nodes are not commonly detected unless a radical hysterectomy is performed for cases with gross cervical stromal invasion.

For pN, histologic examination of regional lymphadenectomy specimens will ordinarily include six or more lymph nodes. For TNM staging, cases with fewer than six resected

Histopathology: Degree of Differentiation. Cases of carcinoma of the corpus uteri should be grouped according to the degree of differentiation of the adenocarcinoma as follows:

G1 5% or less of a nonsquamous or nonmorular solid growth pattern
G2 6–50% of a nonsquamous or nonmorular solid growth pattern
G3 More than 50% of a nonsquamous or nonmorular solid growth pattern

Notes on Pathologic Grading

1. Notable nuclear atypia, which exceeds that which is routinely expected for the architectural grade, increases the tumor grade by 1.
2. Serous, clear cell, and mixed mesodermal tumors are *high risk* and considered Grade 3.
3. Adenocarcinomas with benign squamous elements (squamous metaplasia) are graded according to the nuclear grade of the glandular component.

Uterine Sarcomas. (Includes Leiomyosarcoma, Endometrial Stromal Sarcoma, Adenosarcoma)

Leiomyosarcoma and Endometrial Stromal Sarcoma

Primary Tumor (T)

TNM Categories	*FIGO Stages*	*Definition*
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor limited to the uterus
T1a	IA	Tumor 5 cm or less in greatest dimension
T1b	IB	Tumor more than 5 cm
T2	II	Tumor extends beyond the uterus, within the pelvis
T2a	IIA	Tumor involves adnexa
T2b	IIB	Tumor involves other pelvic tissues
T3	III*	Tumor infiltrates abdominal tissues
T3a	IIIA	One site
T3b	IIIB	More than one site
T4	IVA	Tumor invades bladder or rectum

Note: Simultaneous tumors of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors.

*In this stage lesions must inifiltrate abdominal tissues and not just protrude into the abdominal cavity.

Regional Lymph Nodes (N)

NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC	Regional lymph node metastasis

Distant Metastasis (M)

M0		No distant metastasis
M1	IVB	Distant metastasis (excluding adnexa, pelvic and abdominal tissues)

Adenosarcoma

Primary Tumor (T)

TNM Categories	*FIGO Stages*	*Definition*
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor limited to the uterus
T1a	IA	Tumor limited to the endometrium/endocervix
T1b	IB	Tumor invades to less than half of the myometrium
T1c	IC	Tumor invades more than half of the myometrium
T2	II	Tumor extends beyond the uterus, within the pelvis
T2a	IIA	Tumor involves adnexa
T2b	IIB	Tumor involves other pelvic tissues
T3	III*	Tumor involves abdominal tissues
T3a	IIIA	One site
T3b	IIIB	More than one site
T4	IVA	Tumor invades bladder or rectum

Note: Simultaneous tumors of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors.

*In this stage lesions must infiltrate abdominal tissues and not just protrude into the abdominal cavity.

Regional Lymph Nodes (N)

NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC	Regional lymph node metastasis

Distant Metastasis (M)

M0		No distant metastasis
M1	IVB	Distant metastasis (excluding adnexa, pelvic and abdominal tissues)

Uterine Sarcomas

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage I	T1	N0	M0
Stage IA*	T1a	N0	M0
Stage IB*	T1b	N0	M0
Stage IC**	T1c	N0	M0

ANATOMIC STAGE/PROGNOSTIC GROUPS (*CONTINUED*)

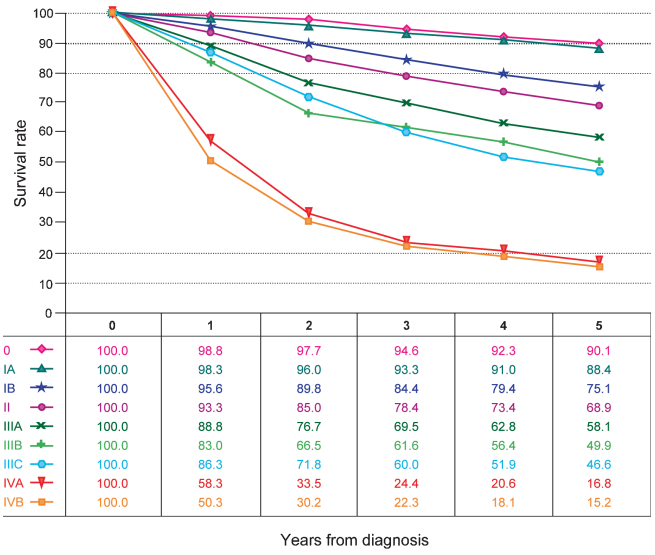
Stage II	T2	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T1, T2, T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

**Note*: Stage IA and IB differ from those applied for leiomyosarcoma and endometrial stromal sarcoma.

***Note*: Stage IC does not apply for leiomyosarcoma and endometrial stromal sarcoma.

HISTOPATHOLOGIC TYPE

Endometrioid carcinomas
Villoglandular adenocarcinoma
Adenocarcinoma with benign squamous elements, squamous metaplasia, or squamous differentiation (adenoacanthoma)
Adenosquamous carcinoma (mixed adenocarcinoma and squamous cell carcinoma)
Mucinous adenocarcinoma
Serous adenocarcinoma (papillary serous)
Clear cell adenocarcinoma
Squamous cell carcinoma
Undifferentiated carcinoma
Malignant mixed mesodermal tumors
Sarcomas: leiomyosarcomas, endometrial stromal sarcomas, adenosarcomas, carcinosarcomas.



	0	1	2	3	4	5
0	100.0	98.8	97.7	94.6	92.3	90.1
IA	100.0	98.3	96.0	93.3	91.0	88.4
IB	100.0	95.6	89.8	84.4	79.4	75.1
II	100.0	93.3	85.0	78.4	73.4	68.9
IIIA	100.0	88.8	76.7	69.5	62.8	58.1
IIIB	100.0	83.0	66.5	61.6	56.4	49.9
IIIC	100.0	86.3	71.8	60.0	51.9	46.6
IVA	100.0	58.3	33.5	24.4	20.6	16.8
IVB	100.0	50.3	30.2	22.3	18.1	15.2

FIGURE 36.1. Observed survival rates for 21,904 cases with carcinoma of the corpus uterus. Data from the National Cancer Data Base (Commission on Cancer of the American College of Surgeons and the American Cancer Society) diagnosed in years 2000–2002. Stage 0 includes 415 patients; Stage IA, 12,868; Stage IB, 2,559; Stage II, 2,098; Stage IIIA, 929; Stage IIIB, 91; Stage IIIC, 1,353; Stage IVA, 229; and Stage IVB, 1,362.

OUTCOMES RESULTS

The significance of clinical compared with surgical/pathologic staging is shown in Figure 36.1. The prognosis for patients with clinical Stage I disease is similar to that for women with surgical Stage III, and those with clinical Stage III cancers have the same prognosis as patients with surgical Stage IV lesions. These findings also emphasize the importance of clearly separating patients who are staged clinically from those who have more accurate surgical/pathologic staging recommended by AJCC and FIGO.

BIBLIOGRAPHY

Cirisano FD, Robboy SF, Dodge RK, et al. The outcome of stage I–II clinically and surgically staged papillary serous and clear cell endometrial cancers when compared with endometrioid carcinoma. Gynecol Oncol. 2000;77:55–65.

Colombi RP. Sarcomatoid carcinomas of the female genital tract (malignant mixed mullerian tumors). Semin Diagn Pathol. 1993;10:169–75.

Creasman W, Morrow P, Bundy B, Homesley H, Graham J, Heller P. Surgical pathologic spread patterns of endometrial cancer: a Gynecologic Oncology Group study. Cancer. 1987;60:2035–41.

Creasman W, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri: FIGO Annual Report. J Epidemiol Biostat. 2001;6:45–86.

Creutzberg CL, van Patten LE, Koper PC, et al. Surgery and postop radiotherapy vs surgery alone for patients with stage I endometrial carcinoma: multicenter randomized trial. PORTEC Study Group. Lancet. 2000;355:1404–11.

FIGO Committee on Gynecologic Cancer. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynecol Obstet. 2009;105:103–4.

FIGO Committee on Gyn Onc Report. FIGO staging for uterine sarcomas. Int J Gynaecol Obstet. 2009;104:179.

Gershenson DM, editor. Guidelines for referral to a gynecologic oncologist: rationale and benefits. Gynecol Oncol. 2000;78:S1–13.

Mariani A, Webb M, Keeney G, Aletti G, Podratz K. Assessment of prognostic factors in stage IIIA endometrial cacer. Gynecol Oncol. 2002;86:38–44.

Marth C, Windbichler G, Petru E, et al. Parity as an independent prognostic factor in malignant mixed mesodermal tumors of the endometrium. Gynecol Oncol. 1997;64:121–5.

Panici PB, Basile S, Maneschi F, et al. Systemic pelvic lymphadenectomy vs no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst. 2008;100(23):1707.

CORPUS UTERI CARCINOMA STAGING FORM
(Carcinosarcomas should be staged as carcinomas)

ANATOMIC STAGE • PROGNOSTIC GROUPS

CLINICAL

GROUP	T	N	M
❑ 0*	Tis	N0	M0
❑ I	T1	N0	M0
❑ IA	T1a	N0	M0
❑ IB	T1b	N0	M0
❑ II	T2	N0	M0
❑ III	T3	N0	M0
❑ IIIA	T3a	N0	M0
❑ IIIB	T3b	N0	M0
❑ IIIC1	T1-T3	N1	M0
❑ IIIC2	T1-T3	N2	M0
❑ IVA	T4	Any N	M0
❑ IVB	Any T	Any N	M1

*FIGO no longer includes Stage 0 (Tis)
Carcinosarcomas should be staged as carcinoma.
❑ Stage unknown

PATHOLOGIC

GROUP	T	N	M
❑ 0*	Tis	N0	M0
❑ I	T1	N0	M0
❑ IA	T1a	N0	M0
❑ IB	T1b	N0	M0
❑ II	T2	N0	M0
❑ III	T3	N0	M0
❑ IIIA	T3a	N0	M0
❑ IIIB	T3b	N0	M0
❑ IIIC1	T1-T3	N1	M0
❑ IIIC2	T1-T3	N2	M0
❑ IVA	T4	Any N	M0
❑ IVB	Any T	Any N	M1

*FIGO no longer includes Stage 0 (Tis)
Carcinosarcomas should be staged as carcinoma.
❑ Stage unknown

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)

REQUIRED FOR STAGING: None

CLINICALLY SIGNIFICANT:

FIGO Stage: _____

Peritoneal cytology results: _____

Pelvic nodal dissection with number of nodes positive/examined: _____

Para-aortic nodal dissection with number of nodes positive/examined: _____

Percentage of non-endometrioid cell type in mixed histology tumors: _____

Omentectomy performed: _____

Histologic Grade (G) *(also known as overall grade)*

Grading system	*Grade*
❑ 2 grade system	❑ Grade I or 1
❑ 3 grade system	❑ Grade II or 2
❑ 4 grade system	❑ Grade III or 3
❑ No 2, 3, or 4 grade system is available	❑ Grade IV or 4

Endometrioid adenocarcinomas should be graded according to the degree of differentiation of the adenocarcinoma as follows:

❑ G1	5% or less of a non-squamous or non-morular solid growth pattern
❑ G2	6% to 50% of a non-squamous or non-morular solid growth pattern
❑ G3	More than 50% of a non-squamous or non-morular solid growth pattern

Notes on Pathologic Grading

1. Notable nuclear atypia, inappropriate for the architectural grade, raises the grade by one.
2. Serous, clear cell, and mixed mesodermal tumors are Grade 3.

General Notes:
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

a prefix designates the stage determined at autopsy: aTNM.

surgical margins is data field recorded by registrars describing the surgical margins of the resected primary site specimen as determined only by the pathology report.

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

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37

Ovary and Primary Peritoneal Carcinoma

At-A-Glance

SUMMARY OF CHANGES

- The definition of TNM and the Stage Grouping for this chapter have not changed from the Sixth Edition
- Primary peritoneal carcinoma has been included in this chapter

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IC	T1c	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIC	T2c	N0	M0
Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T3c	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

ICD-O-3 TOPOGRAPHY CODES

C56.9 Ovary
C48.1 Specified parts of peritoneum (female only)
C48.2 Peritoneum (female only)
C48.8 Overlapping lesion of retroperitoneum and peritoneum (female only)

ICD-O-3 HISTOLOGY CODE RANGES

8000–8576, 8590–8671, 8930–9110 (C56.9 only)
8000–8576, 8590–8671, 8930–8934, 8940–9110 (C48.1–C48.8 only)

ANATOMY

Primary Site. The ovaries are a pair of solid, flattened ovoids 2–4 cm in diameter that are connected by a peritoneal fold to the broad ligament and by the infundibulopelvic ligament to the lateral wall of the pelvis. They are attached medially to the uterus by the utero-ovarian ligament.

In some cases, an adenocarcinoma is primary in the peritoneum. The ovaries are not involved or are only involved with minimal surface implants. The clinical presentation, surgical therapy, chemotherapy, and prognosis of these peritoneal tumors mirror those of papillary serous carcinoma of the ovary. Patients who undergo prophylactic oophorectomy for a familial history of ovarian cancer appear to retain a 1–2% chance of developing peritoneal adenocarcinoma, which is histopathologically and clinically similar to primary ovarian cancer.

Regional Lymph Nodes. The lymphatic drainage occurs by the infundibulopelvic and round ligament trunks and an external iliac accessory route into the following regional nodes:

External iliac
Internal iliac (hypogastric)
Obturator
Common iliac
Para-aortic

OVARY STAGING FORM

CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS		PATHOLOGIC *Extent of disease through completion of definitive surgery*
❒ y clinical – staging completed after neoadjuvant therapy but before subsequent surgery	**TUMOR SIZE:** _____	**LATERALITY:** ☐ left ☐ right ☐ bilateral	❒ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery

TNM CATEGORY	FIGO STAGE	PRIMARY TUMOR (T)	TNM CATEGORY	FIGO STAGE
❑ TX		Primary tumor cannot be assessed	❑ TX	
❑ T0		No evidence of primary tumor	❑ T0	
❑ T1	I	Tumor limited to ovaries (one or both)	❑ T1	I
❑ T1a	IA	Tumor limited to one ovary; capsule intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings	❑ T1a	IA
❑ T1b	IB	Tumor limited to both ovaries; capsules intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings	❑ T1b	IB
❑ T1c	IC	Tumor limited to one or both ovaries with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings	❑ T1c	IC
❑ T2	II	Tumor involves one or both ovaries with pelvic extension and/or implants	❑ T2	II
❑ T2a	IIA	Extension and/or implants on uterus and/or tube(s). No malignant cells in ascites or peritoneal washings	❑ T2a	IIA
❑ T2b	IIB	Extension to and/or implants on other pelvic tissues. No malignant cells in ascites or peritoneal washings	❑ T2b	IIB
❑ T2c	IIC	Pelvic extension and/or implants (T2a or T2b) with malignant cells in ascites or peritoneal washings	❑ T2c	IIC
❑ T3	III	Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis	❑ T3	III
❑ T3a	IIIA	Microscopic peritoneal metastasis beyond pelvis (no macroscopic tumor)	❑ T3a	IIIA
❑ T3b	IIIB	Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension	❑ T3b	IIIB
❑ T3c	IIIC	Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis	❑ T3c	IIIC
		Note: Liver capsule metastasis T3/Stage III; liver parenchymal metastasis M1/Stage IV. Pleural effusion must have positive cytology for M1/Stage IV.		

TNM CATEGORY	FIGO STAGE	REGIONAL LYMPH NODES (N)	TNM CATEGORY	FIGO STAGE
❑ NX		Regional lymph nodes cannot be assessed	❑ NX	
❑ N0		No regional lymph node metastasis	❑ N0	
❑ N1	IIIC	Regional lymph node metastasis	❑ N1	IIIC

TNM CATEGORY	FIGO STAGE	DISTANT METASTASIS (M)	TNM CATEGORY	FIGO STAGE
❑ M0		No distant metastasis (no pathologic M0; use clinical M to complete stage group)		
❑ M1	IV	Distant metastasis (excludes peritoneal metastasis)	❑ M1	IV

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FALLOPIAN TUBE STAGING FORM

CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS	PATHOLOGIC *Extent of disease through completion of definitive surgery*
❒ y clinical – staging completed after neoadjuvant therapy but before subsequent surgery	**TUMOR SIZE:** _____ **LATERALITY:** ☐ left ☐ right ☐ bilateral	❒ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery

TNM CATEGORY	FIGO STAGE	PRIMARY TUMOR (T)	TNM CATEGORY	FIGO STAGE
❑ TX		Primary tumor cannot be assessed	❑ TX	
❑ T0		No evidence of primary tumor	❑ T0	
❑ Tis	*	Carcinoma *in situ* (limited to tubal mucosa)	❑ Tis	*
❑ T1	I	Tumor limited to the fallopian tube(s)	❑ T1	I
❑ T1a	IA	Tumor limited to one tube, without penetrating the serosal surface; no ascites	❑ T1a	IA
❑ T1b	IB	Tumor limited to both tubes, without penetrating the serosal surface; no ascites	❑ T1b	IB
❑ T1c	IC	Tumor limited to one or both tubes with extension onto or through the tubal serosa, or with malignant cells in ascites or peritoneal washings	❑ T1c	IC
❑ T2	II	Tumor involves one or both fallopian tubes with pelvic extension	❑ T2	II
❑ T2a	IIA	Extension and/or metastasis to the uterus and/or ovaries	❑ T2a	IIA
❑ T2b	IIB	Extension to other pelvic structures	❑ T2b	IIB
❑ T2c	IIC	Pelvic extension with malignant cells in ascites or peritoneal washings	❑ T2c	IIC
❑ T3	III	Tumor involves one or both fallopian tubes, with peritoneal implants outside the pelvis	❑ T3	III
❑ T3a	IIIA	Microscopic peritoneal metastasis outside the pelvis	❑ T3a	IIIA
❑ T3b	IIIB	Macroscopic peritoneal metastasis outside the pelvis 2 cm or less in greatest dimension	❑ T3b	IIIB
❑ T3c	IIIC	Peritoneal metastasis outside the pelvis and more than 2 cm in diameter	❑ T3c	IIIC
		* FIGO no longer includes Stage 0 (Tis)		
		Note: Liver capsule metastasis is T3/Stage III; liver parenchymal metastasis M1/Stage IV. Pleural effusion must have positive cytology for M1/Stage IV.		

TNM CATEGORY	FIGO STAGE	REGIONAL LYMPH NODES (N)	TNM CATEGORY	FIGO STAGE
❑ NX		Regional lymph nodes cannot be assessed	❑ NX	
❑ N0		No regional lymph node metastasis	❑ N0	
❑ N1	IIIC	Regional lymph node metastasis	❑ N1	IIIC

TNM CATEGORY	FIGO STAGE	DISTANT METASTASIS (M)	TNM CATEGORY	FIGO STAGE
❑ M0		No distant metastasis (no pathologic M0; use clinical M to complete stage group)		
❑ M1	IV	Distant metastasis (excludes metastasis within the peritoneal cavity)	❑ M1	IV

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factor scoring system. The prognostic scores are 0, 1, 2, and 4 for the individual risk factors. The current prognostic scoring system eliminates the ABO blood group risk factors that were featured in the WHO scoring system and upgrades the risk factor for liver metastasis from 2 to 4, the highest category. Low risk is a score of 6 or less, and high risk is a score of 7 or greater.

PROGNOSTIC FEATURES

Outcomes Results. Gestational trophoblastic tumors may require only uterine evacuation for treatment, but even when chemotherapy is required, cure rates approach 100%. Prognostic factors are listed in the Prognostic Scoring Index. Patients with low-risk disease are usually treated with single-agent chemotherapy, whereas combined, multiple-agent chemotherapy usually results in a cure for high-risk patients.

DEFINITIONS OF TNM

Primary Tumor (T)

TNM Categories	*FIGO Stages*	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor confined to uterus
T2	II	Tumor extends to other genital structures (ovary, tube, vagina, broad ligaments) by metastasis or direct extension

Distant Metastasis (M)

TNM Categories	*FIGO Stages*	
M0		No distant metastasis
M1		Distant metastasis
M1a	III	Lung metastasis
M1b	IV	All other distant metastasis

ANATOMIC STAGE/PROGNOSTIC GROUPS

Group	T	M	Risk Factors
Stage I	T1	M0	Unknown
Stage IA	T1	M0	Low risk
Stage IB	T1	M0	High risk
Stage II	T2	M0	Unknown
Stage IIA	T2	M0	Low risk
Stage IIB	T2	M0	High risk
Stage III	Any T	M1a	Unknown
Stage IIIA	Any T	M1a	Low risk
Stage IIIB	Any T	M1a	High risk
Stage IV	Any T	M1b	Unknown
Stage IVA	Any T	M1b	Low risk
Stage IVB	Any T	M1b	High risk

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)
(Recommended for Collection)

Required for staging	Risk factors (Table 39.1)
Clinically significant	FIGO Stage

HISTOLOGIC GRADE (G)

Grade is reported in registry systems by the grade value. A two-grade, three-grade, or four-grade system may be used. If a grading system is not specified, generally the following system is used:

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

HISTOPATHOLOGIC TYPE

- Hydatidiform mole
  - Complete
  - Partial
- Invasive hydatidiform mole
- Choriocarcinoma
- Placental site trophoblastic tumors

BIBLIOGRAPHY

Horn LC, Bilek K. Histologic classification and staging of gestational trophoblastic disease. Gen Diagn Pathol. 1997;143:87–101.

Lage JM. Protocol for the examination of specimens from patients with gestational trophoblastic malignancies: a basis for checklists. Cancer Committee, College of American Pathologists. Arch Pathol Lab Med. 1999;123:50–4.

Ngan HYS, Odicino F, Maisonneuve P, et al. Gestational trophoblastic diseases. FIGO annual report. J Epidemiol Biostat. 2001;6:175–84.

GESTATIONAL TROPHOBLASTIC TUMORS STAGING FORM

CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS		PATHOLOGIC *Extent of disease through completion of definitive surgery*
❒ y clinical – staging completed after neoadjuvant therapy but before subsequent surgery	**TUMOR SIZE:** _____	**LATERALITY:** ☐ left ☐ right ☐ bilateral	❒ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery

TNM CATEGORY	FIGO STAGE	PRIMARY TUMOR (T)	TNM CATEGORY	FIGO STAGE
❑ TX		Primary tumor cannot be assessed	❑ TX	
❑ T0		No evidence of primary tumor	❑ T0	
❑ T1	I	Tumor confined to uterus	❑ T1	I
❑ T2	II	Tumor extends to other genital structures (ovary, tube, vagina, broad ligaments) by metastasis or direct extension	❑ T2	II
		REGIONAL LYMPH NODES (N)		
		There is no regional nodal designation in the staging of these tumors. Nodal metastases should be classified as metastatic (M1) disease.		
TNM CATEGORY	FIGO STAGE	DISTANT METASTASIS (M)	TNM CATEGORY	FIGO STAGE
❑ M0		No distant metastasis (no pathologic M0; use clinical M to complete stage group)		
❑ M1		Distant metastasis	❑ M1	
❑ M1a	III	Lung metastasis	❑ M1a	III
❑ M1b	IV	All other distant metastasis	❑ M1b	IV

ANATOMIC STAGE • PROGNOSTIC GROUPS

CLINICAL

GROUP	T	N	M	RISK SCORE
❑ I	T1		M0	Unknown
❑ IA	T1		M0	Low risk
❑ IB	T1		M0	High risk
❑ II	T2		M0	Unknown
❑ IIA	T2		M0	Low risk
❑ IIB	T2		M0	High risk
❑ III	Any T		M1a	Unknown
❑ IIIA	Any T		M1a	Low risk
❑ IIIB	Any T		M1a	High risk
❑ IV	Any T		M1b	Unknown
❑ IVA	Any T		M1b	Low risk
❑ IVB	Any T		M1b	High risk

❑ Stage unknown

PATHOLOGIC

GROUP	T	N	M	RISK SCORE
❑ I	T1		M0	Unknown
❑ IA	T1		M0	Low risk
❑ IB	T1		M0	High risk
❑ II	T2		M0	Unknown
❑ IIA	T2		M0	Low risk
❑ IIB	T2		M0	High risk
❑ III	Any T		M1a	Unknown
❑ IIIA	Any T		M1a	Low risk
❑ IIIB	Any T		M1a	High risk
❑ IV	Any T		M1b	Unknown
❑ IVA	Any T		M1b	Low risk
❑ IVB	Any T		M1b	High risk

❑ Stage unknown

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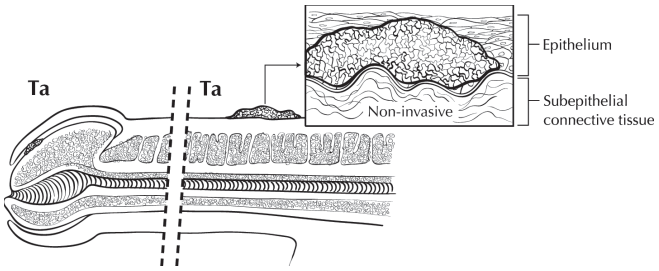

FIGURE 40.1. Ta: Noninvasive verrucous carcinoma.

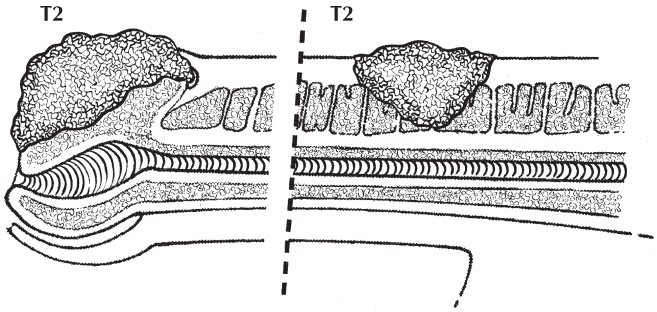

FIGURE 40.3. T2: Tumor invading corpus spongiosum or cavernosum.

Clinical Staging

Primary Tumor. Clinical examination by palpation should be performed. Penile imaging studies may occasionally be useful. Histologic confirmation provided by an adequate excisional-incisional biopsy to determine the extent of anatomic invasion, tumor grade, and the presence of lymphovascular invasion is required.

Regional Lymph Nodes. Clinical examination by palpation of the inguinal region is required. Computed tomography is a useful adjunct to palpation in patients with palpable inguinal adenopathy or those in whom palpation is unreliable (i.e., obese, prior inguinal surgery)

Distant Metastasis. Clinical examination along with cross-sectional imaging and chest radiography should be performed as appropriate.

Pathologic Staging. Complete resection of the primary site with appropriate margins is required. Lymphadenectomy is performed in those patients felt to be at significant risk for metastasis by virtue of palpable adenopathy or histopathologic features of the primary tumor. Pathologic confirmation can also be achieved via lymph node biopsy of clinically suspicious lymph nodes. The definitions of primary tumor (T) for Ta, T1, T2, T3, and T4 are illustrated in Figures 40.1–40.5.

DEFINITIONS OF TNM

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Ta	Noninvasive verrucous carcinoma*
T1a	Tumor invades subepithelial connective tissue without lymph vascular invasion and is not poorly differentiated (i.e., grade 3–4)
T1b	Tumor invades subepithelial connective tissue with lymph vascular invasion or is poorly differentiated
T2	Tumor invades corpus spongiosum or cavernosum
T3	Tumor invades urethra
T4	Tumor invades other adjacent structures

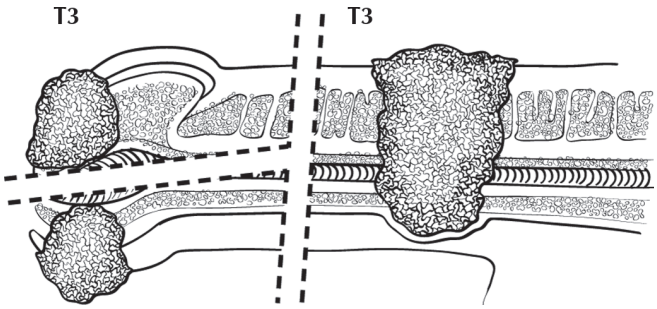

FIGURE 40.4. T3: Tumor invading urethra.

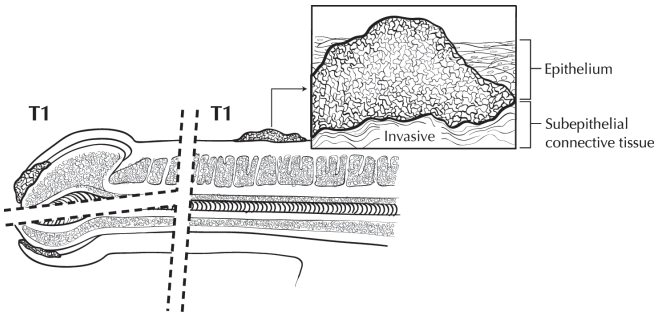

FIGURE 40.2. T1: Tumor invading subepithelial connective tissue; T1a: no vascular invasion and not poorly differentiated; and T1b: high grade and/or poorly differentiated.

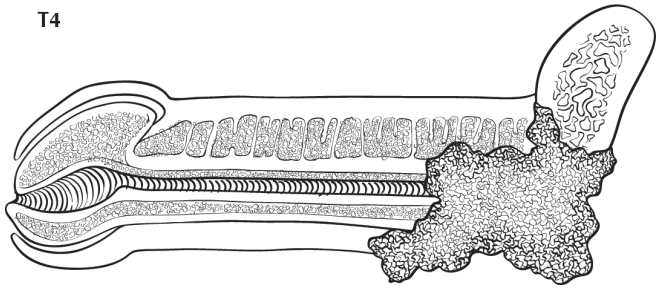

FIGURE 40.5. T4: Tumor invading other adjacent structures including prostate.

PENIS STAGING FORM

CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS		PATHOLOGIC *Extent of disease through completion of definitive surgery*
❒ y clinical – staging completed after neoadjuvant therapy but before subsequent surgery	**TUMOR SIZE:** _____	**LATERALITY:** ☐ left ☐ right ☐ bilateral	❒ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	PRIMARY TUMOR (T)		
❑ TX	Primary tumor cannot be assessed		❑ TX
❑ T0	No evidence of primary tumor		❑ T0
❑ Tis	Carcinoma *in situ*		❑ Tis
❑ Ta	Noninvasive verrucous carcinoma*		❑ Ta
❑ T1a	Tumor invades subepithelial connective tissue without lymph vascular invasion and is not poorly differentiated (i.e., grade 3-4)		❑ T1a
❑ T1b	Tumor invades subepithelial connective tissue with LVI or is poorly differentiated		❑ T1b
❑ T2	Tumor invades corpus spongiosum or cavernosum		❑ T2
❑ T3	Tumor invades urethra		❑ T3
❑ T4	Tumor invades other adjacent structures		❑ T4
	*Note: Broad pushing penetration (invasion) is permitted - destructive invasion is against this diagnosis		
	REGIONAL LYMPH NODES (N)		
❑ NX	Regional lymph nodes cannot be assessed*		
pNX	Regional lymph nodes cannot be assessed**		❑ pNX
❑ N0	No palpable or visibly enlarged inguinal lymph nodes*		
pN0	No regional lymph node metastasis**		❑ pN0
❑ N1	Palpable mobile unilateral inguinal lymph node*		
pN1	Metastasis in a single inguinal lymph node**		❑ pN1
❑ N2	Palpable mobile multiple or bilateral inguinal lymph nodes*		
pN2	Metastasis in multiple or bilateral inguinal lymph nodes**		❑ pN2
❑ N3	Palpable fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral*		
pN3	Extranodal extension of lymph node metastasis or pelvic lymph node(s) unilateral or bilateral**		❑ pN3
	*Based upon palpation, imaging **Based upon biopsy, or surgical excision		
	DISTANT METASTASIS (M)		
❑ M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)		
❑ M1	Distant metastasis*		❑ M1
	*Note: Lymph node metastasis outside of the true pelvis in addition to visceral or bone sites.		

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Prostate

(Sarcomas and transitional cell carcinomas are not included)

At-A-Glance

SUMMARY OF CHANGES

- Extraprostatic invasion with microscopic bladder neck invasion (T4) is included with T3a
- Gleason Score now recognized as the preferred grading system
- Prognostic factors have been incorporated in the Anatomic Stage/Prognostic Groups
  - Gleason Score
  - Preoperative prostate-specific antigen (PSA)

ANATOMIC STAGE/PROGNOSTIC GROUPS*

Group	T	N	M	PSA	Gleason
I	T1a – c	N0	M0	PSA < 10	Gleason ≤ 6
	T2a	N0	M0	PSA < 10	Gleason ≤ 6
	T1 – 2a	N0	M0	PSA X	Gleason X
IIA	T1a – c	N0	M0	PSA < 20	Gleason 7
	T1a – c	N0	M0	PSA ≥ 10 < 20	Gleason ≤ 6
	T2a	N0	M0	PSA ≥ 10 < 20	Gleason ≤ 6
	T2a	N0	M0	PSA < 20	Gleason 7
	T2b	N0	M0	PSA < 20	Gleason ≤ 7
	T2b	N0	M0	PSA X	Gleason X
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1 – 2	N0	M0	PSA ≥ 20	Any Gleason
	T1 – 2	N0	M0	Any PSA	Gleason ≥ 8
III	T3a – b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

* When either PSA or Gleason is not available, grouping should be determined by T stage and/or either PSA or Gleason as available.

ICD-O-3 TOPOGRAPHY CODES

C61.9 Prostate gland

ICD-O-3 HISTOLOGY CODE RANGES

8000–8110, 8140–8576, 8940–8950, 8980–8981

INTRODUCTION

Prostate cancer is the most common noncutaneous cancer in men, with increasing incidence in older age groups. Prostate cancer has a tendency to metastasize to bone. Earlier detection is possible with a blood test, prostate-specific antigen (PSA), and the diagnosis is generally made using transrectal ultrasound (TRUS) guided biopsy.

The incidence of both clinical and latent carcinoma increases with age. However, this cancer is rarely diagnosed clinically in men under 40 years of age. There are substantial limitations in the ability of both digital rectal examination (DRE) and TRUS to precisely define the size or local extent of disease; DRE is currently the most common modality used to define the local stage. Heterogeneity within the T1c category resulting from inherent limitations of either DRE or imaging to quantify the cancer may be balanced by the inclusion of other prognostic factors, such as histologic grade, PSA level, and possibly extent of cancer on needle biopsies that contain cancer. Diagnosis of clinically suspicious areas of the prostate can be confirmed histologically by needle biopsy. Less commonly, prostate cancer may be diagnosed by inspection of the

before the first definitive treatment may be used for clinical staging. Imaging techniques may be valuable in some cases; TRUS is the most commonly used imaging tool, but it has a poor ability to identify tumor location and extent. Tumor that is found in one or both lobes by needle biopsy, but is not palpable or visible by imaging, is classified as T1c. Considerable uncertainty exists about the ability of imaging to define the extent of a nonpalpable lesion (see the definition of T1c below). For research purposes, investigators should specify whether clinical staging into the T1c category is based on DRE only or on DRE plus TRUS. In general, most patients diagnosed in an environment of ubiquitous PSA screening will be at a low risk of positive nodes or metastases, and the risk of false-positive imaging studies in asymptomatic patients has exceeded the frequency of true-positive or true-negative studies in several reports. For this reason, in patients with Gleason scores less than 7 and PSA values <20 ng/ml, imaging studies will oftentimes not be helpful in staging and should not be routinely performed.

If either the DRE or PSA test suggests neoplasm, a transrectal ultrasound-guided needle biopsy of the prostate gland is usually performed in healthy men suspected of as having prostate cancer. Alternatively, prostate cancer may be found in the tissue obtained during a transurethral resection of the prostate (TURP), although this procedure is becoming less common. Recent studies, however, support the notion that there are few clinical differences in outcome for patients with T1c compared to T2a. The major value of maintaining the category defined as T1c appears to be that it helps to define the clinical circumstances that resulted in a diagnosis being made (i.e., screening) and the lack of palpable disease. The distinction between T1c by palpation and T2a based on imaging is problematic however, because of (1) inconsistent use of imaging as a clinical staging tool, (2) interobserver variability of imaging modalities, and (3) the lack of sensitivity and specificity of imaging technologies.

The digital rectal examination (DRE) is still considered the "gold standard" for staging although it is insensitive for detecting extracapsular tumor extension. Although imaging could one day potentially improve clinical staging accuracy, interobserver reproducibility, problems with patient selection and contradictory results have limited the utility of imaging in clinical staging, and imaging alone cannot replace the DRE as the clinical staging standard. Transrectal ultrasound (TRUS) has not been proven to be satisfactory for predicting extracapsular extension. Color Doppler and power Doppler identify increased vascularity but have not yet been shown to improve staging accuracy. Similarly, contrast-enhanced and 3D US has not yet been tested or shown to improve the delineation of the cancer and prostate capsule. Endorectal coil magnetic resonance imaging MRI (erMRI) provides high spatial resolution. Three major techniques that have been used to stage prostate cancer with MRI are T2 weighted MRI, MR spectroscopic imaging (MRSI), and dynamic contrast-enhanced MRI (DCE-MRI). None of these approaches have been proven to be consistently helpful in staging attempts. Since the significant weight of the clinical data utilizes DRE, it remains the critical component of clinical staging.

Pathologic Staging. Documenting and reporting pathologic staging parameters in radical prostatectomy specimens is a key component in providing optimal management for patients.

In general, total prostatectomy including regional lymph node dissection with full histologic evaluation is required for complete pathologic classification. However, under certain circumstances, pathologic T classification can be determined with other means. For example, (1) positive biopsy of the rectum permits a pT4 classification without prostatectomy, and (2) a biopsy revealing carcinoma in extraprostatic soft tissue permits a pT3 classification, as does a biopsy revealing adenocarcinoma infiltrating the seminal vesicles. There is no pT1 category because there is insufficient tissue to assess the highest pT category.

In addition to pathologic stage, independent prognostic factors for survival have been identified for prostate cancer. These include number of positive biopsy cores, comorbid illnesses, Gleason score, serum PSA, and surgical margin status.

It is of relevance to review studies assessing the practicality and prognostic significance of previous versions of the AJCC system with respect to prostate cancer particularly in terms of the clinical and pathological sub staging of pT2, pT3, and pT4 subgroups.

pT2. The sixth edition of the AJCC TNM staging system subdivides pT2 disease into three categories pT2a, pT2b, pT2c as determined by involvement of one half of one side, more than one half of one side, and involvement of both sides of the prostate gland. This system has been relied upon as a broad surrogate to describe cancer volume, which can be correlated to risk of clinical relapse. Several retrospective outcome data analyses have challenged the utility of this subdivision and these data sets were reviewed during the creation of the seventh edition of the AJCC pathologic staging system. Insufficient evidence was found to justify collapsing pT2a and pT2b stages into a single stage, and in fact conflicting results exist in the currently available literature. No data exist to allow correlation of PT2 stage subgroupings with survival in localized prostate cancer due to the indolent and prolonged clinical course of the disease. Continued follow-up and analysis of large multi-institutional data sets and central cancer registry data is encouraged to allow resolution of this question in future versions of the TNM system.

pT3. The sixth edition of the AJCC TNM staging system subdivides pT3 disease into two categories pT3a and pT3b as determined by the presence of extracapsular invasion in any location and presence of seminal vesicle invasion with or without extracapsular invasion. The 1992 version of the AJCC TNM system (fifth edition) subdivided patients with extracapsular extension into either unilateral or bilateral and separated seminal vesicle involvement. Several retrospective outcome data analyses have challenged the utility of eliminating this subdivision in the subsequent sixth edition.

A thorough review of these analyses has revealed conflicting evidence regarding the correlation of subdividing unilateral and bilateral extracapsular extension and biochemical recurrence rates following surgery. Again, definitive data do not exist to allow correlation of particular pT3 stage subgroupings with survival in localized prostate cancer, and a reversion to the previous subdividing classification was not made. Data continue to be accumulated in the NCDB and other institutional databases to help determine the pT3 staging system.

pT4. In the sixth edition of the AJCC TNM system pathologic T4 substage included patients with microscopic finding of bladder invasion. Four large retrospective analyses have addressed this issue, and each series has revealed that microscopic involvement of the bladder neck tissue by prostate cancer does not independently predict a significantly worse prognosis than extracapsular extension in general. Therefore, microscopic bladder neck invasion will now be considered within the category of pT3a.

Surgical Margin Status. Perhaps one of the more extensively debated aspects of pathologic staging and risk stratification is one that is technically not an element of the current AJCC TNM staging system, namely the status of surgical resection margins in radical prostatectomy specimens. There is controversy regarding the "parameters or elements" to be reported in the case of identifying positive surgical margins in resected glands. While most agree that the pT stage regardless of the margin status needs to be documented, there is no consensus on what aspects of surgical margin involvement are important to report. Although the status of surgical margins per se is not an element, the prognostic importance of the phenomenon including its potential impact for further postsurgical treatment and outcome is an important prognostic factor. In reporting pathologic results of prostatectomy specimens pT stage should be reported along with margin status and a positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease) as is currently the case.

PROGNOSTIC FEATURES

An increasing number of proposed molecular markers (such as ploidy, p53, and bcl-2) as well as other clinical features have been identified that may predict stage at diagnosis and outcomes following therapy. A number of algorithms have been published that enable the merging of these data to predict local stage, risk of positive nodes, or risk of treatment failure. Each of these predictive tools employ common as well as unique variables and vary in their evaluation technique. Within the confines of the TNM staging, the clinical predictors of serum prostate-specific antigen, Gleason score, and tumor stage all have a clear, recognized, and significant impact on prognosis.

Recent studies have demonstrated that Gleason score provides extremely important information about prognosis. In an analysis, conducted by the Radiation Therapy Oncology Group (RTOG), of nearly 1,500 men treated on prospective randomized trials, Gleason score was the single most important predictor of death from prostate cancer. Combined with the AJCC stage, investigators demonstrated that four prognostic subgroups could be identified that allowed disease-specific survival to be predicted at 5, 10, and 15 years. Additional studies conducted by the RTOG also demonstrated that a pretreatment PSA > 20 ng/ml predicts a greater likelihood of distant failure and a greater need for hormonal therapy. A recent validation study confirmed that a PSA > 20 ng/ml was associated with a greater risk of prostate cancer death.

Thus, in addition to the AJCC clinical stage, pretreatment PSA and Gleason score provide important prognostic information that might affect decisions regarding therapy. In an attempt to better stratify these patients compared to the previous stage groups and avoid the large number of patients previously placed in stage group 1, the seventh edition includes a new prognostic staging for clinically localized (T1 and T2) disease that include these clinically based variables. Any type of grouping scheme such as this will not apply equally well to every individual patient situation, and this grouping still is primarily based on anatomic clinical T staging, the crux of the TNM staging historically. Other clinical features as well as pathologic features postprostatectomy, such as the number/percentage of positive biopsies and surgical margin status, likely provide additional prognostic information, and other prognostic tools that go well beyond the TNM structure may be more accurate for an individual patient. As a result, data continue to be collected in the National Cancer Database by registrars to provide long-term confirmatory data on the independent impact of multiple variables on prognosis.

OUTCOMES BY STAGE, GRADE, AND PSA

A number of endpoints are useful in assessing disease outcomes following therapy. Because the vast majority of patients diagnosed with prostate cancer are diagnosed with clinically localized disease, similar to pretreatment tools, multiple predictive models for clinical outcome have been proposed posttherapy. Biochemical (or PSA)-free recurrence indicates the likelihood that a patient treated for prostate cancer remains free of recurrent disease as manifested by a rising PSA. Prostate cancer-specific survival and overall survival are key endpoints that many studies do not evaluate due to the length of follow-up required. Biochemical failure can be a useful surrogate endpoint to predict risk of death from prostate cancer in patients with a prolonged expected survival; however, the natural history of biochemical failure progressing to clinical disease recurrence is highly variable and may depend on multiple variables including TNM characteristics as well as PSA and PSA kinetics, Gleason sum, treatment modality, and timing of biochemical recurrence. Studies continue to evaluate predictors of ultimate outcome for patients following different therapies.

DEFINITIONS OF TNM

Primary Tumor (T)

Clinical

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor neither palpable nor visible by imaging
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy (e.g., because of elevated PSA)
T2	Tumor confined within prostate*
T2a	Tumor involves one-half of one lobe or less
T2b	Tumor involves more than one-half of one lobe but not both lobes
T2c	Tumor involves both lobes
T3	Tumor extends through the prostate capsule**
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall (Figure 41.1)

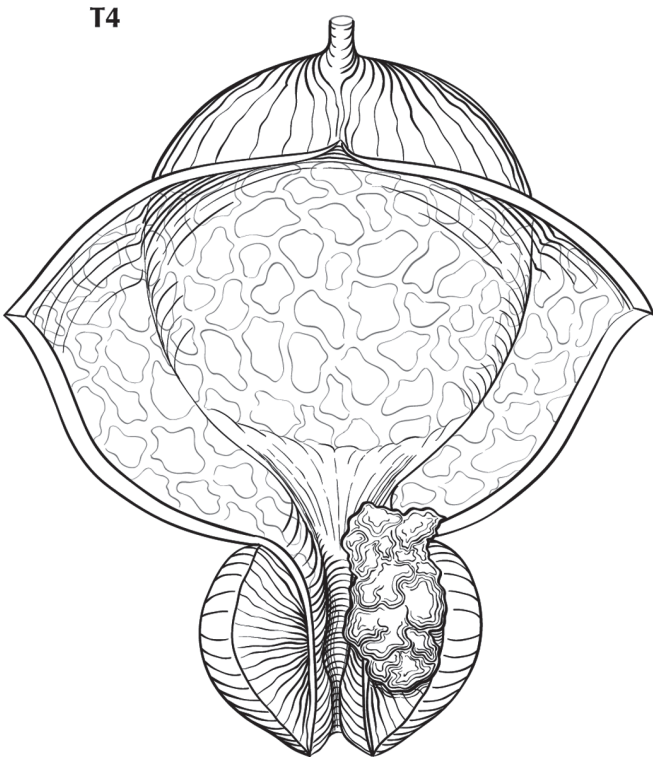

FIGURE 41.1. T4 tumor invading adjacent structures other than seminal vesicles, such as bladder, rectum, levator muscles, and/or pelvic wall.

**Note*: Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.

***Note*: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.

Pathologic (pT)*

pT2	Organ confined
pT2a	Unilateral, one-half of one side or less
pT2b	Unilateral, involving more than one-half of side but not both sides
pT2c	Bilateral disease
pT3	Extraprostatic extension
pT3a	Extraprostatic extension or microscopic invasion of bladder neck**
pT3b	Seminal vesicle invasion
pT4	Invasion of rectum, levator muscles, and /or pelvic wall

**Note*: There is no pathologic T1 classification.

***Note*: Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).

Regional Lymph Nodes (N)

Clinical

NX	Regional lymph nodes were not assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

Pathologic

pNX	Regional nodes not sampled
pN0	No positive regional nodes
pN1	Metastases in regional node(s)

Distant Metastasis (M)*

M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

**Note*: When more than one site of metastasis is present, the most advanced category is used. pM1c is most advanced.

ANATOMIC STAGE/PROGNOSTIC GROUPS*

Group	T	N	M	PSA	Gleason
I	T1a – c	N0	M0	PSA < 10	Gleason ≤ 6
	T2a	N0	M0	PSA < 10	Gleason ≤ 6
	T1 – 2a	N0	M0	PSA X	Gleason X
IIA	T1a – c	N0	M0	PSA < 20	Gleason 7
	T1a – c	N0	M0	PSA ≥ 10 < 20	Gleason ≤ 6
	T2a	N0	M0	PSA ≥ 10 < 20	Gleason ≤ 6
	T2a	N0	M0	PSA < 20	Gleason 7
	T2b	N0	M0	PSA < 20	Gleason ≤ 7
	T2b	N0	M0	PSA X	Gleason X

PROSTATE STAGING FORM

	DISTANT METASTASIS (M)	
❑ M0	No distant metastasis	
❑ M1	Distant metastasis	❑ M1
❑ M1a	Non-regional lymph node(s)	❑ M1a
❑ M1b	Bone(s)	❑ M1b
❑ M1c	Other site(s) with or without bone disease	❑ M1c
	*Note: When more than one site of metastasis is present, the most advanced category is used. pM1c is most advanced	

ANATOMIC STAGE • PROGNOSTIC GROUPS

CLINICAL

GROUP	T	N	M	PSA	Gleason
❑ I	T1a–c	N0	M0	PSA <10	Gleason ≤ 6
	T2a	N0	M0	PSA <10	Gleason ≤ 6
	T1–2a	N0	M0	PSA X	Gleason X
❑ IIA	T1a–c	N0	M0	PSA < 20	Gleason 7
	T1a–c	N0	M0	PSA ≥10 < 20	Gleason ≤ 6
	T2a	N0	M0	PSA ≥10 < 20	Gleason ≤ 6
	T2a	N0	M0	PSA < 20	Gleason 7
	T2b	N0	M0	PSA < 20	Gleason ≤ 7
	T2b	N0	M0	PSA X	Gleason X
❑ IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1–2	N0	M0	PSA ≥ 20	Any Gleason
	T1–2	N0	M0	Any PSA	Gleason ≥ 8
❑ III	T3a–b	N0	M0	Any PSA	Any Gleason
❑ IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

*When either PSA or Gleason is not available, grouping should be determined by T stage and/or either PSA or Gleason as available.

❑ Stage unknown

PATHOLOGIC

GROUP	T	N	M	PSA	Gleason
❑ I	T1a–c	N0	M0	PSA <10	Gleason ≤ 6
	T2a	N0	M0	PSA <10	Gleason ≤ 6
	T1–2a	N0	M0	PSA X	Gleason X
❑ IIA	T1a–c	N0	M0	PSA < 20	Gleason 7
	T1a–c	N0	M0	PSA ≥ 10 < 20	Gleason ≤ 6
	T2a	N0	M0	PSA ≥ 10 < 20	Gleason ≤ 6
	T2a	N0	M0	PSA < 20	Gleason 7
	T2b	N0	M0	PSA < 20	Gleason ≤ 7
	T2b	N0	M0	PSA X	Gleason X
❑ IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1–2	N0	M0	PSA ≥ 20	Any Gleason
	T1–2	N0	M0	Any PSA	Gleason ≥ 8
❑ III	T3a–b	N0	M0	Any PSA	Any Gleason
❑ IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

*When either PSA or Gleason is not available, grouping should be determined by T stage and/or either PSA or Gleason as available.

❑ Stage unknown

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)

REQUIRED FOR STAGING: Prostate Specific Antigen: _____
Gleason score: _____

CLINICALLY SIGNIFICANT:

Gleason primary and secondary patterns: _____

Gleason Tertiary Pattern: _____

Clinical Staging procedures performed: _____

Number of biopsy cores examined: _____

Number of biopsy cores positive for cancer: _____

General Notes:
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

(continued from previous page)

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Testis

At-A-Glance

SUMMARY OF CHANGES

- The definition of TNM and the Stage Grouping for this chapter have not changed from the Sixth Edition

ANATOMIC STAGE/PROGNOSTIC GROUPS

Group	T	N	M	S (Serum Tumor Markers)
Stage 0	pTis	N0	M0	S0
Stage I	pT1–4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
Stage IS	Any pT/Tx	N0	M0	S1–3
Stage II	Any pT/Tx	N1–3	M0	SX
Stage IIA	Any pT/Tx	N1	M0	S0
	Any pT/Tx	N1	M0	S1
Stage IIB	Any pT/Tx	N2	M0	S0
	Any pT/Tx	N2	M0	S1
Stage IIC	Any pT/Tx	N3	M0	S0
	Any pT/Tx	N3	M0	S1
Stage III	Any pT/Tx	Any N	M1	SX
Stage IIIA	Any pT/Tx	Any N	M1a	S0
	Any pT/Tx	Any N	M1a	S1
Stage IIIB	Any pT/Tx	N1–3	M0	S2
	Any pT/Tx	Any N	M1a	S2
Stage IIIC	Any pT/Tx	N1–3	M0	S3
	Any pT/Tx	Any N	M1a	S3
	Any pT/Tx	Any N	M1b	Any S

ICD-O-3 TOPOGRAPHY CODES

C62.0 Undescended testis
C62.1 Descended testis
C62.9 Testis, NOS

ICD-O-3 HISTOLOGY CODE RANGES

8000–8576, 8590–8670, 8940–8950, 8980–8981, 9060–9090, 9100–9105

INTRODUCTION

Cancers of the testis are usually found in young adults and account for less than 1% of all malignancies in males. However, during the twentieth century, the incidence has more than doubled. Cryptorchidism is a predisposing condition, and other associations include atypical germ cells and multiple atypical nevi. Germ cell tumors of the testis are categorized into two main histologic types: seminomas and nonseminomas. The latter group is composed of either individual or combinations of histologic subtypes, including embryonal carcinoma, teratoma, choriocarcinoma, and yolk sac tumor. The presence of elevation in serum tumor markers, including alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and lactate dehydrogenase (LDH), is frequent in this disease. Staging and prognostication are based on determination of the extent of disease and assessment of serum tumor markers. The TNM staging system for male germ cell tumors incorporates serum tumor maker elevation as a separate category of staging information. Cancer of the testis is highly curable, even in cases with advanced, metastatic disease.

Since the sixth edition of the *AJCC Cancer Staging Manual,* there are no changes in anatomic or tumor marker staging that require a change in the AJCC staging for testis cancer.

ANATOMY

Primary Site. The testes are composed of convoluted seminiferous tubules with a stroma containing functional endocrine interstitial cells. Both are encased in a dense capsule, the tunica albuginea, with fibrous septa extending into the testis and separating them into lobules. The tubules converge and exit at the mediastinum of the testis into the rete testis and efferent ducts, which join a single duct. This duct – the epididymis – coils outside the upper and lower poles of the testicle and then joins the vas deferens, a muscular conduit that accompanies the vessels and lymphatic channels of the spermatic cord. The major route for local extension of cancer is through the lymphatic channels. The tumor emerges from the mediastinum of the testis and courses through the spermatic cord. Occasionally, the epididymis is invaded early, and then the external iliac nodes may become involved. If there has been previous scrotal or inguinal surgery or if invasion of the scrotal wall is found (though this is rare), then the lymphatic spread may be to inguinal nodes.

Regional Lymph Nodes. The following nodes are considered regional:

Interaortocaval
Para-aortic (periaortic)
Paracaval
Preaortic
Precaval
Retroaortic
Retrocaval

The left and right testicles demonstrate different patterns of primary drainage that mirror the differences in venous drainage. The left testicle primarily drains to the paraaortic lymph nodes and the right testicle primarily drains to the interaortocaval lymph nodes. The intrapelvic, external iliac, and inguinal nodes are considered regional only after scrotal or inguinal surgery prior to the presentation of the testis tumor. All nodes outside the regional nodes are distant. Nodes along the spermatic vein are considered regional.

Metastatic Sites. Distant spread of testicular tumors occurs most commonly to the lymph nodes, followed by metastases to the lung, liver, bone, and other visceral sites. Stage is dependent on the extent of disease and on the determination of serum tumor markers. Extent of disease includes assessment for involvement and size of regional lymph nodes, evidence of disease in nonregional lymph nodes, and metastases to pulmonary and nonpulmonary visceral sites. The stage is subdivided on the basis of the presence and degree of elevation of serum tumor markers. Serum tumor markers are measured immediately after orchiectomy and, if elevated, should be measured serially after orchiectomy to determine whether normal decay curves are followed. The physiological half-life of AFP is 5–7 days, and the half-life of HCG is 24–48 h. The presence of prolonged half-life times implies the presence of residual disease after orchiectomy. It should be noted that in some cases, tumor marker release may occur (e.g., in response to chemotherapy or handling of a primary tumor intraoperatively) and may cause artificial elevation of circulating tumor marker levels. The serum level of LDH has prognostic value in patients with metastatic disease and is included for staging.

RULES FOR CLASSIFICATION

Clinical Staging. Staging of testis tumors includes determination of the T, N, M, and S categories. Clinical examination and histologic assessment are required for clinical staging. Radiographic assessment of the chest, abdomen, and pelvis is necessary to determine the N and M status of disease. Serum tumor markers, including AFP, hCG, and LDH, should be obtained prior to orchiectomy, but levels after orchiectomy are used to complete the status of the serum tumor markers (S), taking into account the half life of AFP and hCG. Stage grouping classification of Stage IS requires persistent elevation of serum tumor markers following orchiectomy.

Pathologic Staging. Histologic evaluation of the radical orchiectomy specimen must be used for the pT classification. The gross size of the tumor should be recorded. Careful gross examination should determine whether

Regional Lymph Nodes (N)

Clinical

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, any one mass greater than 2 cm but not more than 5 cm in greatest dimension
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

Pathologic (pN)

pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and less than or equal to five nodes positive, none more than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than five nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional nodal or pulmonary metastasis
M1b	Distant metastasis other than to nonregional lymph nodes and lung

ANATOMIC STAGE/PROGNOSTIC GROUPS

Group	T	N	M	S (Serum Tumor Markers)
Stage 0	pTis	N0	M0	S0
Stage I	pT1–4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
Stage IS	Any pT/Tx	N0	M0	S1–3
Stage II	Any pT/Tx	N1–3	M0	SX
Stage IIA	Any pT/Tx	N1	M0	S0
	Any pT/Tx	N1	M0	S1
Stage IIB	Any pT/Tx	N2	M0	S0
	Any pT/Tx	N2	M0	S1
Stage IIC	Any pT/Tx	N3	M0	S0
	Any pT/Tx	N3	M0	S1
Stage III	Any pT/Tx	Any N	M1	SX
Stage IIIA	Any pT/Tx	Any N	M1a	S0
	Any pT/Tx	Any N	M1a	S1
Stage IIIB	Any pT/Tx	N1–3	M0	S2
	Any pT/Tx	Any N	M1a	S2
Stage IIIC	Any pT/Tx	N1–3	M0	S3
	Any pT/Tx	Any N	M1a	S3
	Any pT/Tx	Any N	M1b	Any S

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)
(Recommended for Collection)

Required for staging

Serum tumor markers (S)

SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH < 1.5 × N* *and* hCG (mIu/ml) <5,000 *and* AFP (ng/ml) <1,000
S2	LDH 1.5–10 × N *or* hCG (mIu/ml) 5,000–50,000 *or* AFP (ng/ml) 1,000–10,000
S3	LDH > 10 × N *or* hCG (mIu/ml) > 50,000 *or* AFP (ng/ml) > 10,000

*N indicates the upper limit of normal for the LDH assay.

Serum tumor marker levels should be measured prior to orchiectomy, but levels after orchiectomy are used for assignment of S category, taking into account the half life of AFP and hCG. Stage grouping classification of Stage IS require persistent elevation of serum tumor markers following orchiectomy.

The Serum Tumor Markers (S) category comprises the following:

- Alpha fetoprotein (AFP) – half life 5–7 days
- Human chorionic gonadotropin (hCG) – half life 1–3 days
- Lactate dehydrogenase (LDH)

Clinically significant

Size of largest metastases in lymph nodes
Radical orchiectomy performed

TESTIS STAGING FORM

CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS		PATHOLOGIC *Extent of disease through completion of definitive surgery*
❒ y clinical – staging completed after neoadjuvant therapy but before subsequent surgery	**TUMOR SIZE:** _____	**LATERALITY:** ☐ left ☐ right ☐ bilateral	❒ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	PRIMARY TUMOR (T) The extent of primary tumor is usually classified after radical orchiectomy and, for this reason, a *pathologic* stage is assigned.		
pTX	Primary tumor cannot be assessed		❑ pTX
pT0	No evidence of primary tumor (e.g., histologic scar in testis)		❑ pT0
pTis	Intratubular germ cell neoplasia (carcinoma *in situ*)		❑ pTis
pT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade into the tunica albuginea but not the tunica vaginalis		❑ pT1
pT2	Tumor limited to the testis and epididymis with vascular/lymphatic invasion, or tumor extending through the tunica albuginea with involvement of the tunica vaginalis		❑ pT2
pT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion		❑ pT3
pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion		❑ pT4
	* Except for pTis and pT4, extent of primary tumor is classified by radical orchiectomy. TX may be used for other categories in the absence of radical orchiectomy.		
	REGIONAL LYMPH NODES (N)		
❑ NX	Regional lymph nodes cannot be assessed		❑ NX
❑ N0	No regional lymph node metastasis		❑ N0
❑ N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, none more than 2 cm in greatest dimension		N1
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and less than or equal to 5 nodes positive, none more than 2 cm in greatest dimension		❑ pN1
❑ N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, any one mass greater than 2 cm but not more than 5 cm in greatest dimension		
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor		❑ pN2
❑ N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		❑ pN3
	DISTANT METASTASIS (M)		
❑ M0	No distant metastasis		
❑ M1	Distant metastasis		❑ M1
❑ M1a	Nonregional nodal or pulmonary metastasis		❑ M1a
❑ M1b	Distant metastasis other than to non-regional lymph nodes and lung		❑ M1b

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

(continued on next page)

TESTIS STAGING FORM

ANATOMIC STAGE • PROGNOSTIC GROUPS

CLINICAL

GROUP	T	N	M	S (serum tumor markers)
❑ 0	pTis	N0	M0	S0
❑ I	pT1–4	N0	M0	SX
❑ IA	pT1	N0	M0	S0
❑ IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
❑ IS	Any pT/Tx	N0	M0	S1–3
❑ II	Any pT/Tx	N1–3	M0	SX
❑ IIA	Any pT/Tx	N1	M0	S0
	Any pT/Tx	N1	M0	S1
❑ IIB	Any pT/Tx	N2	M0	S0
	Any pT/Tx	N2	M0	S1
❑ IIC	Any pT/Tx	N3	M0	S0
	Any pT/Tx	N3	M0	S1
❑ III	Any pT/Tx	Any N	M1	SX
❑ IIIA	Any pT/Tx	Any N	M1a	S0
	Any pT/Tx	Any N	M1a	S1
❑ IIIB	Any pT/Tx	N1–3	M0	S2
	Any pT/Tx	Any N	M1a	S2
❑ IIIC	Any pT/Tx	N1–3	M0	S3
	Any pT/Tx	Any N	M1a	S3
	Any pT/Tx	Any N	M1b	Any S

❑ Stage unknown

PATHOLOGIC

GROUP	T	N	M	S (serum tumor markers)
❑ 0	pTis	N0	M0	S0
❑ I	pT1–4	N0	M0	SX
❑ IA	pT1	N0	M0	S0
❑ IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
❑ IS	Any pT/Tx	N0	M0	S1–3
❑ II	Any pT/Tx	N1–3	M0	SX
❑ IIA	Any pT/Tx	N1	M0	S0
	Any pT/Tx	N1	M0	S1
❑ IIB	Any pT/Tx	N2	M0	S0
	Any pT/Tx	N2	M0	S1
❑ IIC	Any pT/Tx	N3	M0	S0
	Any pT/Tx	N3	M0	S1
❑ III	Any pT/Tx	Any N	M1	SX
❑ IIIA	Any pT/Tx	Any N	M1a	S0
	Any pT/Tx	Any N	M1a	S1
❑ IIIB	Any pT/Tx	N1–3	M0	S2
	Any pT/Tx	Any N	M1a	S2
❑ IIIC	Any pT/Tx	N1–3	M0	S3
	Any pT/Tx	Any N	M1a	S3
	Any pT/Tx	Any N	M1b	Any S

❑ Stage unknown

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)

REQUIRED FOR STAGING: Serum Tumor Markers (S) _____

SX Marker studies not available or not performed
S0 Marker study levels within normal limits
S1 LDH < 1.5 X N* **AND** hCG (mIu/ml) < 5000 **AND** AFP (ng/ml) < 1000
S2 LDH 1.5–10 x N **OR** hCG (mIu/ml) 5000–50,000 **OR** AFP (ng/ml) 1000–10,000
S3 LDH > 10 x N **OR** hCG (mIu/ml) > 50,000 **OR** AFP (ng/ml) > 10,000

*N indicates the upper limit of normal for the LDH assay.

Serum tumor marker levels should be measured prior to orchiectomy, but levels after orchiectomy are used for assignment of S category, taking into account the half life of AFP and hCG. Stage grouping classification of Stage IS requires persistent elevation of serum tumor markers following orchiectomy.

The Serum Tumor Markers (S) category is comprised of the following:
Alpha Fetoprotein (AFP) — half life 5–7 days
Human Chorionic Gonadotropin (hCG) — half life 1–3 days
Lactate Dehydrogenase (LDH)

CLINICALLY SIGNIFICANT:
Size of Largest Metastases in Lymph Nodes: _____
Radical Orchiectomy Performed: _____

General Notes:
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

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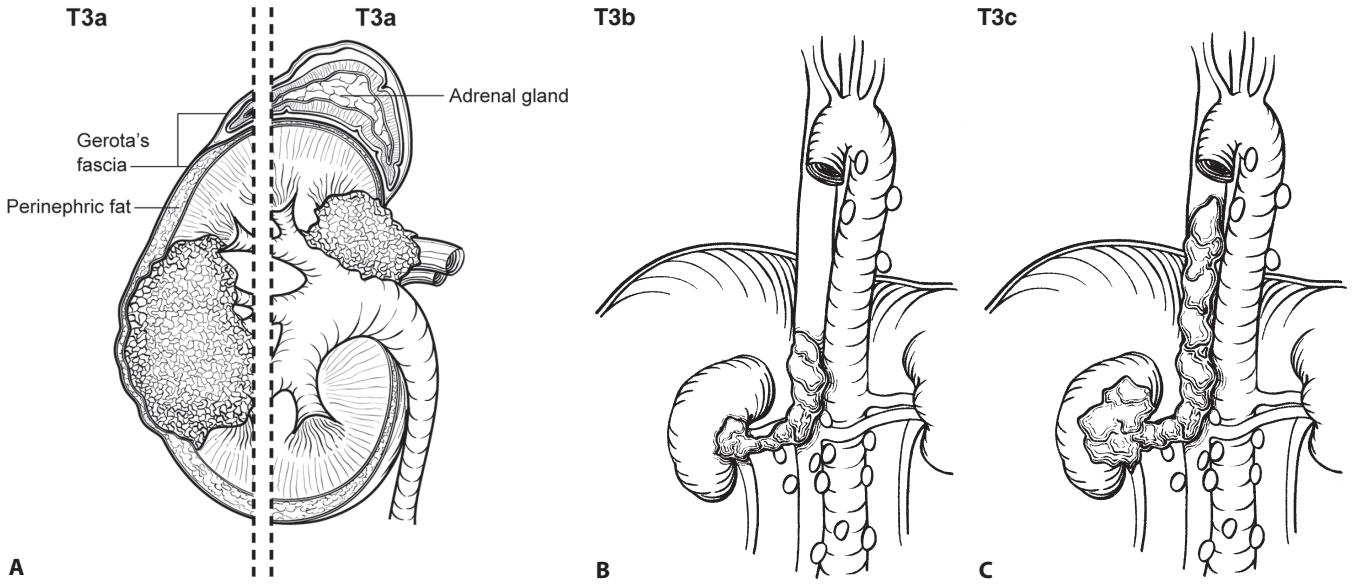


FIGURE 43.6. (**A**) (*Left*) T3a: Invasion into perirenal and/or renal sinus fat but not beyond Gerota's fascia. (*Right*) T3a: In addition to perirenal and/or renal sinus fat, tumor grossly invades into the renal vein. (**B**) T3b: Tumor grossly extends into the vena cava below the diaphragm. (**C**) T3c: Tumor grossly extends into vena cava above diaphragm or invades the wall of the vena cava.

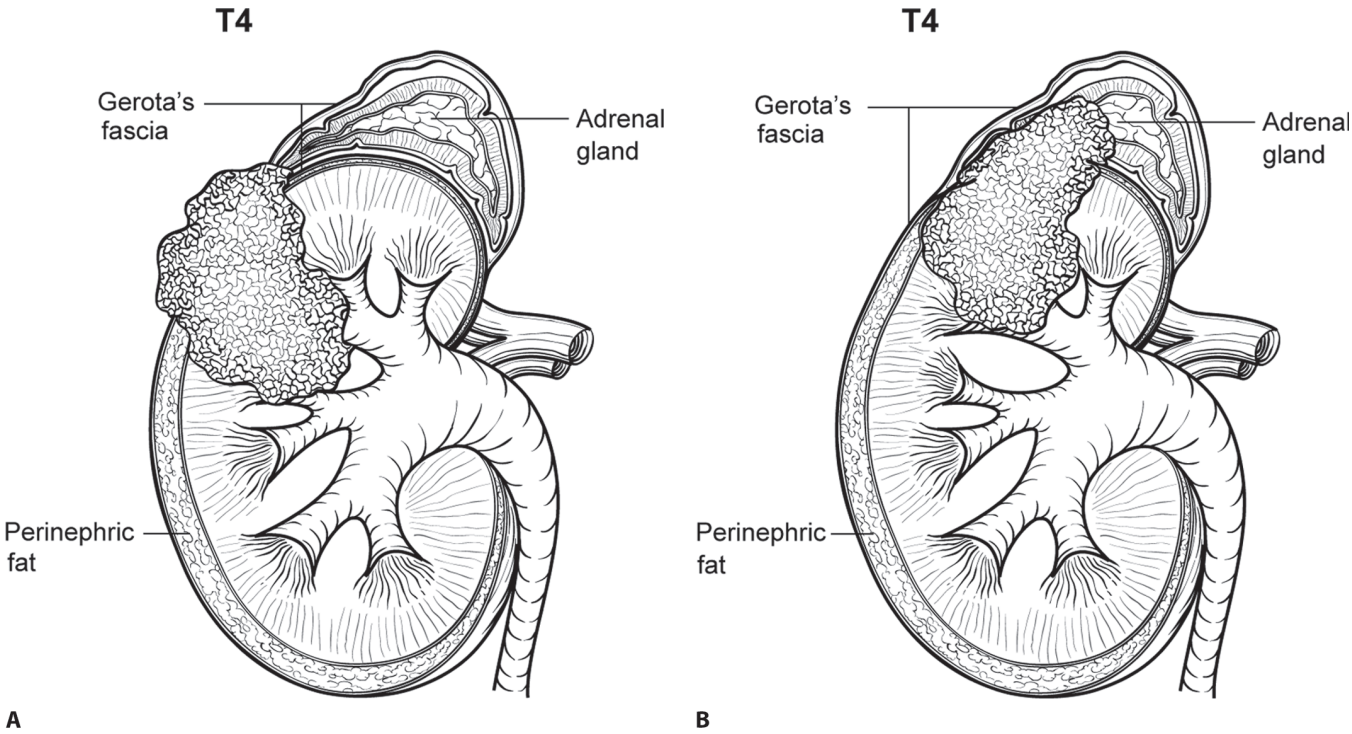


FIGURE 43.7. (**A**) T4: Invasion beyond Gerota's fascia. (**B**) T4: Invasion into ipsilateral adrenal gland.

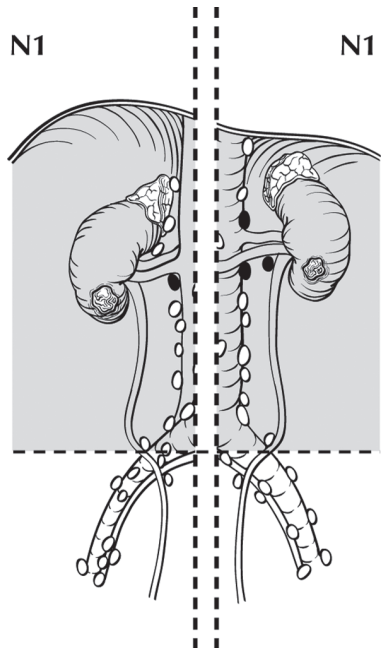


FIGURE 43.8. N1 disease is defined as a single or multiple regional lymph node involvement.

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 or T2	N1	M0
	T3	N0 or N1	M0
StageIV	T4	Any N	M0
	Any T	Any N	M1

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)
(Recommended for Collection)

Required for staging	None
Clinically significant	Invasion beyond capsule into fat or peri-sinus tissues Venous involvement Adrenal extension Fuhrman grade Sarcomatoid features Histologic tumor necrosis Extranodal extension Size of metastasis in lymph nodes

HISTOLOGIC GRADE

A four-tier classification system for nuclear grade is preferred and the protocol used should be specified.

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

HISTOPATHOLOGIC TYPE

Classification should be based on the WHO 2004 recommendations. Each of the more common histopathologic types of renal cell carcinoma have distinct molecular characteristics and are associated with prognostic or predictive significance, as reflected by their integration in predictive algorithms for renal cell carcinoma. The main categories are as follows:

Clear cell (conventional) renal carcinoma
Papillary renal cell carcinoma
Chromophobe renal cell carcinoma
Collecting duct carcinoma and renal medullary carcinoma
Unclassified renal cell carcinoma
Others

BIBLIOGRAPHY

Campbell SC, Novick AC, Bukowski RM. Renal tumors. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. Campbell-Walsh urology. 9th ed. Philadelphia, PA: Elsevier; 2006. Chapter 46, p. 1567–637.

Cindolo L, Patard JJ, Chiodini P, et al. Comparison of predictive accuracy of four prognostic models for nonmetastatic renal cell carcinoma after nephrectomy. Cancer. 2005;104:1362.

Dimashkieh H, Lohse C, Blute M, Kwon E, Leibovich B, Cheville J. Extranodal extension in regional lymph nodes is associated with outcome in patients with renal cell carcinoma. J Urol. 2006;176:1978–83.

Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. J Urol. 2002;168(6):2395–400.

Han KR, Bui MH, Pantuck AJ, et al. TNM T3a renal cell carcinoma: adrenal gland involvement is not the same as renal fat invasion. J Urol. 2003;169(3):899–903; discussion 904.

Igor F, Blute M, Leibovich B, Cheville J, Lohse C, Kwon E, Zincke H. pT2 Classification for renal cell carcinoma. Can its accuracy be improved? J Urol. 2005;173:380–4.

Kattan MW, Reuter V, Motzer RJ, Katz J, Russo P. A postoperative prognostic nomogram for renal cel carcinoma. J Urol. 2001;166(1):63–7.

Kim H, Seligson D, Liu X, Janzen N, Bui M, Yu H, et al. Using tumor markers to predict the survival of patients with metastatic renal cell carcinoma. J Urol. 2005;173:1496–501.

Klatte T, Patard JJ, Goel RH, et al. Prognostic impact of tumor size on pT2 RCC: An international multicenter experience. J Urol. 2007;178:35–40.

Kontak JA, Campbell SC. Prognostic factors in renal cell carcinoma. Urol Clin North Am. 2003;30(3):467–80.

Lam JS, Patard JJ, Leppert JT, et al. Prognostic significance of T3a renal cell carcinoma with adrenal gland involvement: an international multicenter experience. J Urol. 2005;173:269.

KIDNEY STAGING FORM

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)

REQUIRED FOR STAGING: None

CLINICALLY SIGNIFICANT:

Invasion beyond capsule into fat or perisinus tissues: _____

Venous involvement: _____

Adrenal Extension: _____

Fuhrman Grade: _____

Sarcomatoid features: _____

Histologic tumor necrosis: _____

Extranodal extension: _____

Size of metastasis in lymph nodes: _____

Histologic Grade (G) *(also known as overall grade)*

Grading system	***Grade***
❑ 2 grade system	❑ Grade I or 1
❑ 3 grade system	❑ Grade II or 2
❑ 4 grade system	❑ Grade III or 3
❑ No 2, 3, or 4 grade system is available	❑ Grade IV or 4

ADDITIONAL DESCRIPTORS

Lymphatic Vessel Invasion (L) and Venous Invasion (V) have been combined into Lymph-Vascular Invasion (LVI) for collection by cancer registrars. The College of American Pathologists' (CAP) Checklist should be used as the primary source. Other sources may be used in the absence of a Checklist. Priority is given to positive results.

- ❑ Lymph-Vascular Invasion Not Present (absent)/Not Identified
- ❑ Lymph-Vascular Invasion Present/Identified
- ❑ Not Applicable
- ❑ Unknown/Indeterminate

Residual Tumor (R)

The absence or presence of residual tumor after treatment. In some cases treated with surgery and/or with neoadjuvant therapy there will be residual tumor at the primary site after treatment because of incomplete resection or local and regional disease that extends beyond the limit of ability of resection.

- ❑ RX Presence of residual tumor cannot be assessed
- ❑ R0 No residual tumor
- ❑ R1 Microscopic residual tumor
- ❑ R2 Macroscopic residual tumor

General Notes:
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

a prefix designates the stage determined at autopsy: aTNM.

surgical margins is data field recorded by registrars describing the surgical margins of the resected primary site specimen as determined only by the pathology report.

neoadjuvant treatment is radiation therapy or systemic therapy (consisting of chemotherapy, hormone therapy, or immunotherapy) administered prior to a definitive surgical procedure. If the surgical procedure is not performed, the administered therapy no longer meets the definition of neoadjuvant therapy.

❑ Clinical stage was used in treatment planning (describe): _____

❑ National guidelines were used in treatment planning ❑ NCCN ❑ Other (describe): _____

_____

_____

Physician signature Date/Time

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

(continued from previous page)

CARCINOMA OF THE EYELID STAGING FORM

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)

REQUIRED FOR STAGING: None

CLINICALLY SIGNIFICANT:

Sentinel Lymph Node Biopsy (SLNB) results: _____
Regional nodes identified on clinical or radiographic examination: _____
Perineural invasion: _____
Tumor necrosis: _____
Pagetoid spread: _____
More than 3 Mohs micrographic surgical layers required: _____
Immunosuppression – patient has HIV: _____
Immunosuppression – history of solid organ transplant or leukemia: _____
Prior radiation to the tumor field: _____
Excluding skin cancer, patient has history of two or more carcinomas: _____
Patient has Muir-Torre syndrome: _____
Patient has xeroderma pigmentosa: _____

For Eyelid Cutaneous Squamous Cell Carcinoma only (see cSCC, Chapter 29):

REQUIRED FOR STAGING: Tumor thickness (in mm): _____
Clark's Level: _____
Presence / absence of perineural invasion: _____
Primary site location on ear or non-glabrous lip: _____
Histologic grade: _____
Size of largest lymph node metastasis: _____

Histologic Grade (G) *(also known as overall grade)*

Grading system	***Grade***
❑ 2 grade system	❑ Grade I or 1
❑ 3 grade system	❑ Grade II or 2
❑ 4 grade system	❑ Grade III or 3
❑ No 2, 3, or 4 grade system is available	❑ Grade IV or 4

ADDITIONAL DESCRIPTORS

Lymphatic Vessel Invasion (L) and Venous Invasion (V) have been combined into Lymph-Vascular Invasion (LVI) for collection by cancer registrars. The College of American Pathologists' (CAP) Checklist should be used as the primary source. Other sources may be used in the absence of a Checklist. Priority is given to positive results.

❑ Lymph-Vascular Invasion Not Present (absent)/Not Identified
❑ Lymph-Vascular Invasion Present/Identified
❑ Not Applicable
❑ Unknown/Indeterminate

Residual Tumor (R)

The absence or presence of residual tumor after treatment. In some cases treated with surgery and/or with neoadjuvant therapy there will be residual tumor at the primary site after treatment because of incomplete resection or local and regional disease that extends beyond the limit of ability of resection.

❑ RX Presence of residual tumor cannot be assessed
❑ R0 No residual tumor
❑ R1 Microscopic residual tumor
❑ R2 Macroscopic residual tumor

General Notes:
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

a prefix designates the stage determined at autopsy: aTNM.

surgical margins is data field recorded by registrars describing the surgical margins of the resected primary site specimen as determined only by the pathology report.

neoadjuvant treatment is radiation therapy or systemic therapy (consisting of chemotherapy, hormone therapy, or immunotherapy) administered prior to a definitive surgical procedure. If the surgical procedure is not performed, the administered therapy no longer meets the definition of neoadjuvant therapy.

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

(continued from previous page)

T1b	Tumor limited to the iris more than 3 clock hours in size
T1c	Tumor limited to the iris with secondary glaucoma
T2	Tumor confluent with or extending into the ciliary body, choroid, or both
T2a	Tumor confluent with or extending into the ciliary body, choroid, or both, with secondary glaucoma
T3	Tumor confluent with or extending into the ciliary body, choroid, or both, with scleral extension
T3a	Tumor confluent with or extending into the ciliary body, choroid, or both, with scleral extension and secondary glaucoma
T4	Tumor with extrascleral extension
T4a	Tumor with extrascleral extension less than or equal to 5 mm in diameter
T4b	Tumor with extrascleral extension more than 5 mm in diameter

**Note*: In clinical practice, the largest tumor basal diameter may be estimated in optic disc diameters (dd, average: 1 dd = 1.5 mm). Tumor thickness may be estimated in diopters (average: 2.5 diopters = 1 mm). However, techniques such as ultrasonography and fundus photography are used to provide more accurate measurements. Ciliary body involvement can be evaluated by the slit-lamp, ophthalmoscopy, gonioscopy, and transillumination. However, high-frequency ultrasonography (ultrasound biomicroscopy) is used for more accurate assessment. Extension through the sclera is evaluated visually before and during surgery, and with ultrasonography, computed tomography, or magnetic resonance imaging.

***Note*: When histopathologic measurements are recorded after fixation, tumor diameter and thickness may be underestimated because of tissue shrinkage.

****Note*: Iris melanomas originate from, and are predominantly located in, this region of the uvea. If less than half of the tumor volume is located within the iris, the tumor may have originated in the ciliary body and consideration should be given to classifying it accordingly.

Ciliary Body and Choroid

Primary ciliary body and choroidal melanomas, as defined in Figure 51.1, are classified according to the four tumor size categories below:

T1	Tumor size category 1
T1a	Tumor size category 1 without ciliary body involvement and extraocular extension
T1b	Tumor size category 1 with ciliary body involvement
T1c	Tumor size category 1 without ciliary body involvement but with extraocular extension less than or equal to 5 mm in diameter
T1d	Tumor size category 1 with ciliary body involvement and extraocular extension less than or equal to 5 mm in diameter
T2	Tumor size category 2
T2a	Tumor size category 2 without ciliary body involvement and extraocular extension
T2b	Tumor size category 2 with ciliary body involvement
T2c	Tumor size category 2 without ciliary body involvement but with extraocular extension less than or equal to 5 mm in diameter
T2d	Tumor size category 2 with ciliary body involvement and extraocular extension less than or equal to 5 mm in diameter
T3	Tumor size category 3
T3a	Tumor size category 3 without ciliary body involvement and extraocular extension
T3b	Tumor size category 3 with ciliary body involvement
T3c	Tumor size category 3 without ciliary body involvement but with extraocular extension less than or equal to 5 mm in diameter
T3d	Tumor size category 3 with ciliary body involvement and extraocular extension less than or equal to 5 mm in diameter
T4	Tumor size category 4
T4a	Tumor size category 4 without ciliary body involvement and extraocular extension
T4b	Tumor size category 4 with ciliary body involvement
T4c	Tumor size category 4 without ciliary body involvement but with extraocular extension less than or equal to 5 mm in diameter
T4d	Tumor size category 4 with ciliary body involvement and extraocular extension less than or equal to 5 mm in diameter
T4e	Any tumor size category with extraocular extension more than 5 mm in diameter

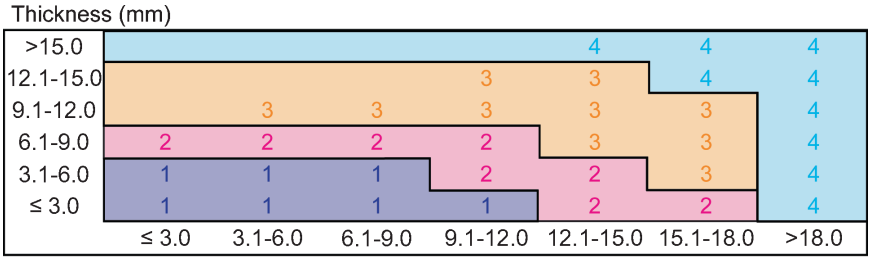
Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis
M1a	Largest diameter of the largest metastasis 3 cm or less
M1b	Largest diameter of the largest metastasis 3.1–8.0 cm
M1c	Largest diameter of the largest metastasis 8.1 cm or more

❑ T3b	Tumor size category 3 with ciliary body involvement	❑ T3b
❑ T3c	Tumor size category 3 without ciliary body involvement but with extraocular extension less than or equal to 5 mm in diameter	❑ T3c
❑ T3d	Tumor size category 3 with ciliary body involvement and extraocular extension less than or equal to 5 mm in diameter	❑ T3d
❑ T4	Tumor size category 4	❑ T4
❑ T4a	Tumor size category 4 without ciliary body involvement and extraocular extension	❑ T4a
❑ T4b	Tumor size category 4 with ciliary body involvement	❑ T4b
❑ T4c	Tumor size category 4 without ciliary body involvement but with extraocular extension less than or equal to 5 mm in diameter	❑ T4c
❑ T4d	Tumor size category 4 with ciliary body involvement and extraocular extension less than or equal to 5 mm in diameter	❑ T4d
❑ T4e	Any tumor size category with extraocular extension more than 5 mm in diameter	❑ T4e
	*__Clinical__: In clinical practice, the largest tumor basal diameter may be estimated in optic disc diameters (dd, average: 1 dd = 1.5 mm). Tumor thickness may be estimated in diopters (average: 2.5 diopters = 1 mm). However, techniques such as ultrasonography and fundus photography are used to provide more accurate measurements. Ciliary body involvement can be evaluated by the slit-lamp, ophthalmoscopy, gonioscopy and transillumination. However, high frequency ultrasonography (ultrasound biomicroscopy) is used for more accurate assessment. Extension through the sclera is evaluated visually before and during surgery, and with ultrasonography, computed tomography or magnetic resonance imaging.	
	†__Pathologic__: When histopathologic measurements are recorded after fixation, tumor diameter and thickness may be underestimated because of tissue shrinkage.	
	REGIONAL LYMPH NODES (N)	
❑ NX	Regional lymph nodes cannot be assessed	❑ NX
❑ N0	No regional lymph node metastasis	❑ N0
❑ N1	Regional lymph node metastasis	❑ N1
	DISTANT METASTASIS (M)	
❑ M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)	
❑ M1	Distant metastasis	❑ M1
❑ M1a	Largest diameter of the largest metastasis ≤3 cm	❑ M1a
❑ M1b	Largest diameter of the largest metastasis 3.1-8.0 cm	❑ M1b
❑ M1c	Largest diameter of the largest metastasis 8.1 cm or more	❑ M1c



Classification for ciliary body and choroid uveal melanoma based on thickness and diameter.

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

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MALIGNANT MELANOMA OF THE UVEA STAGING FORM

ANATOMIC STAGE • PROGNOSTIC GROUPING

CLINICAL

GROUP	T	N	M
❑ I	T1a	N0	M0
❑ IIA	T1b-d	N0	M0
	T2a	N0	M0
❑ IIB	T2b	N0	M0
	T3a	N0	M0
❑ IIIA	T2c-d	N0	M0
	T3b-c	N0	M0
	T4a	N0	M0
❑ IIIB	T3d	N0	M0
	T4b-c	N0	M0
❑ IIIC	T4d-e	N0	M0
❑ IV	Any T	N1	M0
	Any T	Any N	M1a-c

❑ Stage unknown

PATHOLOGIC

GROUP	T	N	M
❑ I	T1a	N0	M0
❑ IIA	T1b-d	N0	M0
	T2a	N0	M0
❑ IIB	T2b	N0	M0
	T3a	N0	M0
❑ IIIA	T2c-d	N0	M0
	T3b-c	N0	M0
	T4a	N0	M0
❑ IIIB	T3d	N0	M0
	T4b-c	N0	M0
❑ IIIC	T4d-e	N0	M0
❑ IV	Any T	N1	M0
	Any T	Any N	M1a-c

❑ Stage unknown

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)

REQUIRED FOR STAGING: Tumor height and largest diameter _____

CLINICALLY SIGNIFICANT:

Measured thickness (depth) _____
Chromosomal alterations _____
Gene expression profile _____
Positron emission tomography/computed tomography _____
Confocal indocyanine green angiography _____
Mitotic count per 40 high power fields (HPF)_____
Mean diameter of the ten largest nucleoli (MLN) _____
Presence of extravascular matrix patterns _____
Microvascular density (MVD) _____
Insulin-like growth factor 1 receptor (IGF1-R) _____
Tumor-infiltrating lymphocytes _____
Tumor-infiltrating macrophages _____
HLA Class I expression _____

Histologic Grade (G) *(also known as overall grade)*

Grading system	*Grade*
❑ 2 grade system	❑ Grade I or 1
❑ 3 grade system	❑ Grade II or 2
❑ 4 grade system	❑ Grade III or 3
❑ No 2, 3, or 4 grade system is available	❑ Grade IV or 4

General Notes:
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

a prefix designates the stage determined at autopsy: aTNM.

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

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53 Carcinoma of the Lacrimal Gland

At-A-Glance

SUMMARY OF CHANGES

The staging system for lacrimal gland carcinomas has been made consistent with that for salivary gland carcinomas by:

- Proposing changes in the size cutoffs between T1, T2, and T3
- By subdividing T4
- By expanding the histologic categories to those used for salivary gland malignancies, since all of these have been reported in the lacrimal gland
- Lacrimal sac tumors have been removed from this section

ANATOMIC STAGE/PROGNOSTIC GROUPS

No stage grouping is presently recommended

ICD-O-3 TOPOGRAPHY CODES

C69.5 Lacrimal gland (excluding lacrimal sac)

ICD-O-3 HISTOLOGY CODE RANGES

8000–8576, 8940–8950, 8980–8981

INTRODUCTION

The retrospective study of 265 epithelial tumors of the lacrimal gland conducted by the Armed Forces Institute of Pathology (AFIP) improved our understanding of the histologic classification and clinical behavior of epithelial tumors of the lacrimal gland. The historic works of Forrest (1954) and Zimmerman (1962) alleviated confusion by applying to epithelial tumors of the lacrimal gland the histopathologic classification of salivary gland tumors. The histologic classification used herein is a modification of the World Health Organization (WHO) classification of salivary gland tumors and is similar to that used in the most recent AFIP fascicle on Tumors of the Eye and Ocular Adnexa (2006).

ANATOMY

Primary Site. In the normal, fully developed orbit, the lacrimal gland is clinically impalpable and is situated in the lacrimal fossa posterior to the superotemporal orbital rim. The gland is not truly encapsulated and is divided into the deep orbital and the superficial palpebral lobes by the levator aponeurosis.

Regional Lymph Nodes. The regional lymph nodes include the following:

Preauricular (parotid)
Submandibular
Cervical

For pN, histologic examination of a regional lymphadenectomy specimen, if performed, will include one or more regional lymph nodes.

Metastatic Sites. The lung is the most common metastatic site, followed by bone and remote viscera.

RULES FOR CLASSIFICATION

Clinical Staging. This includes a complete history (with emphasis on duration of symptoms, pain, or dysesthesia)

HISTOPATHOLOGIC TYPE

The major malignant primary epithelial tumors include the following:

Low Grade

- Carcinoma ex pleomorphic adenoma [where the carcinoma is noninvasive or minimally invasive as defined by the WHO classification (extension ≤1.5 mm beyond the capsule – into surrounding tissue)]
- Polymorphous low-grade carcinoma
- Mucoepidermoid carcinoma, grades 1 and 2
- Epithelial-myoepithelial carcinoma
- Cystadenocarcinoma and papillary cystadenocarcinoma
- Acinic cell carcinoma
- Basal cell adenocarcinoma
- Mucinous adenocarcinoma

High Grade

- Carcinoma ex pleomorphic adenoma (malignant mixed tumor) that includes adenocarcinoma and adenoid cystic carcinoma arising in a pleomorphic adenoma [where the carcinoma is invasive as defined by the WHO classification (extension >1.5 mm beyond the capsule – into surrounding tissue)]
- Adenoid cystic carcinoma, not otherwise specified
- Adenocarcinoma, not otherwise specified
- Mucoepidermoid carcinoma, grade 3
- Ductal adenocarcinoma
- Squamous cell carcinoma
- Sebaceous adenocarcinoma
- Myoepithelial carcinoma
- Lymphoepithelial carcinoma

Other Rare and Unclassifiable Carcinomas

BIBLIOGRAPHY

Cheuk W, Chan JKC. Advances in salivary gland pathology. Histopathology. 2007;51:1–20.

Font RL, Gamel JW. Epithelial tumors of the lacrimal gland: an analysis of 265 cases. In: Jakobiec FA, editor. Ocular and adnexal tumors. Birmingham, AL: Aesculapius; 1978. Chapter 53.

Font RL, Croxatto JO, Rao NA. Tumors of the lacrimal gland. In: Silverberg SG, Sobin LH, editors. AFIP atlas of tumor pathology: tumors of the eye and ocular adnexa, series 4, fascicle 5. Washington, DC: American Registry of Pathology and Armed Forces Institute of Pathology; 2006. p. 223–46.

Forrest AW. Epithelial lacrimal gland tumors: pathology as a guide to prognosis. Trans Am Acad Ophthalmol Otolaryngol. 1954;58(6):848–66.

Henderson JW. Orbital tumors. 3rd ed. New York: Raven; 1994.

Jakobiec FA, Bilyk JR, Font RL. Lacrimal gland tumors. In: Spencer WH, editor. Ophthalmic pathology: an atlas and textbook, vol. 4. 4th ed. Philadelphia, PA: Saunders; 1996. p. 2485–2525.

Luukaa H, Klemi P, Leivo I, et al. Prognostic significance of Ki-67 and p53 as tumor markers in salivary gland malignancies in Finland: An evaluation of 212 cases. Acta Oncol. 2006;45:669–75.

Tellado MV, McLean IW, Specht CS, et al. Adenoid cystic carcinomas of the lacrimal gland in childhood and adolescence. Ophthalmology. 1997;104:1622–5.

Vangveeravong S, Katz SE, Rootman J, et al. Tumors arising in the palpebral lobe of the lacrimal gland. Ophthalmology. 1996;103:1606–12.

Weis E, Rootman J, Joly TJ, et al. Epithelial lacrimal gland tumors: pathologic classification and current understanding. Arch Ophthalmol. 2009;127:1016–1028.

World Health Organization Classification of Tumours. Pathology and genetics of head and neck tumours. Lyon: IARC; 2005.

Zimmerman LE, Sanders TE, Ackerman LV. Epithelial tumors of the lacrimal gland: prognostic and therapeutic significance of histologic types. In: Zimmerman LE, editor. Tumors of the eye and adnexa, international ophthalmology clinics. Boston, MA: Little, Brown; 1962. p. 337–67.

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Sarcoma of the Orbit

At-A-Glance

SUMMARY OF CHANGES

- A listing of site-specific categories is now included in T4
- The anatomy description was expanded
- Regional lymph nodes were defined

ANATOMIC STAGE/PROGNOSTIC GROUPS

No stage grouping is presently recommended

ICD-O-3 TOPOGRAPHY CODES

C69.6 Orbit, NOS
C69.8 Overlapping lesion of eye and adnexa

ICD-O-3 HISTOLOGY CODE RANGES

8800–8936, 8940–9136, 9141–9508, 9520–9582

INTRODUCTION

The commonly encountered primary malignant neoplasms of the orbit include soft tissue sarcomas (rhabdomyosarcoma, osteogenic sarcoma, leiomyosarcoma, etc.), lymphoproliferative tumors (lymphoma, plasma cell tumors, etc.), and melanocytic tumors.

ANATOMY

The orbit is a cone-shaped bony structure with a volume of 30 ml in which the 7-ml globe is positioned centrally and anteriorly. All the support systems of the globe, including the optic nerve and its meninges, lacrimal gland and lymphoid tissue, extraocular muscles, fibroadipose tissue, peripheral nerves, ganglionic tissue, and blood vessels are designed to be confined within approximately 25 ml of space surrounding the eyeball. Many types of tissues are crowded in this limited space and give origin to a variety of primary carcinomatous, sarcomatous, lymphoid and melanocytic tumors. Secondary neoplasia (from adjacent structures such as paranasal sinuses, conjunctiva, globe, etc.) as well as metastatic tumors from distant organs are encountered in the orbit. Also, and because of their immediate proximity, the orbital primary tumors often present invasions into CNS, nasal cavity, and paranasal sinuses. Orbit has two unique histopathological features that may have some influence on tumor dissemination to and from this location. Orbit does not contain a lymphatic vascular network and its venous channels do not have valves.

Primary Site. Orbital sarcomas originate from fat (liposarcoma), striated muscle (rhabdomyosarcoma), smooth muscle (leiomyosarcoma), cartilage (chondrosarcoma), bone (osteogenic sarcoma), fibroconnective tissue (fibrosarcoma, fibrous histiocytoma), vascular tissues (angiosarcoma, hemangiopericytoma), peripheral nerve (Schwannoma, paraganglioma), and optic nerve tissues (glioma, meningioma) as well as from primitive mesenchymal cells within the orbit.

Regional Lymph Nodes. Although there is no organized lymphatic network behind the orbital septum, the drainage of the orbit is into the submandibular, parotid, and cervical lymph nodes through vascular anastamosis. The venous drainage of the orbit is primarily into the cavernous sinus. Preauricular, submandibular, and cervical nodes may receive drainage secondarily from orbit via the lymphatics of conjunctiva and eyelids. For pN, the examination of a regional lymphadenectomy specimen would ordinarily include one or more lymph node(s).

with cerebriform nuclei (Sézary cells), and lymphadenopathy. The Sézary cells also have a mature memory T-cell phenotype (CD3+, CD4+) with loss of CD7 and CD26.

DEFINITIONS OF TNM

ISCL/EORTC Revision to the Classification of *Mycosis fungoides* and Sézary Syndrome

Skin	
T1	Limited patches,* papules, and/or plaques** covering less than 10% of the skin surface. May further stratify into T1a (patch only) vs. T1b (plaque ± patch)
T2	Patches, papules or plaques covering 10% or more of the skin surface. May further stratify into T2a (patch only) vs. T2b (plaque ± patch)
T3	One or more tumors*** (≥1-cm diameter)
T4	Confluence of erythema covering 80% or more of body surface area
Node	
N0	No clinically abnormal peripheral lymph nodes****; biopsy not required
N1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN0-2
N1a	Clone negative*****
N1b	Clone positive*****
N2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN3
N2a	Clone negative*****
N2b	Clone positive*****
N3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3–4 or NCI LN4; clone positive or negative
Nx	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral	
M0	No visceral organ involvement
M1	Visceral involvement (must have pathology confirmation^ and organ involved should be specified)
Peripheral Blood Involvement	
B0	Absence of significant blood involvement: 5% or less of peripheral blood lymphocytes are atypical (Sézary) cells^^
B0a	Clone negative*****
B0b	Clone positive*****
B1	Low blood tumor burden: more than 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B2
B1a	Clone negative*****
B1b	Clone positive*****
B2	High blood tumor burden: 1000/μL Sézary cells^^ or more with positive clone*****

From Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood. 2007;110(6):1713–22, with permission of the American Society of Hematology.

*For skin, patch indicates any size skin lesion without significant elevation or induration. Presence/absence of hypo- or hyperpigmentation, scale, crusting, and/or poikiloderma should be noted.

**For skin, plaque indicates any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting, and/or poikiloderma should be noted. Histologic features such as folliculotropism or large-cell transformation (>25% large cells), CD30+ or CD30–, and clinical features such as ulceration are important to document.

***For skin, tumor indicates at least one 1-cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also note if histologic evidence of large-cell transformation has occurred. Phenotyping for CD30 is encouraged.

****For node, abnormal peripheral lymph node(s) indicates any palpable peripheral node that on physical examination is firm, irregular, clustered, fixed or 1.5 cm or larger in diameter. Node groups examined on physical examination include cervical, supraclavicular, epitrochlear, axillary, and inguinal. Central nodes, which are not generally amenable to pathologic assessment, are not currently considered in the nodal classification unless used to establish N3 histopathologically.

*****A T-cell clone is defined by PCR or Southern blot analysis of the T-cell receptor gene.

^For viscera, spleen and liver may be diagnosed by imaging criteria.

^^For blood, Sézary cells are defined as lymphocytes with hyperconvoluted cerebriform nuclei. If Sézary cells are not able to be used to determine tumor burden for B2, then one of the following modified ISCL criteria along with a positive clonal rearrangement of the TCR may be used instead: (1) expanded CD4+ or CD3+ cells with CD4/CD8 ratio of 10 or more, (2) expanded CD4+ cells with abnormal immunophenotype including loss of CD7 or CD26.

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