PART VI
Skin

23

Carcinoma of the Skin

(Excluding Eyelid, Vulva, and Penis)

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
C63.2 Scrotum, NOS

SUMMARY OF CHANGES

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

INTRODUCTION

This chapter applies to non-melanomatous cancers of the skin, which are predominantly basal cell carcinomas and squamous cell carcinomas. Skin cancers are largely related to solar exposure and are relatively common, although their frequency varies with geographic latitude and population at risk. For example, they occur in 729 individuals per 100,000 population in Hawaii but in only 195 per 100,000 in the northern United States. Higher rates are found in Australia and New Zealand, and the incidence generally is rising rapidly. Basal cell carcinomas are the most common cancer in humans, and are four to five times more common than squamous cell carcinomas of the skin. For the most part, non-melanomatous skin cancers have a good prognosis and nearly always can be treated with curative intent. Refer to Chapter 40 for staging of carcinoma of the eyelid and to Chapter 24 for malignant melanoma of the skin.

ANATOMY

Primary Site. The skin is made up of three layers: an outermost epidermis, a middle dermis, and an inner subcutis. The epidermis consists predominantly of stratified squamous epithelium, the outermost layer of which is keratinized. The innermost layer consists primarily of germinative cells and melanocytes. The dermis is made up of connective tissue and elastic fibers immersed in an amorphous matrix of mucoproteins and mucopolysaccharides. The subcutis is predominantly adipose tissue. The sebaceous and other glands of the skin, as well as hair follicles—collectively called adnexal structures—are found in the dermis and subjacent subcutis. All of the components of the skin (epidermis, dermis, and adnexal structures within the subcutis) can give rise to malignant neoplasms.

Cancers of the skin most commonly arise on those surfaces exposed to sunlight (including the face, ears, hands, and scalp, especially in balding men), and the role of sunlight in the induction of cutaneous cancer has been well described. Approximately four-fifths of all cutaneous squamous cell cancers and approximately two-thirds of all basal cell cancers occur in unprotected sun-exposed skin of lightly pigmented persons. Squamous cell carcinoma can also arise in skin that was previously scarred or ulcerated—that is, at sites of burns and chronic ulcers. Radiation in other than ultraviolet forms, chemicals, and genetic syndromes are also proven causes of cutaneous carcinomas.

Skin cancers rarely cause symptoms. Signs vary depending on the local site of origin and whether the precursor lesion is an actinic keratosis or a cutaneous ulcer. Squamous cell tumors developing at the site of actinic keratoses usually begin as hyperkeratotic papules or plaques or as ulcers. Induration, which is usually absent in actinic keratoses, may develop early in squamous cell cancer. Further progression is associated with thickening of the plaque, ulceration, and bleeding. Tumors that arise in cutaneous ulcers or burn scars present as an expanding mass at the site. High-risk tumors (higher local recurrence rate or high risk for metastasis) are found on the lip, scalp, ears, eyelids, and nose.

Basal cell carcinomas initially appear clinically as firm, translucent papules coursed by telangiectatic blood vessels. Central areas of crusting and depression, associated with ulceration, usually occur late. Bleeding, however, may be described in early as well as late lesions. Pigmentation occurs uncommonly and may lead clinically to confusion with cutaneous melanoma. Morpheaform basal cell carcinoma (basal cell carcinoma with a fibrotic component) may look

and feel like localized patches of scleroderma, or a scar, and is generally without telangiectasia or measurable elevation.

Primary Growth. Local extension is the predominant mode of growth of non-melanomatous skin cancers. Basal cell carcinomas that remain untreated for long periods will eventually erode adjacent structures, such as bone, and into local vasculature. Perineural invasion in morpheaform basal cell cancers is often observed, and it is associated with a high rate of incomplete excision and recurrence. Squamous cell carcinoma may also invade the perineural space, and this feature is associated with increased local recurrence. Squamous cell carcinoma may also penetrate into other local structures, including muscle, bone, and vasculature.

Regional Lymph Nodes. Skin cancers characteristically spread by local extension. Involvement of regional lymph nodes infrequently occurs and is usually associated with large size and invasiveness into the dermis and subcutaneous fat. Which specific lymph node chains are involved depends on the location of the primary lesion, because tumor cells are passively borne along with the "draining" lymphatic fluid, usually to the geographically closest node(s). In this context, for tumors of the lower torso or lower extremities, the inguinal nodes are considered the regional basin and should be designated N1. For pN (pathologic staging), histologic examination of a regional lymphadenectomy specimen should include careful examination of all resected nodes.

Hematogenously Borne Metastases. Basal cell and squamous cell cancers that arise in actinically damaged skin are relatively slow growing and rarely metastasize. Metastases are more likely to arise from squamous cell tumors that originate in scars or ulcers. Tumors that metastasize have often been present for a long time before metastases are observed. The most common visceral metastatic site is the lung, especially for squamous cell carcinomas. Other sites of distant spread are unusual. Non-melanoma skin cancers arising in transplant patients may be more aggressive and may metastasize more readily and more widely.

RULES FOR CLASSIFICATION

The clinical and pathologic classifications are identical. However, pathologic staging uses the symbol p as a prefix.

Clinical Staging. The assessment of skin cancer is based on inspection and palpation of the involved area and the regional lymph nodes. Imaging studies of the underlying bony structures are important for any lesion that appears fixed to underlying fascia, muscle, or bone.

Pathologic Staging. Complete resection of the entire site is required. Confirmation of lymph node involvement is also necessary when involvement is suspected. The degree of malignancy of squamous cell cancer of the skin generally is related to the degree of anaplasia within the tumor. Low-grade tumors show considerable cell differentiation, uniform cell size, infrequent cellular mitoses and nuclear irregularity, and intact intercellular bridges. High-grade tumors show little differentiation, are often of spindle cell in character, show necrosis, exhibit high mitotic activity, and are often deeply invasive. Depth of invasion can often be correlated with degree of tumor aggressiveness.

DEFINITION OF TNM

Definitions for clinical (cTNM) and pathologic (pTNM) classifications are the same.

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
T2	Tumor more than 2 cm, but not more than 5 cm, in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor invades deep extradermal structures (i.e., cartilage, skeletal muscle, or bone)

Note: In case of multiple simultaneous tumors, the tumor with the highest T category will be classified and the number of separate tumors will be indicated in parentheses, e.g., T2 (5).

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)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

STAGE GROUPING

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

HISTOPATHOLOGIC TYPE

The classification applies only to carcinomas of the skin, primarily squamous cell and basal cell varieties. It also applies

to the adenocarcinomas that develop from sweat or sebaceous glands and to a spindle cell variant of squamous cell carcinoma. There should be microscopic verification of the disease to permit grouping of cases by histologic type. A form of *in situ* squamous cell carcinoma or intraepidermal squamous cell carcinoma is often referred to as Bowen disease. This lesion should be coded as Tis. Squamous cell tumors may also be described as verrucous.

HISTOLOGIC GRADE (G)

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

PROGNOSTIC FACTORS

In squamous cell carcinoma, tumor aggressiveness correlates well with tumor size, duration, location, origin, and degree of anaplasia. Large tumors are usually present for longer periods or are rapidly growing. Long-standing tumors tend to grow extensively and to invade other structures, such as local vasculature, nervous tissue, or soft tissue. Tumors of the scalp, ears, lips, nose, eyelids, or soft tissues readily invade subcutaneous tissue and have a greater risk of subclinical tumor extension.

Anaplastic squamous cell carcinomas readily tend to invade locally and to metastasize earlier than well-differentiated tumors, regardless of location.

Although they have been noted in cases of large ulcerated and recurrent lesions, metastases from basal cell carcinomas are rare. However, basal cell cancers are often locally destructive.

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HISTOLOGIES—CARCINOMA OF THE SKIN

8010/2 Carcinoma *in situ*, NOS
8010/3 Carcinoma, NOS
8011/3 Epithelioma, malignant
8012/3 Large cell carcinoma, NOS
8013/3 Large cell neuroendocrine carcinoma
8014/3 Large cell carcinoma with rhabdoid phenotype
8015/3 Glassy cell carcinoma
8020/3 Carcinoma, undifferentiated, NOS
8021/3 Carcinoma, anaplastic, NOS
8022/3 Pleomorphic carcinoma
8030/3 Giant cell and spindle cell carcinoma
8031/3 Giant cell carcinoma
8032/3 Spindle cell carcinoma, NOS
8033/3 Pseudosarcomatous carcinoma
8034/3 Polygonal cell carcinoma
8035/3 Carcinoma with osteoclast-like giant cells
8041/3 Small cell carcinoma, NOS
8042/3 Oat cell carcinoma
8043/3 Small cell carcinoma, fusiform cell
8044/3 Small cell carcinoma, intermediate cell
8045/3 Combined small cell carcinoma
8046/3 Non–small cell carcinoma
8050/2 Papillary carcinoma *in situ*
8050/3 Papillary carcinoma, NOS
8051/3 Verrucous carcinoma, NOS
8052/2 Papillary squamous cell carcinoma non-invasive
8052/3 Papillary squamous cell carcinoma
8070/2 Squamous cell carcinoma *in situ*, NOS
8070/3 Squamous cell carcinoma, NOS
8071/3 Squamous cell carcinoma, keratinizing, NOS
8072/3 Squamous cell carcinoma, large cell
8073/3 Squamous cell carcinoma, small cell, non-keratinizing
8074/3 Squamous cell carcinoma, spindle cell
8075/3 Squamous cell carcinoma, adenoid
8076/2 Squamous cell carcinoma *in situ* with questionable stromal invasion
8076/3 Squamous cell carcinoma, microinvasive

HISTOLOGIES—CARCINOMA OF THE SKIN (CONT.)

8077/2 Squamous intraepithelial neoplasia, grade III
8078/3 Squamous cell carcinoma with horn formulation
8080/2 Queyrat erythroplasia
8081/2 Bowen disease
8082/3 Lymphoepithelial carcinoma
8083/3 Basaloid squamous cell carcinoma
8084/3 Squamous cell carcinoma, clear cell type
8090/3 Basal cell carcinoma
8091/3 Multifocal superficial basal cell carcinoma
8092/3 Infiltrating basal cell carcinoma, NOS
8093/3 Basal cell carcinoma, fibroepithelial
8094/3 Basosquamous carcinoma
8095/3 Metatypical carcinoma
8097/3 Basal cell carcinoma, nodular
8098/3 Adenoid basal carcinoma
8102/3 Trichilemmocarcinoma
8110/3 Pilomatrix carcinoma
8140/2 Adenocarcinoma *in situ*, NOS
8140/3 Adenocarcinoma, NOS
8141/3 Scirrhous adenocarcinoma
8190/3 Trabecular adenocarcinoma
8200/3 Adenoid cystic carcinoma
8201/3 Cribriform carcinoma, NOS
8247/3 Merkel cell carcinoma
8390/3 Skin appendage carcinoma
8400/3 Sweat gland adenocarcinoma
8401/3 Apocrine adenocarcinoma
8402/3 Nodular hidradenoma, malignant
8403/3 Malignant eccrine spiradenoma
8407/3 Sclerosing sweat duct carcinoma
8408/3 Eccrine papillary adenocarcinoma
8409/3 Eccrine poroma, malignant
8410/3 Sebaceous adenocarcinoma
8413/3 Eccrine adenocarcinoma
8420/3 Ceruminous adenocarcinoma
8430/3 Mucoepidermoid carcinoma
8440/3 Cystadenocarcinoma, NOS
8490/3 Signet ring cell carcinoma
8560/3 Adenosquamous carcinoma
8562/3 Epithelial-myoepithelial carcinoma
8570/3 Adenocarcinoma with squamous metaplasia
8571/3 Adenocarcinoma with cartilaginous and osseous metaplasia
8572/3 Adenocarcinoma with spindle cell metaplasia
8573/3 Adenocarcinoma with apocrine metaplasia
8940/3 Mixed tumor, malignant, NOS
8941/3 Carcinoma in pleomorphic adenoma

CARCINOMA OF THE SKIN *(EXCLUDING EYELID, VULVA, AND PENIS)*

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____ Laterality: ☐ Bilateral ☐ Left ☐ Right

DEFINITIONS

Clinical	*Pathologic*	**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
☐	☐	T2	Tumor more than 2 cm, but not more than 5 cm, in greatest dimension[1]
☐	☐	T3	Tumor more than 5 cm in greatest dimension
☐	☐	T4	Tumor invades deep extradermal structures (i.e., cartilage, skeletal muscle, or bone)

Notes

1. In case of multiple simultaneous tumors, the tumor with the highest T category will be classified and the number of separate tumors will be indicated in parentheses, e.g., T2 (5)

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)

☐	☐	MX	Distant metastasis cannot be assessed
☐	☐	M0	No distant metastasis
☐	☐	M1	Distant metastasis

Biopsy of metastatic site performed ..... ☐ Y ..... ☐ N

Source of pathologic metastatic specimen _____

Stage Grouping

☐	☐	0	Tis	N0	M0
☐	☐	I	T1	N0	M0
☐	☐	II	T2	N0	M0
			T3	N0	M0
☐	☐	III	T4	N0	M0
			Any T	N1	M0
☐	☐	IV	Any T	Any N	M1

Histologic Grade (G)

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

(continued on reverse side)

Residual Tumor (R)

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

Additional Descriptors

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.

Prognostic Indicators (if applicable)

Notes

Additional Descriptors

Lymphatic Vessel Invasion (L)

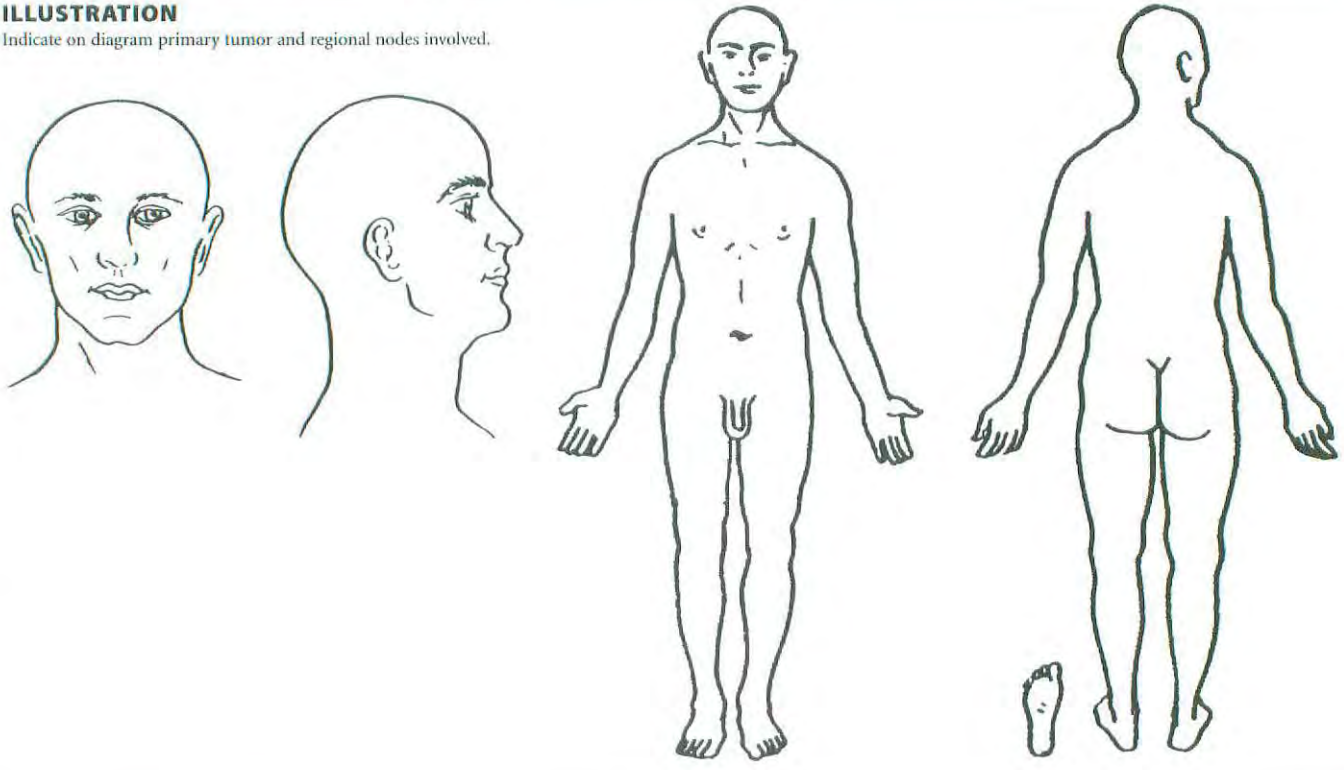
LX Lymphatic vessel invasion cannot be assessed
L0 No lymphatic vessel invasion
L1 Lymphatic vessel invasion

Venous Invasion (V)

VX Venous invasion cannot be assessed
V0 No venous invasion
V1 Microscopic venous invasion
V2 Macroscopic venous invasion

ILLUSTRATION

Indicate on diagram primary tumor and regional nodes involved.



Physician's Signature _____ Date _____

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Melanoma of the Skin

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

SUMMARY OF CHANGES

- Melanoma thickness and ulceration, but not level of invasion, are used in the T category (except for T1 melanomas).
- The number of metastatic lymph nodes, rather than their gross dimensions and the delineation of clinical occult (i.e., "microscopic") vs. clinically apparent (i.e., "macroscopic") nodal metastases, are used in the N category.
- The site of distant metastases and the presence of elevated serum lactic dehydrogenase (LDH) are used in the M category.
- All patients with Stage I, II, or III disease are upstaged when a primary melanoma is ulcerated.
- Satellite metastases around a primary melanoma and in-transit metastases have been merged into a single staging entity that is grouped into Stage IIIc disease.
- A new convention for defining clinical and pathologic staging has been developed that takes into account the new staging information gained from intraoperative lymphatic mapping and sentinel node excision.

INTRODUCTION

Melanoma of the skin continues to increase in frequency, with 47,700 new cases and 9,200 deaths in the year 2000.[1] Melanoma can arise from skin anywhere on the body. It occurs most commonly in fair-skinned persons, especially those with a history of significant sun exposure.

A completely revised melanoma staging system is described herein, along with operational definitions. In addition, a major database analysis of prognostic factors involving 17,600 patients from 13 cancer centers and organizations was performed to validate the staging categories and groupings.[2] Within each stage grouping and its subgroups, there is a uniform risk for distant metastases and a uniform survival probability. This revised version of melanoma staging more accurately reflects the prognosis and natural history of melanoma and will therefore be more applicable to treatment planning and clinical trials involving melanoma. The major differences between the new version of the melanoma staging system and the version that appeared in the Fifth Edition are summarized in Table 24.1. The chapter summary above outlines the major revisions, while more details about the staging rationale and interpretation have been published elsewhere.[3–5]

ANATOMY

Primary Sites. Cutaneous melanoma can occur anywhere on the skin. It occurs most commonly on the extremities in

TABLE 24.1. Differences between the previous (1997) version and the present (2002) version of the melanoma staging system (adapted from Balch et al.[3])

Factor	*Old System*	*New System*	*Comments*
Thickness	Secondary prognostic factor; thresholds of 0.75, 1.50, 4.0 mm	Primary determinant of T staging; thresholds of 1.0, 2.0, 4.0 mm	Correlation of metastatic risk is a continuous variable
Level of invasion	Primary determinant of T staging	Used only for defining T1 melanomas	Correlation only significant for thin lesions; variability in interpretation
Ulceration	Not included	Included as a second determinant of T and N staging	Signifies a locally advanced lesion; dominant prognostic factor for grouping Stages I, II, and III
Satellite metastases	In T category	In N category	Merged with in-transit lesions
Thick melanomas (> 4.0 mm)	Stage III	Stage IIC	Stage III defined as regional metastases
Dimensions of nodal metastases	Dominant determinant of N staging	Not used	No evidence of significant prognostic correlation
Number of nodal metastases	Not included	Primary determinant of N staging	Thresholds of 1 vs. 2–3 vs. ≥ 4 nodes
Metastatic tumor burden	Not included	Included as a second determinant of N staging	Clinically occult ("microscopic") vs. clinically apparent ("macroscopic") nodal volume
Lung metastases	Merged with all other visceral metastases	Separate category as M1b	Has a somewhat better prognosis than other visceral metastases
Elevated serum LDH	Not included	Included as a second determinant of M staging	
Clinical vs. pathologic staging	Did not account for sentinel node technology	Sentinel node results incorporated into definition of pathologic staging	Large variability in outcome between clinical and pathologic staging; pathologic staging encouraged prior to entry into clinical trials

females and on the trunk in males. Melanomas located on the palms, soles, and nailbeds (acral lentiginous melanoma), although they occur infrequently, are distinctive because they can occur in individuals of any ethnic origin and in persons with no history of significant sun exposure.

Regional Lymph Nodes. The regional lymph nodes are the most common site of metastases. The widespread use of cutaneous lymphoscintigraphy, lymphatic mapping, and sentinel lymph node biopsies has greatly enhanced the ability to identify the presence or absence of, and to stage, nodal metastases. Intralymphatic regional metastases may also become clinically manifest either as satellite metastases (defined arbitrarily as intralymphatic metastases occurring within 2 cm of the primary melanoma) or as in-transit metastases (defined arbitrarily as intralymphatic metastases occurring more than 2 cm from the primary melanoma but before the first echelon of regional lymph nodes). By convention, the term *regional nodal metastases* refers to disease confined to one nodal basin or two contiguous nodal basins, as in patients with nodal disease in combinations of femoral/iliac, axillary/supraclavicular, cervical/supraclavicular, axillary/femoral, or bilateral axillary or femoral metastases.

Metastatic Sites. Melanoma can metastasize to virtually any organ site. Metastases most commonly occur in the skin or soft tissues, the lung, and the liver.

RULES FOR CLASSIFICATION

The primary difference between the definitions of clinical and pathologic stage grouping is whether the regional lymph nodes are staged by clinical/radiologic exam or by pathological exam (after partial or complete lymphadenectomy).

Clinical Staging. By convention, clinical staging should be performed after complete excision of the primary melanoma (including microstaging) and after information about metastases to either regional or distant anatomic sites has been obtained after clinical, radiologic, and laboratory assessment. The microstaging of a primary melanoma is performed after an excisional biopsy of a primary melanoma, with pathologic assessment of tumor thickness (Breslow method), level of invasion (Clark method), and any ulceration of the overlying epidermis. All of these parameters are used in melanoma staging.

Clinical Stages I and II are confined to those patients who have no evidence of metastases, at either regional or distant sites, based on clinical, radiologic, and/or laboratory evaluation. Stage III melanoma patients are those with clinical or radiologic evidence of regional metastases, either metastases in the regional lymph nodes or intralymphatic metastases manifesting as either satellite or in-transit metastases. Clinical Stage III groupings rely on clinical and/or radiologic assessment of the regional lymph nodes, which is inherently difficult, especially with respect to assessing both the presence

and the number of metastatic nodes. Therefore, no subgroup definitions of clinically staged patients with nodal or intralymphatic regional metastases have been made. They are all categorized as clinical Stage III disease. Clinical Stage IV melanoma patients have metastases at any distant site and are not substaged further.

Pathologic Staging. Pathologic staging uses all of the same staging information described above under Clinical Staging *plus* information gained from pathologic evaluation of the regional lymph nodes after partial (i.e., sentinel) or complete lymphadenectomy (i.e., after elective or therapeutic lymph node dissection), along with pathologic confirmation of metastases identified by clinical or radiological examinations.

Pathologic Stage I melanoma and Stage II melanoma comprise those patients who have no evidence of regional or distant metastases, based on absence of nodal metastases after careful pathologic examination of the regional lymph nodes, and absence of distant metastases, based on routine clinical and radiologic examination. Pathologic Stage III melanoma patients have pathologic evidence of regional metastases, either in the regional lymph nodes or the intralymphatic sites. The quantitative classification for pathologic nodal status requires that pathologists perform a careful examination of the surgically resected nodal basin and report on the actual number of lymph nodes examined and the number of nodal metastases identified. Pathologic Stage IV melanoma patients have histologic documentation of metastases at one or more distant sites.

With the widespread use of sentinel node lymphadenectomy, it is clear that there is considerable stage migration of patients who have previously been staged as "node negative" but who in fact had undetected nodal metastases. These previously understaged Stage III patients have revealed an extraordinary heterogeneity of metastatic risk for Stage III melanoma. Thus the survival rates among various subgroups of pathologic Stage III patients vary widely, ranging from 9% to 63% 10-year survival.[2]

DEFINITION OF TNM

Patients with melanoma *in situ* are categorized as Tis. Those patients with melanoma presentations that are indeterminate or cannot be microstaged should be categorized as Tx. The T category of melanoma is classified primarily by measuring the thickness of the melanoma as defined by Dr. Alexander Breslow.[6,7] The T category thresholds of melanoma thickness are defined in whole integers (i.e., at 1.0, 2.0, and 4.0 mm). Melanoma ulceration is the absence of an intact epidermis overlying the primary melanoma, assessed by histopathologic examination.[8–10] The level of invasion, as defined by Dr. Wallace Clark,[11] is used to define subcatagories of T1 melanomas but not for thicker melanomas (i.e., T2, T3, or T4).

Regional metastases most commonly present in the regional lymph nodes. The actual number of nodal metastases identified by the pathologist must be reported for staging purposes. A second staging definition is related to tumor burden: microscopic vs. macroscopic. Thus those 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, melanoma patients with both clinical evidence of nodal metastases *and* pathologic examination documenting the number of nodal metastases (after therapeutic lymphadenectomy) are defined by convention as having "macroscopic" or "clinically apparent" nodal metastases. Regional metastases also include intralymphatic metastases, defined as the presence of clinical or microscopic satellites around a primary melanoma, and/or in-transit metastases between the primary melanoma and the regional lymph nodes.

Distant metastases are staged primarily by the organ or site(s) in which they are located. A second factor in staging is the presence or absence of an elevated serum LDH. An elevated serum LDH should be used only when there are two or more determinations obtained more than 24 hours apart, because an elevated serum LDH on a single determination can be falsely positive as a result of hemolysis or other factors unrelated to melanoma metastases.

Primary Tumor (T)

TX	Primary tumor cannot be assessed (e.g., shave biopsy or regressed melanoma)
T0	No evidence of primary tumor
Tis	Melanoma *in situ*
T1	Melanoma ≤ 1.0 mm in thickness with or without ulceration
T1a	Melanoma ≤ 1.0 mm in thickness and level II or III, no ulceration
T1b	Melanoma ≤ 1.0 mm in thickness and level IV or V or with ulceration
T2	Melanoma 1.01–2 mm in thickness with or without ulceration
T2a	Melanoma 1.01–2.0 mm in thickness, no ulceration
T2b	Melanoma 1.01–2.0 mm in thickness, with ulceration
T3	Melanoma 2.01–4 mm in thickness with or without ulceration
T3a	Melanoma 2.01–4.0 mm in thickness, no ulceration
T3b	Melanoma 2.01–4.0 mm in thickness, with ulceration
T4	Melanoma greater than 4.0 mm in thickness with or without ulceration
T4a	Melanoma > 4.0 mm in thickness, no ulceration
T4b	Melanoma > 4.0 mm in thickness, with ulceration

Regional Lymph Nodes (N)

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

N1a Clinically occult (microscopic) metastasis
N1b Clinically apparent (macroscopic) metastasis
N2 Metastasis in two to three regional nodes or intralymphatic regional metastasis without nodal metastases
N2a Clinically occult (microscopic) metastasis
N2b Clinically apparent (macroscopic) metastasis
N2c Satellite or in-transit metastasis *without* nodal metastasis
N3 Metastasis in four or more regional nodes, or matted metastatic nodes, or in-transit metastasis or satellite(s) *with* metastasis in regional node(s)

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
M1a Metastasis to skin, subcutaneous tissues or distant lymph nodes
M1b Metastasis to lung
M1c Metastasis to all other visceral sites or distant metastasis at any site associated with an elevated serum lactic dehydrogenase (LDH)

STAGE GROUPING

Patients with primary melanomas with no evidence of regional or distant metastases (either clinically or pathologically) are divided into two stages: Stage I for early-stage patients with "low risk" for metastases and melanoma-specific mortality and Stage II for those with "intermediate risk" for metastases and melanoma-specific mortality. There are no substages for clinical Stage III melanoma, because criteria for subgrouping can be inaccurate. Pathologic Stage III patients with regional metastases make up a very heterogeneous group that has been divided into three subgroups according to prognostic risk. Stage IIIA patients have up to three microscopic nodal metastases arising from a non-ulcerating primary melanoma and have an "intermediate risk" for distant metastases and melanoma-specific survival. Stage IIIB patients have up to three macroscopic nodal metastases arising from a non-ulcerating melanoma, or have up to three microscopic nodal metastases arising from an ulcerating melanoma, or have intralymphatic metastases without nodal metastases. They constitute a "high-risk" group prognostically. The remaining patients are Stage IIIC and are at "very high risk" for distant metastases and melanoma-specific mortality. The presence of melanoma ulceration "upstages" the prognosis of Stage I, II, and III patients compared to patients with melanomas of equivalent thickness without ulceration or those with nodal metastases arising from a non-ulcerating melanoma. There are no subgroups of Stage IV melanoma.

CLINICAL STAGE GROUPING

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	Any T	N1	M0
	Any T	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

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

PATHOLOGIC STAGE GROUPING

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

Note: 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.

TABLE 24.2. Five-year survival rates of pathologically staged patients (adapted from Balch et al.[2])

	IA	*IB*	*IIA*	*IIB*	*IIC*	*IIIA*	*IIIB*	*IIIC*
Ta: Non-ulcerated Melanoma	T1a	T2a	T3a	T4a		N1a	N1b	N3
	95%	**89%**	**79%**	**67%**		N2a	N2b	
						67%	**54%**	**28%**
Tb: Ulcerated Melanoma		T1b	T2b	T3b	T4b		N1a	N1b
		91%	**77%**	**63%**	**45%**		N2a	N2b
								N3
							52%	**24%**

HISTOPATHOLOGIC TYPE

Melanoma *in situ*
Malignant melanoma, NOS
Superficial spreading melanoma
Nodular melanoma
Lentigo maligna melanoma
Acral lentiginous melanoma,
Desmoplastic melanoma,
Epithelioid cell melanoma
Spindle cell melanoma
Balloon cell melanoma
Blue nevus, malignant
Malignant melanoma in giant pigmented nevus

The following histologies are no longer appropriate for or relevant to the staging of melanoma:

Malignant melanoma, regressing
Meningeal melanomatosis
Amelanotic melanoma
Malignant melanoma in junctional nevus
Precancerous melanosis
Mucosal lentiginous melanoma
Mixed epithelioid and spindle cell melanoma
Spindle cell melanoma, type A
Spindle cell melanoma, type B
Lentigo maligna

PROGNOSTIC FACTORS AND SURVIVAL RESULTS

A summary of survival rates and the demographics of the melanoma patient database used to validate the staging criteria have been published.[2,3] Fifteen-year survival rates for patients with Stages I to IV melanoma are shown in Fig. 24.1.

The AJCC Melanoma Database, which consists of prospectively accumulated melanoma outcome data merged into a single database for the purpose of validating the proposed revisions to the melanoma staging system,[2] includes 17,600 patients with complete clinical and pathologic information for analyzing all of the factors required for the proposed TNM classification and stage grouping.

TABLE 24.3. Cox regression analysis for 13,581 melanoma patients without evidence of nodal or distant metastases (adapted from Balch et al.[2])

Variable	*Chi-Square Value (Wald)*	*P-Value*	*Risk Ratio*	*95% C.I.**
Thickness	244.3	< 0.00001	1.558	1.473–1.647
Ulceration	189.5	< 0.00001	1.901	1.735–2.083
Age	45.6	< 0.00001	1.101	1.071–1.132
Site	41.0	< 0.00001	1.338	1.224–1.463
Level	32.7	< 0.00001	1.214	1.136–1.297
Gender	15.1	0.001	0.836	0.764–0.915

*CI, confidence interval

Ten-year survival rates for each of the T categories are shown in Fig. 24.2. Survival rates for patients with an ulcerated melanoma are proportionately lower than those for patients with a non-ulcerated melanoma of equivalent T category but are remarkably similar to those for patients with a non-ulcerated melanoma of the next highest T category (Fig. 24.2 and Table 24.2). The level of invasion does not reflect prognosis as accurately as tumor thickness, for reasons that have been discussed in previous publications.[4,5,8,12–15] Nevertheless, level of invasion did provide additional prognostic discrimination in the specific subgroup of thin (i.e., T1) melanomas.[2]

In a multivariate analysis of 13,581 patients with localized melanoma (either clinically or pathologically), the two most significant independent characteristics of the primary melanoma were tumor thickness and ulceration (Table 24.3). Indeed, no other feature of the melanoma or of the patient with localized melanoma had the predictive capability of these two factors. Other statistically significant prognostic factors were patient age, site of the primary melanoma, level of invasion, and gender (Table 24.3).

Complete clinical and histopathologic data were available for 1151 patients with lymph node metastases. A Cox multivariate analysis demonstrated that three factors were most significant (with $p < 0.0001$): (1) the number of metastatic nodes, (2) the tumor burden at the time of staging (i.e., microscopic vs. macroscopic), and (3) the presence or absence of ulceration of the primary melanoma (Table 24.4). There was a significantly lower survival (calculated from the time the primary melanoma was diagnosed) for those patients who presented with macroscopic (i.e., palpable) nodal metastases (pN1b, N2b) than for those with microscopic (i.e., non-palpable) nodal metastases, (pN1a, N2a), even after accounting for lead-time bias ($p < 0.0001$). (Fig. 24.3, Table 24.5). Diminishing 5-year survival with increasing tumor burden based on increasing number of metastatic nodes present was observed for all subgroups ($p < 0.0001$) (Table 24.5).

Ulceration of a primary melanoma was the only primary-tumor feature that still predicted an adverse outcome in Stage III disease (Table 24.5, Fig. 24.3). When all three of the most

TABLE 24.4. Cox regression analysis for 1,151 Stage III (nodal metastases) patients (adapted from Balch et al.[2])

Variable	*Chi-Square Value (Wald)*	*P-Value*	*Risk Ratio*	*95% C.I.*
Number of metastatic nodes	57.616	< 0.00001	1.257	1.185–1.334
Tumor burden	40.301	< 0.00001	1.792	1.497–2.146
Ulceration	23.282	< 0.00001	1.582	1.313–1.906
Site	17.843	0.0001	1.461	1.225–1.746
Age	13.369	0.0003	1.118	1.053–1.187
Thickness	1.964	0.1611	1.091	0.966–1.233
Level	0.219	0.6396	1.033	0.901–1.186
Gender	0.006	0.9407	1.007	0.836–1.213

important prognostic factors were taken into account, 5-year survival rates were remarkably heterogeneous ranging from 69% in Stage IIIA patients who had three or fewer microscopic nodal metastases arising from a non-ulcerating primary to 13% for Stage IIIC patients who had four or more metastatic nodal metastases arising from an ulcerated primary melanoma (Table 24.5).

Intralymphatic metastases portend a very poor prognosis.[5,16,17] The available data show no substantial difference in survival outcome for these two anatomically defined entities (satellite metastases and in-transit matastases).[5] Therefore, they are both assigned to a separate N2c classification in the absence of synchronous nodal metastases, because both have a prognosis equivalent to that of multiple nodal metastases. Furthermore, the available data demonstrate that patients with a combination of satellites/in-transit metastases and nodal metastases have a worse outcome than patients who experience either event alone, so these patients are assigned to the N3 classification regardless of the number of synchronous metastatic nodes.

The prognostic influence of different distant metastatic sites was analyzed in 1,158 Stage IV patients, using various combinations of sites of metastases. The most significant differences in 1-year survival rates were noted when lung metastases were compared to all other visceral sites and non-visceral sites (i.e., skin, subcutaneous, distant lymph nodes) (Fig. 24.4). Although it is uncommon in staging classifications to include serum factors prognostically, serum LDH was among the most predictive factors of poor outcome in all published studies where it was analyzed in a multivariate analysis, even after accounting for site and number of metastases.[18–23]

Significant differences were identified when survival rates for melanoma patients who were clinically staged were compared to those whose nodal disease was staged pathologically.[3] These survival differences between clinically and pathologically staged patients were statistically significant among all T substages except T4b (Table 24.6). These results highlight the compelling prognostic value of knowing the nodal status, as identified by lymphatic mapping and sentinel lymphadenectomy, in those situations where accurate staging is important.

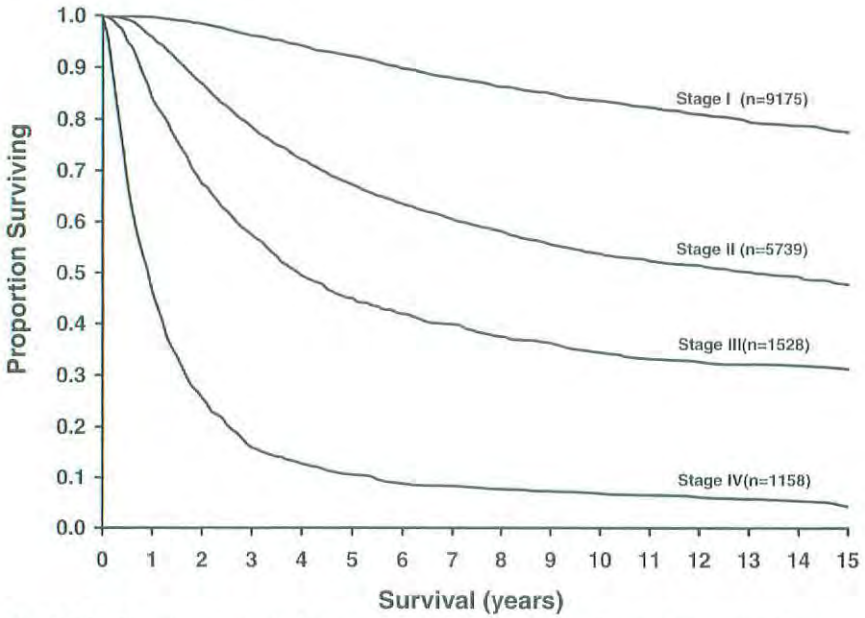

Fig. 24.1. Fifteen-year survival curves for the melanoma staging system, comparing localized melanoma (Stages I and II), regional metastases (Stage III), and distant metastases (Stage IV).[3] The numbers in parentheses are the numbers of patients from the AJCC melanoma staging database used to calculate the survival rates. The differences between the curves are highly significant ($p < 0.0001$).

TABLE 24.5. Five-year survival rates for Stage III (nodal metastases) patients stratified by number of metastatic nodes, ulceration, and tumor burden (adapted from Balch et al.[2])

Melanoma	*Microscopic % ± S.E.*			*Macroscopic % ± S.E.*		
Ulceration	*1+ Nodes*	*2–3 Nodes*	*> 3+ Nodes*	*1+ Nodes*	*2–3 Nodes*	*> 3+ Nodes*
Absent	69 ± 3.7 (n = 252)	63 ± 5.6 (n = 130)	27 ± 9.3 (n = 57)	59 ± 4.7 (n = 122)	46 ± 5.5 (n = 93)	27 ± 4.6 (n = 109)
Present	52 ± 4.1 (n = 217)	50 ± 5.7 (n = 111)	37 ± 8.8 (n = 46)	29 ± 5.0 (n = 98)	25 ± 4.4 (n = 109)	13 ± 3.5 (n = 104)

n indicates the number of patients

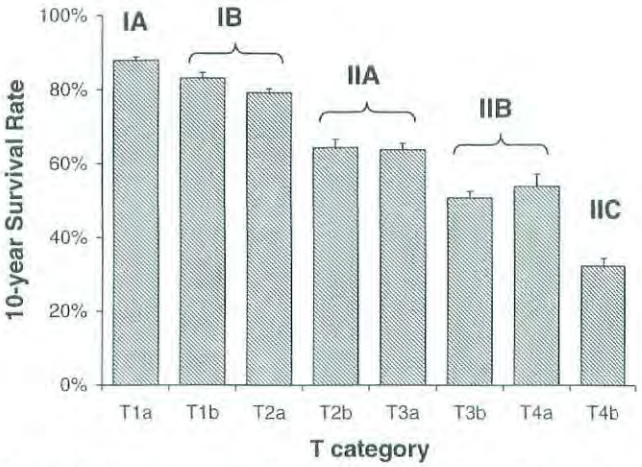

Fig. 24.2. Ten-year survival rates from the AJCC melanoma staging database comparing the different T categories and the stage groupings for Stages I and II melanoma.[3] Note that the stage groupings involve upstaging to account for melanoma ulceration, where thinner melanomas with ulceration are grouped with the next greatest T substage for non-ulcerated melanomas.

The prognostic factors used to validate the melanoma staging system should be the primary stratification criteria and the end-results reporting criteria of melanoma clinical trials. It is recommended that all melanoma patients who have clinically negative regional lymph nodes and may be considered for later entry into surgical and adjuvant therapy clinical trials should have pathologic staging with sentinel lymphadenectomy to ensure prognostic homogeneity within assigned treatment groups. In this way, investigators will be better able to discern between the natural-history impact and the treatment impact being studied in melanoma clinical trials. Moreover, the use of a consistent set of criteria will facilitate the comparability of melanoma clinical trials and thereby accelerate the progress of multidisciplinary melanoma treatment approaches.

MELANOMA GROWTH PATTERNS

The data used to derive the TNM categories were largely based on melanomas with superficial spreading and nodular growth patterns. There is some evidence that other growth

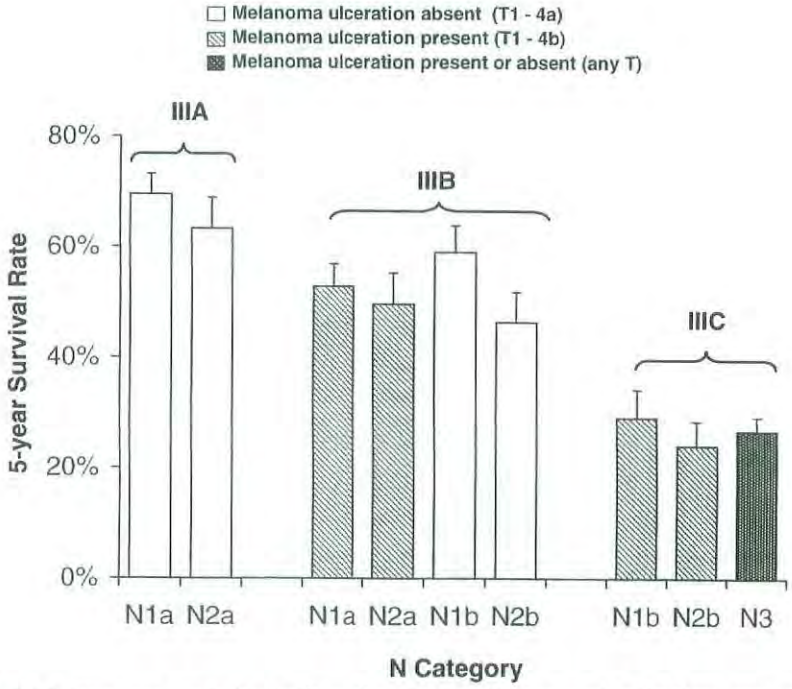

Fig. 24.3. Five-year survival rates from the AJCC melanoma staging database, comparing the different N categories and the stage groupings for Stage III melanoma[3]. The survival results are significantly different when the primary melanoma is ulcerated compared to the equivalent N category of patients without ulceration. See Tables 24.1 and 24.2 for definitions.

TABLE 24.6. Five-year survival rates for 5,346 patients with clinically negative nodal metastases who were pathologically staged after either RND or SLN (adapted from Balch et al.[3])

T stage	*Path Nodes (N)*	*5-Year Survival, % ± S.E.*	*P-value**
T1a	N− (*n* = 379)	94 ± 2.0	0.0035
	N+ (*n* = 15)	64 ± 17.7	
T1b	N− (*n* = 319)	90 ± 2.5	0.0039
	N+ (*n* = 18)	76 ± 14.9	
T2a	N− (*n* = 1480)	94 ± 0.8	< 0.0001
	N+ (*n* = 150)	73 ± 5.6	
T2b	N− (*n* = 408)	83 ± 2.3	< 0.0001
	N+ (*n* = 62)	56 ± 8.8	
T3a	N− (*n* = 808)	86 ± 1.6	< 0.0001
	N+ (*n* = 177)	59 ± 6.0	
T3b	N− (*n* = 639)	72 ± 2.1	< 0.0001
	N+ (*n* = 176)	49 ± 4.5	
T4a	N− (*n* = 203)	75 ± 3.9	0.0116
	N+ (*n* = 66)	61 ± 7.4	
T4b	N− (*n* = 330)	53 ± 3.1	0.2403
	N+ (*n* = 116)	44 ± 5.5	

*The p-value based on the comparison of survival curves using the log rank test.
RND: regional lymph node dissection
SLN: sentinel lymphadenectomy

patterns, namely lentigo maligna melanoma, acral lentiginous melanoma, and desmoplastic melanoma, may have a different etiology and natural history.[24–29] At present, the same staging criteria should be used for melanomas with these growth patterns, even though their prognosis may differ somewhat from the more commonly occurring superficial spreading and nodular growth patterns.

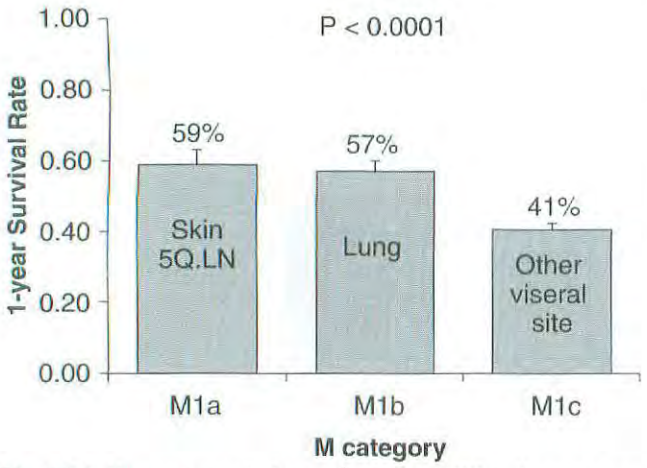

Fig. 24.4. One-year survival rates from the AJCC melanoma staging database comparing the different M categories.[3] See Table 24.1 for definitions. There is a significant difference when skin, subcutaneous and lung metastases are compared to all other sites ($p < 0.0001$).

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HISTOLOGIES—MALIGNANT MELANOMA OF THE SKIN

8720/2	Melanoma *in situ*
8720/3	Malignant melanoma, NOS
8721/3	Nodular melanoma
8722/3	Balloon cell melanoma
8742/3	Lentigo maligna melanoma
8743/3	Superficial spreading melanoma
8744/3	Acral lentiginous melanoma, malignant
8745/3	Desmoplastic melanoma, malignant
8761/3	Malignant melanoma in giant pigmented nevus
8771/3	Epithelioid cell melanoma
8772/3	Spindle cell melanoma
8780/3	Blue nevus, malignant

MELANOMA OF THE SKIN

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____ Laterality: ☐ Bilateral ☐ Left ☐ Right

DEFINITIONS

Clinical	*Pathologic*		
		Primary Tumor (T)	
☐	☐	TX	Primary tumor cannot be assessed (e.g., shave biopsy or regressed melanoma)
☐	☐	T0	No evidence of primary tumor
☐	☐	Tis	Melanoma *in situ*
☐	☐	T1	Melanoma ≤ 1.0 mm with or without ulceration
☐	☐	T1a	Melanoma ≤ 1.0 mm in thickness and level II or III, no ulceration
☐	☐	T1b	Melanoma ≤ 1.0 mm in thickness and level IV or V or with ulceration
☐	☐	T2	Melanoma 1.01–2.0 mm in thickness with or without ulceration
☐	☐	T2a	Melanoma 1.01–2.0 mm in thickness, no ulceration
☐	☐	T2b	Melanoma 1.01–2.0 mm in thickness, with ulceration
☐	☐	T3	Melanoma 2.01–4 mm in thickness with or without ulceration
☐	☐	T3a	Melanoma 2.01–4.0 mm in thickness, no ulceration
☐	☐	T3b	Melanoma 2.01–4.0 mm in thickness, with ulceration
☐	☐	T4	Melanoma greater than 4.0 mm in thickness with or without ulceration
☐	☐	T4a	Melanoma >4.0 mm in thickness, no ulceration
☐	☐	T4b	Melanoma >4.0 mm in thickness, with ulceration
		Regional Lymph Nodes (N)	
☐	☐	NX	Regional lymph nodes cannot be assessed
☐	☐	N0	No regional lymph node metastasis
☐	☐	N1	Metastasis in one lymph node
☐	☐	N1a	Clinically occult (microscopic) metastasis
☐	☐	N1b	Clinically apparent (macroscopic) metastasis
☐	☐	N2	Metastasis in 2 to 3 regional nodes or intralymphatic regional metastasis without nodal metastasis
☐	☐	N2a	Clinically occult (microscopic) metastasis
☐	☐	N2b	Clinically apparent (macroscopic) metastasis
☐	☐	N2c	Satellite or in-transit metastasis without nodal metastasis
☐	☐	N3	Metastasis in four or more regional nodes, or matted metastatic nodes, or in-transit metastasis or satellite(s) with metastasis in regional node(s)

Distant Metastasis (M)

- ☐ MX Distant metastasis cannot be assessed
- ☐ M0 No distant metastasis
- ☐ M1 Distant metastasis
- ☐ M1a Metastasis to skin, subcutaneous tissues, or distant lymph nodes
- ☐ M1b Metastasis to lung
- ☐ M1c Metastasis to all other visceral sites or distant metastasis at any site associated with an elevated serum lactic dehydrogenase (LDH)
  Biopsy of metastatic site performed ..... ☐Y ..... ☐N
  Source of pathologic metastatic specimen _____

Residual Tumor (R)

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

(continued on reverse side)

Pathologic Stage Grouping[1]

☐	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/b	N2c	M0
☐	IIIC	T1-4b	N1b	M0
		T1-4b	N2b	M0
		Any T	N3	M0
☐	IV	Any T	Any N	M1

Clinical Stage Grouping[2]

☐	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
		Any T	N2	M0
		Any T	N3	M0
☐	IV	Any T	Any N	M1

Additional Descriptors

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.

Prognostic Indicators (if applicable)

Notes

1. 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 pathological evaluation of their lymph nodes.

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

Additional Descriptors

Lymphatic Vessel Invasion (L)

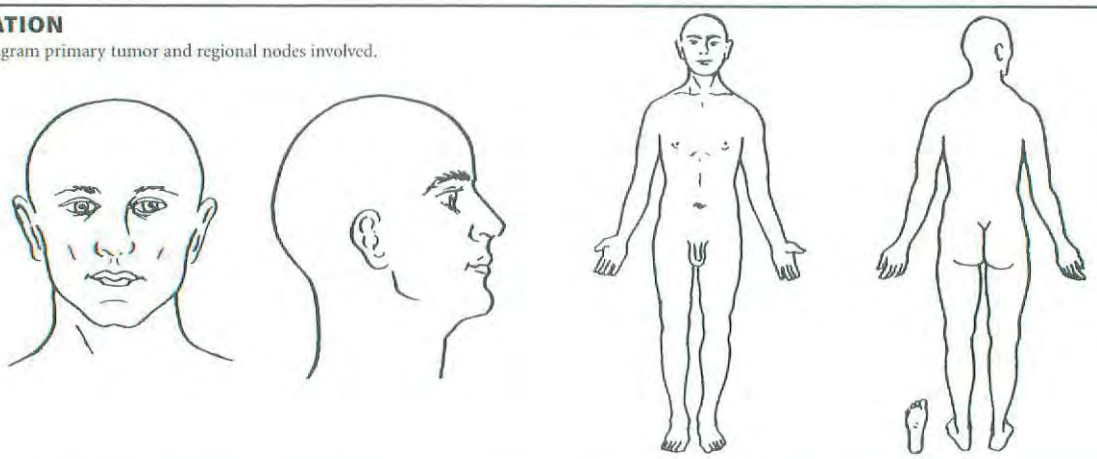
LX Lymphatic vessel invasion cannot be assessed
L0 No lymphatic vessel invasion
L1 Lymphatic vessel invasion

Venous Invasion (V)

VX Venous invasion cannot be assessed
V0 No venous invasion
V1 Microscopic venous invasion
V2 Macroscopic venous invasion

ILLUSTRATION

Indicate on diagram primary tumor and regional nodes involved.



Physician's Signature _____ Date _____

PART VII
Breast

25

Breast

C50.0 Nipple
C50.1 Central portion of breast
C50.2 Upper inner quadrant of breast
C50.3 Lower inner quadrant of breast
C50.4 Upper outer quadrant of breast
C50.5 Lower outer quadrant of breast
C50.6 Axillary tail of breast
C50.8 Overlapping lesion of breast
C50.9 Breast, NOS

SUMMARY OF CHANGES

- Micrometastases are distinguished from isolated tumor cells on the basis of size and histologic evidence of malignant activity.
- Identifiers have been added to indicate the use of sentinel lymph node dissection and immunohistochemical or molecular techniques.
- Major classifications of lymph node status are designated according to the number of involved axillary lymph nodes as determined by routine hematoxylin and eosin staining (preferred method) or by immunohistochemical staining.
- The classification of metastasis to the infraclavicular lymph nodes has been added as N3.
- Metastasis to the internal mammary nodes, based on the method of detection and the presence or absence of axillary nodal involvement, has been reclassified. Microscopic involvement of the internal mammary nodes detected by sentinel lymph node dissection using lymphoscintigraphy but not by imaging studies or clinical examination is classified as N1. Macroscopic involvement of the internal mammary nodes as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination is classified as N2 if it occurs in the absence of metastases to the axillary lymph nodes or as N3 if it occurs in the presence of metastases to the axillary lymph nodes.
- Metastasis to the supraclavicular lymph nodes has been reclassified as N3 rather than M1.

INTRODUCTION

This staging system for carcinoma of the breast applies to infiltrating (including microinvasive) and *in situ* carcinomas. Microscopic confirmation of the diagnosis is mandatory, and the histologic type and grade of carcinoma should be recorded.

ANATOMY

Primary Site. The mammary gland, situated on the anterior chest wall, is composed of glandular tissue with a dense fibrous stroma. The glandular tissue consists of lobules that group together into 15–25 lobes arranged approximately in a spoke-like pattern. Multiple major and minor ducts connect the milk-secreting lobular units to the nipple. Small milk ducts course throughout the breast, converging into larger collecting ducts that open into the lactiferous sinus at the base of the nipple. Most cancers form initially in the terminal duct lobular units of the breast. Glandular tissue is more abundant in the upper outer portion of the breast; as a result, half of all breast cancers occur in this area.

Chest Wall. The chest wall includes ribs, intercostal muscles, and serratus anterior muscle, but not the pectoral muscles.

Regional Lymph Nodes. The breast lymphatics drain by way of three major routes: axillary, transpectoral, and internal mammary. Intramammary lymph nodes are coded as axillary lymph nodes for staging purposes. Supraclavicular lymph nodes are classified as regional lymph nodes for staging purposes. Metastasis to any other lymph node, including cervical or contralateral internal mammary lymph nodes, is classified as distant (M1) (refer to Fig. 25.1.)

The regional lymph nodes are as follows:

1. Axillary (ipsilateral): interpectoral (Rotter's) nodes and lymph nodes along the axillary vein and its tributaries that may be (but are not required to be) divided into the following levels:
   a. Level I (low-axilla): lymph nodes lateral to the lateral border of pectoralis minor muscle.
   b. Level II (mid-axilla): lymph nodes between the medial and lateral borders of the pectoralis minor muscle and the interpectoral (Rotter's) lymph nodes.
   c. Level III (apical axilla): lymph nodes medial to the medial margin of the pectoralis minor muscle, including those designated as apical.
2. Internal mammary (ipsilateral): lymph nodes in the intercostal spaces along the edge of the sternum in the endothoracic fascia.
3. Supraclavicular: lymph nodes in the supraclavicular fossa, a triangle defined by the omohyoid muscle and tendon (lateral and superior border), the internal jugular vein (medial border), and the clavicle and subclavian vein (lower border). Adjacent lymph nodes outside of this triangle are considered to be lower cervical nodes (M1).

Metastatic Sites. Tumor cells may be disseminated by either the lymphatic or the blood vascular system. The four major sites of involvement are bone, lung, brain, and liver, but tumor cells are also capable of metastasizing to many other sites.

RULES FOR CLASSIFICATION

Clinical Staging. Clinical staging includes physical examination, with careful inspection and palpation of the skin, mammary gland, and lymph nodes (axillary, supraclavicular, and cervical), imaging, and pathologic examination of the breast or other tissues as appropriate to establish the diagnosis of breast carcinoma. The extent of tissue examined pathologically for clinical staging is not so great as that required for pathologic staging (see Pathologic Staging below). Imaging findings are considered elements of staging if they are collected within 4 months of diagnosis in the absence of disease progression or through completion of surgery(ies), whichever is longer. Such imaging findings would include the size of the primary tumor and of chest wall invasion, and the presence or absence of regional or distant metastasis. Im-

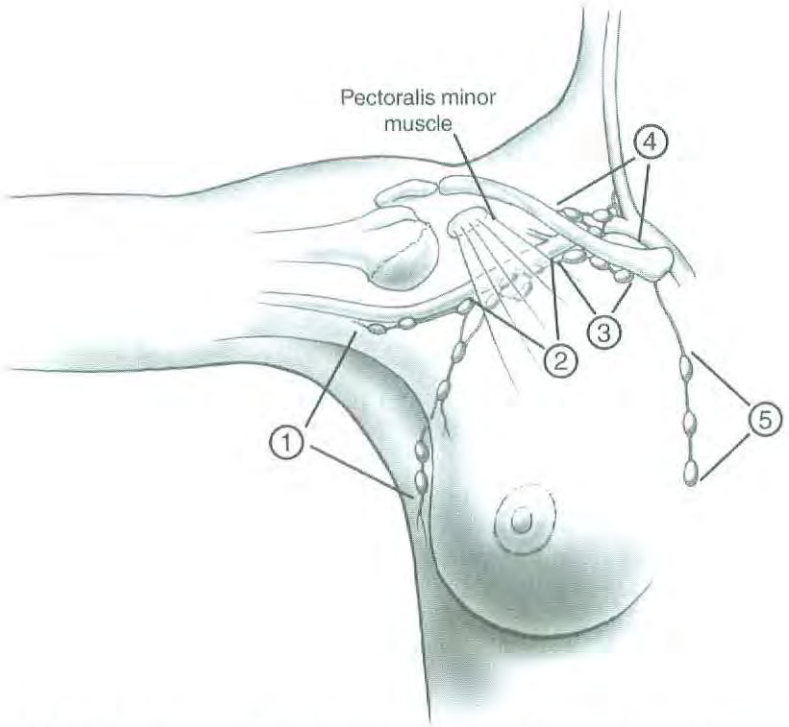


Fig. 25.1. Schematic diagram of the breast and regional lymph nodes. ① Low axillary, Level I; ② Mid-axillary, Level II; ③ High axillary, apical, Level III; ④ Supraclavicular; ⑤ Internal mammary nodes.

aging findings and surgical findings obtained after a patient has been treated with neoadjuvant chemotherapy, hormonal therapy, immunotherapy, or radiation therapy are not considered elements of initial staging.

Pathologic Staging. Pathologic staging includes all data used for clinical staging, plus data from surgical exploration and resection as well as pathologic examination of the primary carcinoma, regional lymph nodes, and metastatic sites (if applicable), including not less than excision of the primary carcinoma with no macroscopic tumor in any margin of resection by pathologic examination. A cancer can be classified pT for pathologic stage grouping if there is only microscopic, but not macroscopic, involvement at the margin. If there is tumor in the margin of resection by macroscopic examination, the cancer is coded pTX because the total extent of the primary tumor cannot be assessed. If the primary tumor is invasive and not only microinvasive, resection of at least the low axillary lymph nodes (Level I)—that is, those lymph nodes located lateral to the lateral border of the pectoralis minor muscle—should be performed for pathologic (pN) classification. Such a resection will ordinarily include six or more lymph nodes. Alternatively, one or more sentinel lymph nodes may be resected and examined for pathologic classification. Certain histologic tumor types (pure tubular carcinoma < 1 cm, pure mucinous carcinoma < 1 cm, and microinvasive carcinoma) have a very low incidence of axillary lymph node metastasis and do not usually require an axillary lymph node dissection. Cancerous nodules in the axillary fat adjacent to the breast, without histologic evidence of residual lymph node tissue, are classified as regional lymph node metastases (N). Pathologic stage grouping includes any of the following combinations of pathologic and clinical classifications: pT pN pM, or pT pN cM, or cT cN pM. If surgery occurs after the patient has received neoadjuvant chemotherapy, hormonal therapy, immunotherapy, or radiation therapy, the prefix "y" should be used with the TNM classification, e.g., ypTNM.

TNM CLASSIFICATION

Primary Tumor (T)

Determining Tumor Size

The clinical measurement used for classifying the primary tumor (T) is the one judged to be most accurate for that particular case (that is, physical examination or imaging such as mammography or ultrasound). The pathologic tumor size for the T classification is a measurement of *only the invasive component.* For example, if there is a 4.0-cm intraductal component and a 0.3-cm invasive component, the tumor is classified T1a. The size of the primary tumor is measured for T classification before any tissue is removed for special studies, such as for estrogen receptors. In patients who have received multiple core biopsies, measuring only the residual lesion may result in significantly underclassifying the T component and thus understaging the tumor. In such cases, original tumor size should be reconstructed on the basis of a combination of imaging and all histologic findings.

Tis Classification

Carcinoma *in situ*, with no evidence of an invasive component, is classified as Tis, with a subclassification indicating type. Cases of ductal carcinoma *in situ* and cases with both ductal carcinoma *in situ* and lobular carcinoma *in situ* are classified Tis (DCIS). Lobular carcinoma *in situ* is increasingly defined as a risk factor for subsequent breast cancer, although there is some evidence that it may occasionally be a precursor of invasive lobular carcinoma. For example, this may be the case with LCIS with more atypical cytology (pleomorphic) as well as more extensive and locally distorting examples of well-developed LCIS.[1] Regardless of this controversy, LCIS is reported as a malignancy by national database registrars and should be designated as such in this classification system—e.g., Tis (LCIS). Paget's disease of the nipple without an associated tumor mass (clinical) or invasive carcinoma (pathologic) is classified Tis (Paget's). Paget's disease with a demonstrable mass (clinical) anywhere within that breast or an invasive component (pathologic) is classified according to the size of the tumor mass or invasive component.

Microinvasion of Breast Carcinoma

Microinvasion is the extension of cancer cells beyond the basement membrane into the adjacent tissues with no focus more than 0.1 cm in greatest dimension. When there are multiple foci of microinvasion, the size of only the largest focus is used to classify the microinvasion. (Do not use the sum of all the individual foci.) The presence of multiple foci of microinvasion should be noted and/or quantified, as it is with multiple larger invasive carcinomas.

Multiple Simultaneous Ipsilateral Primary Carcinomas

The following guidelines are used in classifying multiple simultaneous ipsilateral primary (infiltrating, macroscopically measurable) carcinomas. These criteria do not apply to one macroscopic carcinoma associated with multiple separate microscopic foci. Most conservatively, tumors are defined as arising independently only if they occur in different quadrants of the breast.

1. Use the largest primary carcinoma to designate T classification. Do not assign a separate T classification for the smaller tumor(s).
2. Enter into the record that this is a case of multiple simultaneous ipsilateral primary carcinomas. The outcome of such cases should be analyzed separately.

Simultaneous Bilateral Breast Carcinomas

Each carcinoma is staged as a separate primary carcinoma in a separate organ.

Inflammatory Carcinoma

Inflammatory carcinoma is a clinicopathologic entity characterized by diffuse erythema and edema (peau d'orange) of

the breast, often without an underlying palpable mass. These clinical findings should involve the majority of the skin of the breast. Classically, the skin changes arise quickly in the affected breast. Thus the term *inflammatory carcinoma* should not be applied to a patient with neglected locally advanced cancer of the breast presenting late in the course of her disease. On imaging, there may be a detectable mass and characteristic thickening of the skin over the breast. This clinical presentation is due to tumor emboli within dermal lymphatics, which may or may not be apparent on skin biopsy. The tumor of inflammatory carcinoma is classified T4d. It is important to remember that inflammatory carcinoma is primarily a clinical diagnosis. Involvement of the dermal lymphatics alone does not indicate inflammatory carcinoma in the absence of clinical findings. In addition to the clinical picture, however, a biopsy is still necessary to demonstrate cancer either within the dermal lymphatics or in the breast parenchyma itself.

Skin of Breast

Dimpling of the skin, nipple retraction, or any other skin change except those described under T4b and T4d may occur in T1, T2, or T3 without changing the classification.

Regional Lymph Nodes (N)

Macrometastasis

Cases in which regional lymph nodes cannot be assessed (previously removed or not removed for pathologic examination) are designated NX or pNX. Cases in which no regional lymph node metastasis is detected are designated N0 or pN0.

In patients who are clinically node-positive, N1 designates metastasis to one or more movable ipsilateral axillary lymph nodes, N2a designates metastasis to axillary lymph nodes that are fixed to each other (matted) or to other structures, and N3a indicates metastasis to ipsilateral infraclavicular lymph nodes. Metastasis to the ipsilateral internal mammary nodes are designated as N2b when they are detected by imaging studies (including CT scan and ultrasound, but excluding lymphoscintigraphy) or by clinical examination and when they do not occur in conjunction with metastasis to the axillary lymph nodes. Metastases to the ipsilateral internal mammary nodes are designated as N3b when they are detected by imaging studies or by clinical examination and when they occur in conjunction with metastasis to the axillary lymph nodes. Metastasis to the ipsilateral supraclavicular lymph nodes are designated as N3c regardless of the presence or absence of axillary or internal mammary nodal involvement.

In patients who are pathologically node-positive with one or more tumor deposits greater than 2 mm, cases with 1 to 3 positive axillary lymph nodes are classified pN1a, cases with 4 to 9 positive axillary lymph nodes are classified pN2a, and cases with 10 or more positive axillary lymph nodes are classified pN3a. Cases with histologically confirmed metastasis to the internal mammary nodes, detected by sentinel lymph node dissection but not by imaging studies (excluding lymphoscintigraphy) or clinical examination, are classified as pN1b if occurring in the *absence* of metastasis to the axillary lymph nodes and as pN1c if occurring in the *presence* of metastases to 1 to 3 axillary lymph nodes. (If 4 or more axillary lymph nodes are involved, the classification pN3b is used.) Clinical involvement with histologic confirmation of the internal mammary nodes by imaging studies (excluding lymphoscintigraphy) in the absence or presence of axillary nodal metastases are classified as pN2b and pN3b, respectively. Histologic evidence of metastasis in ipsilateral supraclavicular lymph node(s) is classified as pN3c. A classification of pN3, regardless of primary tumor size or grade, is classified as Stage IIIC. A case in which the classification is based only on sentinel lymph node dissection is given the additional designation (sn) for "sentinel node"—for example, pN1 (sn). For a case in which an initial classification is based on a sentinel lymph node dissection but a standard axillary lymph node dissection is subsequently performed, the classification is based on the total results of the axillary lymph node dissection (that is, including the sentinel node).

Isolated Tumor Cells and Micrometastases

Isolated tumor cells (ITCs) are defined as single cells or small clusters of cells not greater than 0.2 mm in largest dimension, usually with no histologic evidence of malignant activity (such as proliferation or stromal reaction). If an additional immunohistochemical examination was made for ITCs in a patient with histologically negative lymph nodes, the regional lymph nodes should be designated as pN0(i−) or pN0(i+), as appropriate.

Micrometastases are defined as tumor deposits greater than 0.2 mm but not greater than 2.0 mm in largest dimension that may have histologic evidence of malignant activity (such as proliferation or stromal reaction). Cases in which only micrometastases are detected (none greater than 2 mm) are classified pN1mi. The classification is designated as (i+) for "immunohistochemical" if micrometastasis was detected only by IHC [e.g., pN1mi (i+)].

If histologically and immunohistochemically negative lymph nodes are examined for evidence of metastasis using molecular methods [reverse transcriptase–polymerase chain reaction (RT-PCR)], the regional lymph nodes are classified as pN0(mol−) or pN0(mol+), as appropriate.

Distant Metastasis (M)

Cases where distant metastasis cannot be assessed are designated MX, cases in which there is no distant metastasis are designated M0, and cases in which one or more distant metastases are identified are designated M1. A negative clinical history and examination are sufficient to designate a case as M0; extensive imaging or other testing is not required. Note that positive supraclavicular lymph nodes are now classified as N3 rather than M1.

DEFINITION OF TNM

Primary Tumor (T)

Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. If the measurement is made by physical examination, the examiner will use the major headings (T1, T2, or T3). If other measurements, such as mammographic or pathologic measurements, are used, the subsets of T1 can be used. Tumors should be measured to the nearest 0.1 cm increment.

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
Tis (DCIS)	Ductal carcinoma *in situ*
Tis (LCIS)	Lobular carcinoma *in situ*
Tis (Paget's)	Paget's disease of the nipple with no tumor

Note: Paget's disease associated with a tumor is classified according to the size of the tumor.

T1	Tumor 2 cm or less in greatest dimension
T1mic	Microinvasion 0.1 cm or less in greatest dimension
T1a	Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
T1b	Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
T1c	Tumor more than 1 cm but not more than 2 cm in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below
T4a	Extension to chest wall, not including pectoralis muscle
T4b	Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

Regional Lymph Nodes (N)

Clinical

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

**Clinically apparent* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.

Pathologic (pN)[a]

pNX	Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis histologically, no additional examination for isolated tumor cells (ITC)

Note: Isolated tumor cells (ITC) are defined as single tumor cells or small cell clusters not greater than 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods but which may be verified on H&E stains. ITCs do not usually show evidence of malignant activity e.g., proliferation or stromal reaction.

pN0(i−)	No regional lymph node metastasis histologically, negative IHC
pN0(i+)	No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm
pN0(mol−)	No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)[b]
pN0(mol+)	No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)[b]

[a]Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," e.g., pN0(i+) (sn).

[b]RT-PCR: reverse transcriptase/polymerase chain reaction.

pN1	Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
pN1mi	Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)
pN1a	Metastasis in 1 to 3 axillary lymph nodes
pN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
pN1c	Metastasis in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent.** (If associated with greater than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden)
pN2	Metastasis in 4 to 9 axillary lymph nodes, or in clinically apparent* internal mammary lymph nodes in the *absence* of axillary lymph node metastasis
pN2a	Metastasis in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastasis in clinically apparent* internal mammary lymph nodes in the *absence* of axillary lymph node metastasis
pN3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent* ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm), or metastasis to the infraclavicular lymph nodes
pN3b	Metastasis in clinically apparent* ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes

**Clinically apparent* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

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

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

STAGE GROUPING

Stage 0	Tis	N0	M0
Stage I	T1*	N0	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

*T1 includes T1mic

Note: Stage designation may be changed if post-surgical 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.

HISTOPATHOLOGIC TYPE

The histopathologic types are the following:

In situ Carcinomas

NOS (not otherwise specified)
Intraductal
Paget's Disease and intraductal

Invasive Carcinomas

NOS
Ductal
Inflammatory
Medullary, NOS
Medullary with lymphoid stroma
Mucinous
Papillary (predominantly micropapillary pattern)

Tubular
Lobular
Paget's Disease and infiltrating
Undifferentiated
Squamous cell
Adenoid cystic
Secretory
Cribriform

HISTOLOGIC GRADE (G)

All invasive breast carcinomas with the exception of medullary carcinoma should be graded. The Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom-Richardson grading system) is recommended.[2,3] The grade for a tumor is determined by assessing morphologic features (tubule formation, nuclear pleomorphism, and mitotic count), assigning a value of 1 (favorable) to 3 (unfavorable) for each feature, and adding together the scores for all three categories. A combined score of 3–5 points is designated as grade 1; a combined score of 6–7 points is grade 2; a combined score of 8–9 points is grade 3.

HISTOLOGIC GRADE (NOTTINGHAM COMBINED HISTOLOGIC GRADE IS RECOMMENDED)

GX	Grade cannot be assessed
G1	Low combined histologic grade (favorable)
G2	Intermediate combined histologic grade (moderately favorable)
G3	High combined histologic grade (unfavorable)

CONSIDERATIONS FOR EVIDENCE-BASED CHANGES TO THE *AJCC CANCER STAGING MANUAL*, 6TH EDITION

Should histologic grade (Nottingham combined histologic grade recommended) be incorporated into the TNM classification system?

It was first recognized by Hansemann in 1890 that the morphological appearance of tumors was associated with the degree of malignancy,[4] and the first formal grading of morphologic features in breast cancer occurred 35 years later.[5] Since then, the histologic grading of invasive breast carcinoma has been clearly shown to provide significant prognostic information.[2,6–9] Different approaches to histologic grading have been described and used. Though all of these approaches offer some degree of prognostic information, there are varying levels of agreement among them, and this makes clinical studies difficult to compare. In addition, grading is by nature subjective, and there can be substantial differences in assessment even when the same grading system is used.[10–13]

Several observers have pointed out that observer variation in estimating histologic grade may have only a small adverse effect in estimating prognosis, especially if the variation in outcome is greater than the variation among observers.[8,14] This may be true in a general way, but it should be remembered that the inclusion of histologic grade in the AJCC staging system will affect data collection and coding for national cancer registrars. Institute-to-institute reproducibility will be an important requirement for data inclusion in these large databases.

The modification of the Bloom and Richardson grading system by Elston and Ellis (the Nottingham combined histologic grade)[2] was designed to make grading criteria more quantitative. Three morphologic features (percentage of tubule formation, degree of nuclear pleomorphism, and accurate mitotic count in a defined field area) are evaluated semiquantitatively, and a numerical score for each is used in calculating the overall grade. Elston and Ellis compiled long-term survival information from 1,831 patients for whom a Nottingham combined histologic grade was assessed, and they found a very strong correlation with prognosis ($p < 0.0001$). In subsequent studies, better interobserver agreement was obtained with the Nottingham combined histologic grade than with previous systems,[15–17] and it is recommended in the College of American Pathologists Consensus Statement.[3] Thus the Nottingham combined histologic grade is strongly recommended in this revision for the histologic grading of tumors.

Even with this more quantitative approach, significant variation in results can stem from technical variations in processing the tumor tissue. The time lag between surgical excision and fixation can vary greatly from one case to another (from 10 min to 4 hr in one published study[18]). A time lag of as little as 2 hours can result in mitotic rate decreases of 10% to 30%,[19,20] and a delay of 24 hours can result in a striking decline of more than 75%.[21] Even with fixation times standardized, the type of fixative used can also be an important element; some commonly used fixatives contribute to suboptimal cell morphology.[17,18] Precise guidelines about these technical details will be important in ensuring data comparability across institutes.

Thus histologic grading has prognostic value, and improved reproducibility is possible with the Nottingham combined histologic grade. The question of how to add grading to the existing TNM classification system remains. Because large tumors (T3, T4) nearly always carry a recommendation for adjuvant therapy, and because many such tumors tend to be high grade, the addition of grading information would not be expected to have a significant effect on treatment planning for this group. Most conservatively, grading should be considered in those cases where it would influence treatment decisions most heavily—that is, for small (T1,T2) node-negative tumors. It is unfortunate, therefore, that available evidence about the interaction between tumor size and histologic grade as they relate to patient outcome is disappointingly meager for these small tumors.

Table 25.1 shows the results of eight retrospective studies that analyzed outcome data on the basis of histologic grade in small tumors.[8,14,18,22–26] Because of the variety of follow-up

TABLE 25.1. Histologic grade and outcome in patients with early-stage breast cancer.

Authors	Patient Description	Number of patients	Follow-up (years)	Grading System[a]	Outcome Measured[b]	Outcome		
						Grade 1	Grade 2	Grade 3
Rosen et al., 1989[21]	T1, N0	644	20	NS	Relapse	10%	23%	30%
Henson et al., 1991[7]	T1, N0 or T0,N1	22,616	10	NS	Relative survival	95%	91%	84%[c]
	T1/2, N1 or T2, N0		10	NS	Relative survival	82%	71%	63%[c]
Rosner & Lane, 1991[22]	T1a/b	113	7	BR	DFR	100%[d]		91%
	T1c	125	7	BR	DFR	91%[d]		79%
	T2	132	7	BR	DFR	65%[d]		70%
Genestie et al., 1998[17]	T1/2, N0/1	877	5	N	OS	96%	88%	80%
					MFS	91%	81%	78%
Kollias et al., 1999[23]	T1a/b, N0	318	10	N	OS	95%	91%	91%
Leitner et al., 1999[24]	T1a/b	218	7	WHO	RFS	100%	97%	88%
Reed et al., 2000[25]	T1/2, N0	228	10	N	RFS	90%	70%	69%
					OS	94%	86%	78%
Lundin et al., 2001[13]	T1, N0	665	5	WHO	DDFS	98%	86%	87%
	T2, N0	244	5	WHO	DDFS	96%	78%	69%

[a]NS: grading system not specified; BR: Bloom-Richardson; N: Nottingham combined histologic grade; WHO: World Health Organization
[b]DFR: disease-free rate; OS: overall survival; MFS: metastasis-free survival; RFS: relapse-free survival; DDFS: distant-disease-free survival
[c]Original Grades 3 and 4 showed no significant difference and were collapsed into Grade 3 for this review.
[d]Original Grades 1 and 2 were collapsed into one category in the original study.

times, grading systems, patient samples, and measured outcomes, it is difficult to extract a consistent picture from these studies. All studies showed a difference between Grade 1 and Grade 3, but the positioning of the Grade 2 intermediate tumors varied, sometimes clustering with Grade 1 and at other times clustering with Grade 3. In those studies that specifically used the Nottingham combined histologic grade,[18,24,26] Grade 2 either clustered with Grade 3 or else was intermediate between Grades 1 and 3 for a variety of outcomes. Three studies specifically looked at T1a/b tumors.[23–25] These studies used three different histologic grading systems and three different outcomes, but they nonetheless showed somewhat smaller outcome differences between Grade 1 and Grade 3 than other studies that included larger tumors.

These tentative observations, coupled with the overall sparseness and variability of the information, strongly suggest that the available data are not yet mature enough to offer guidance in incorporating histologic grade into the staging system for breast cancer. Because the evidence indicating that histologic grade is an important prognostic factor in breast cancer is so robust, it seems certain that emerging data will support the incorporation of grade into the AJCC staging system in the near future.

Should the classification of pathologic lymph node status in node-negative patients be amplified to include information about isolated tumor cells detected by immunohistochemical techniques?

Isolated tumor cells (ITCs) are defined as single tumor cells or small clusters of cells that are not greater than 0.2 mm in size and that usually show no histologic evidence of malignant activity (such as proliferation or stromal reaction). Although there is a growing feeling that ITCs detected by immunohistochemical staining may be prognostically relevant, their clinical significance has not yet been demonstrated. Even with larger clusters of single cells, it is not clear whether a finding of ITC would justify an axillary lymph node dissection. This is especially true for ITCs found in sentinel lymph nodes in cases where the primary tumor is very small and the probability of metastasis in a nonsentinel lymph node seems to be virtually zero.[27]

Clearly, organized large-scale data collection is essential for determining the clinical significance of ITCs. For this reason, a uniform shorthand is now suggested for describing pN0 patients where there has been immunohistochemical examination for ITCs. The added designation of "i+" or "i−" indicates that immunohistochemical staining was performed with positive or negative results.

Should micrometastases (pN1mi) detected by immunohistochemical staining and not verified by H&E staining be classified as pN1?

Micrometastases are defined as tumor deposits greater than 0.2 mm and no greater than 2.0 mm in size. Unlike isolated tumor cells, micrometastases may show histologic evidence of metastatic activity, such as proliferation or stromal reaction. The use of immunohistochemical techniques (IHC) to detect occult micrometastases has increased dramatically with the growing acceptance of sentinel lymph node dissection. The reported incidence of nodal micrometastases detected by IHC in patients who are histologically node-negative has ranged from 12% to 29%.[28–32]

The unresolved issue is whether micrometastases detected by IHC and not verified by standard histologic staining have a significant impact on patient outcome. Retrospective

studies have reported decreases in disease-free survival ranging from 10% to 22% in some subgroups of patients where micrometastatic axillary disease was detected by immunohistochemical techniques. A significant percentage of histologically node-negative patients ultimately experience distant recurrence and die of their disease, and it has been suggested that some of this subgroup of patients may be those with occult micrometastases in the axillary nodes, but bone marrow and other metastases may occur with no axillary involvement.[30,31,33]

The premise that H&E verification is required to validate the metastatic potential of lesions detected by IHC is under increasing scrutiny. Cell deposits identified only by IHC are increasingly being used to make clinical recommendations without H&E verification. The size of the micrometastatic focus may prove to be critical; a 1-mm IHC-positive lesion may contain as many as 500,000 cells, and this would clearly meet the proliferation requirement for metastatic potential, regardless of H&E verification. Nonetheless, verification by H&E staining is recommended by the College of American Pathologists, because it provides more definitive cytologic and histologic evidence of malignancy than is usually available from immunostained preparations and avoids overinterpretation of staining artifacts.

Should size criteria be used to distinguish between isolated tumor cells and micrometastases?

Isolated tumor cells should theoretically be distinguishable from micrometastases on the basis of metastatic characteristics, such as proliferation or stromal reaction.[34] This distinction can be highly subjective, however, and replication among pathologists and among institutions may be difficult. This revision incorporates size criteria to assist in making this distinction, with isolated tumor cell groups defined as not greater than 0.2 mm in diameter and micrometastases defined as greater than 0.2 mm and not greater than 2.0 mm in diameter. The use of 2.0 mm as an upper size limit for micrometastases, originally proposed by Huvos and colleagues in 1971,[35] is consistent with standards already used in the AJCC staging system. The use of 0.2 mm as a lower limit was selected because it significantly reduces the likelihood that ITCs will be recorded as micrometastases, without making it necessary to estimate actual cell number counts in ITCs. The resulting classification of patients with metastatic tumor deposits no greater than 0.2 mm as pN0 is consistent with the low recurrence rates typically seen in this patient group.

How should RT-PCR be used in the detection of small tumor deposits?

An even finer level of resolution in the detection of isolated tumor cells and micrometastases is potentially available with the use of reverse transcriptase–polymerase chain reaction (RT-PCR). Verbanac and colleagues[36] recently reported that this technique was able to identify a neoplastic marker in a significant percentage of sentinel nodes that were negative for disease by both histologic and immunohistochemical staining. This is not altogether surprising, given that RT-PCR is theoretically capable of identifying single cells. However, it seems unlikely that such cells would become clinically important. There is evidence that such highly sensitive tests produce false positive results. Furthermore, because an entire block of lymph node tissue is digested in preparation for RT-PCR, it would be technically challenging to determine the exact size of the original lesion.

Pending further developments in this area, this edition of the *AJCC Cancer Staging Manual* will classify any lesion identified by RT-PCR alone as pN0 (the classification it would have had using standard histologic staining) for the purposes of staging. All cases that were histologically negative for regional lymph node metastasis and in which an additional examination for tumor cells was made with RT-PCR will have the appended designation (mol+) or (mol−), as appropriate.

Should the classification of pathological lymph node status in node-positive (all nodes with deposits greater than 0.2 mm) patients be changed to reflect more clearly the prognostic significance of number of affected nodes?

In past editions of the *AJCC Cancer Staging Manual*, the TNM system has used similar definitions for clinical lymph node status and pathological lymph node status. This has had the unfortunate result of assigning number of affected lymph nodes to subcategories of the pN1 classification, effectively ignoring this important prognostic indicator.

In this revision, patients with 1 to 3 positive axillary lymph nodes (with at least one tumor deposit greater than 2 mm and all tumor deposits greater than 0.2 mm) are classified as pN1a, patients with 4 to 9 positive axillary lymph nodes are classified as pN2a, and patients with 10 or more positive axillary lymph nodes are classified as pN3a. This recognition of the prognostic importance of the absolute number of involved lymph nodes is in keeping with current clinical practice and is supported by a large body of clinical data. The decision to separate patients with 1 to 3 positive nodes from patients with 4 or more positive nodes is consistent with survival data reported by Carter and colleagues (see Fig. 25.2).[37] These researchers examined 5-year survival rates by tumor size and lymph node status in 24,740 breast cancer cases recorded in the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. In each size group of tumors (< 2 cm, 2–5 cm, > 5 cm) they found an inverse relationship between overall survival and number of positive nodes. In patients with tumors < 2 cm in size, for example, the relative 5-year survival was 96.3% for patients with negative nodes, 87.4% for patients with 1 to 3 positive nodes, and 66.0% for patients with 4 or more positive nodes.

The decision to separate patients with 10 or more positive nodes into the N3a category, though somewhat more arbitrary, is based on the recognition that survival rates continue to decrease with increasing numbers of positive axillary lymph nodes. In a survey of 20,547 cases of breast carcinoma collected by the American College of Surgeons, Nemoto and colleagues[38] demonstrated that expected survival declined

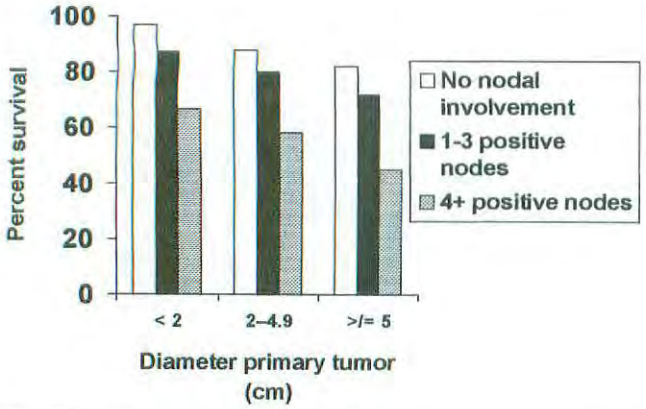


Fig. 25.2. Five-year relative survival of breast cancer as a function of both tumor diameter and number of positive axillary lymph nodes. (From Carter, et al: Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer 63:181–187, 1989. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

linearly with increasing number of axillary lymph nodes that were positive by histologic examination, up to a total of 21 positive nodes (Fig. 25.3). The specific breakpoint used here (≥ 10) is in common usage. (See, for example, the report on the NSABP B-11 protocol in Paik et al.[39] and various other clinical studies.[40–42])

The change in classification of axillary lymph node-positive patients reorganizes the pathologic staging system to reflect more closely the current practice standards used by clinicians in stratifying patients for prognosis and treatment decisions.

Should a finding of positive internal mammary lymph nodes retain a current classification of N3?

Data from the National Cancer Data Base (1985–1991) were analyzed to compare 5-year relative survival rates in all Stage IIIB breast cancer patients versus only Stage IIIB cancer patients with positive internal mammary nodes (N3)(L.L. Douglas, personal communication). For all Stage IIIB cancers ($n = 9775$), the relative 5-year survival rate was 47.6% with a 99% confidence interval of 45.7–49.5. For Stage IIIB cases with N3 only ($n = 717$), the relative survival rate was 45.2% with a 99% confidence interval of 38.6–51.9. This suggests no survival difference between N3 patients and the Stage IIIB group as a whole. In a separate report, Veronesi and colleagues[43] reported the results of a randomized trial carried out from 1964 to 1968 in which T1–3, N0–1 breast cancer patients were treated with a Halsted mastectomy or with an extended mastectomy that included removal of the internal mammary nodes. In the 342 patients treated with extended mastectomy, the 5-year overall survival rate was 44% in patients with positive internal mammary nodes, compared with 78% in patients with negative internal mammary nodes. These survival rates are consistent with those taken from the National Cancer Data Base.

TABLE 25.2. Survival rates in breast cancer patients as a function of nodal status in the axillary and internal mammary lymph nodes

		% Survival		
Author	*N*	*IM−/AX+*	*IM+/AX−*	*Both positive*
Bucalossi et al., 1971[45]	610	56	79	28
Caceres, 1967[44]	425	52	56	24
Li & Shen, 1983[45]	1242	60	73	38
Urban & Marjani, 1971[46]	500	68	64	54
Veronesi et al., 1983[47]	995	72	88	56

IM: Internal mammary lymph nodes; AX: axillary lymph nodes

A problem with these reports is that neither one considers the independent survival effects of positive internal mammary lymph nodes (IM) in the absence of positive axillary lymph nodes (AX). Table 25.2 shows the results of five studies that compared survival rates in patients who were IM−/AX+, IM+/AX−, and IM+/AX+.[44–48] Although the survival rates in the first two categories were similar, there was a significant decrease in survival in patients who were IM+ and AX+.

On the basis of these findings, this revision classifies clinically positive internal mammary lymph nodes that are detected by imaging studies (including CT scan or ultrasound, but excluding lymphoscintigraphy) or by clinical examina-

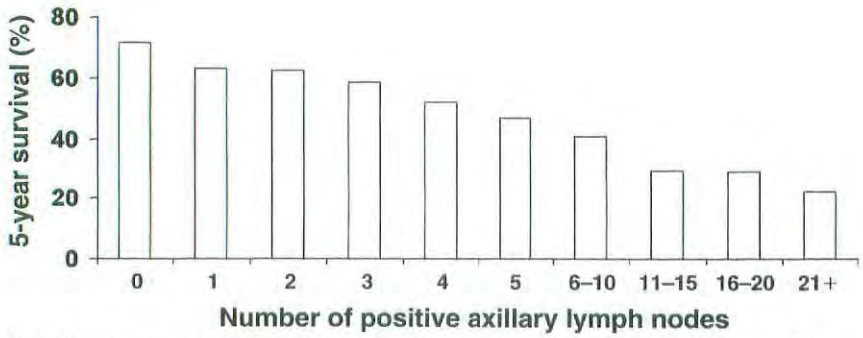


Fig. 25.3. Survival of 20,547 women with breast cancer according to the number of histologically involved axillary nodes. (Data from Nemoto et al: Management and survival of female breast cancer: results of a national survey by the American College of Surgeons. Cancer 45:2917–2924, 1980.)

tion as N2b when they occur in the *absence* of positive axillary lymph nodes and as N3b when they occur in the *presence* of positive axillary lymph nodes. In cases where proven microscopic disease is detected in the internal mammary lymph nodes, the classification is based on whether the disease was clinically occult. For positive internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not by imaging studies (excluding lymphoscintigraphy), the pathologic classification is pN1b in the *absence* of positive axillary lymph nodes and is pN1c in the *presence* of 1 to 3 positive axillary lymph nodes. Positive internal mammary nodes discovered by sentinel lymph node dissection but in the presence of 4 or more positive axillary lymph nodes are considered pN3b to reflect the increased tumor burden. For positive internal mammary nodes with histologic macroscopic disease detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination, the classification is pN2b in the *absence* of positive axillary lymph nodes and is pN3b in the *presence* of positive axillary lymph nodes.

Should a finding of positive supraclavicular lymph nodes be classified as N3 rather than M1?

As early as 1907, it was recognized that clinically evident supraclavicular lymph nodes (SCLN) conferred a poor prognosis for breast cancer patients.[49] Clinical studies carried out from 1966 to 1995 reported 5-year survival rates ranging from 5% to 34% (median 18%).[50] The bad prognosis led to the conclusion that SCLN metastasis qualified as distant metastasis (M1) rather than as an advanced regional lymph node metastasis (N3), and this change was incorporated into the 1997 revision of the *AJCC Cancer Staging Manual*.[51]

An examination of these earlier studies reveals a bias against treating patients aggressively when a positive SCLN was treated as a distant metastasis. Because patients with distant metastases are considered incurable, most studies used only locoregional therapy (surgery and/or irradiation) in the treatment of SCLN-positive patients, and such therapy was considered palliative.

A recent study by Brito and colleagues[52] provides evidence that aggressive treatment of SCLN-positive patients results in outcomes comparable to those in patients with locally advanced breast cancer (LABC, Stage IIIB) without distant metastasis. In this study, 70 patients with SCLN-positive LABC received intensive treatment that included induction chemotherapy, surgery, post-surgical chemotherapy, and irradiation. At a median follow-up time of 8.5 years, there was no difference in disease-free survival or overall survival in LABC patients with positive SCLN and no other sign of distant metastasis compared with Stage IIIB patients without distant metastasis. Both Stage IIIB and SCLN-positive patients differed significantly in overall survival when compared with Stage IV patients (Fig. 25.4). These findings indicate that classifying SCLN as a distant metastasis may be a disservice to patients, because it implies incurability and may lead to suboptimal therapy. Patients with ipsilateral SCLN metastases and no other distant metastases should be classified as N3 rather than M1, because their clinical course and outcomes are similar to patients with stage IIIB LABC. To clarify the significance of N3 disease, the new category Stage IIIC has been instituted for any T, N3 that includes pN3a, pN3b, or pN3c.

Are there other prognostic factors that are powerful enough to consider for inclusion in the TNM grading system?

Prognostic factors provide information about potential patient outcome in the absence of systemic therapy. These factors tend to reflect biologic characteristics of the tumor, such as proliferation, invasiveness, and metastatic capacity. Prognostic factors must be carefully distinguished from predictive factors, which reflect response to a particular therapeutic agent or combination of agents.

A clinically useful prognostic factor is one that is statistically significant (its prognostic value only rarely occurs by chance), independent (it retains its prognostic value when combined with other factors), and clinically relevant (it has a major impact on prognostic accuracy). Axillary lymph node status has been shown definitively to be the single most important prognostic factor for disease-free and overall survival in breast cancer patients.[3]

In the Fifth Edition of the *AJCC Cancer Staging Manual*,[51] it was reported that approximately 80 potential prognostic variables had been identified for human breast cancer. Since that time, additional factors have been suggested (various growth factors with their receptors and binding proteins; proteases, including cathepsin-D, urokinase-type plasminogen activator, and matrix metalloproteinases). Simultaneously, some factors that were once considered promising have yielded ambiguous or disappointing results in outcome studies (p53, HER2/neu), often because technical approaches have not been standardized and data are difficult to compare between studies.

In addition to axillary lymph node status, the College of American Pathologists Consensus Report[3] and the clinical practice guidelines from the American Society of Clinical Oncology[53,54] have identified tumor size, histopathologic grade, and mitotic index as clinically useful prognostic factors. (This revision recommends the routine use of the Nottingham combined histologic grading system, which incorporates mitotic index into the measurement of tumor grade.) DNA ploidy was reported to be an unreliable prognostic marker in both studies. Estrogen receptor status, although a good predictive factor for response to hormonal therapy, is a relatively weak prognostic factor. Promising results have been reported in some cases for p53, but lack of standardization and data comparability are ongoing problems. Similar problems affect the use of HER2/neu as a prognostic factor, although it should be routinely measured in patients to predict the likelihood of their response to Herceptin® should they relapse after standard adjuvant therapy. Factors such as Ki-67 continue to have technical problems that limit inter-user reproducibility.

It is expected that ongoing studies will provide more definitive evidence about the clinical usefulness of many of

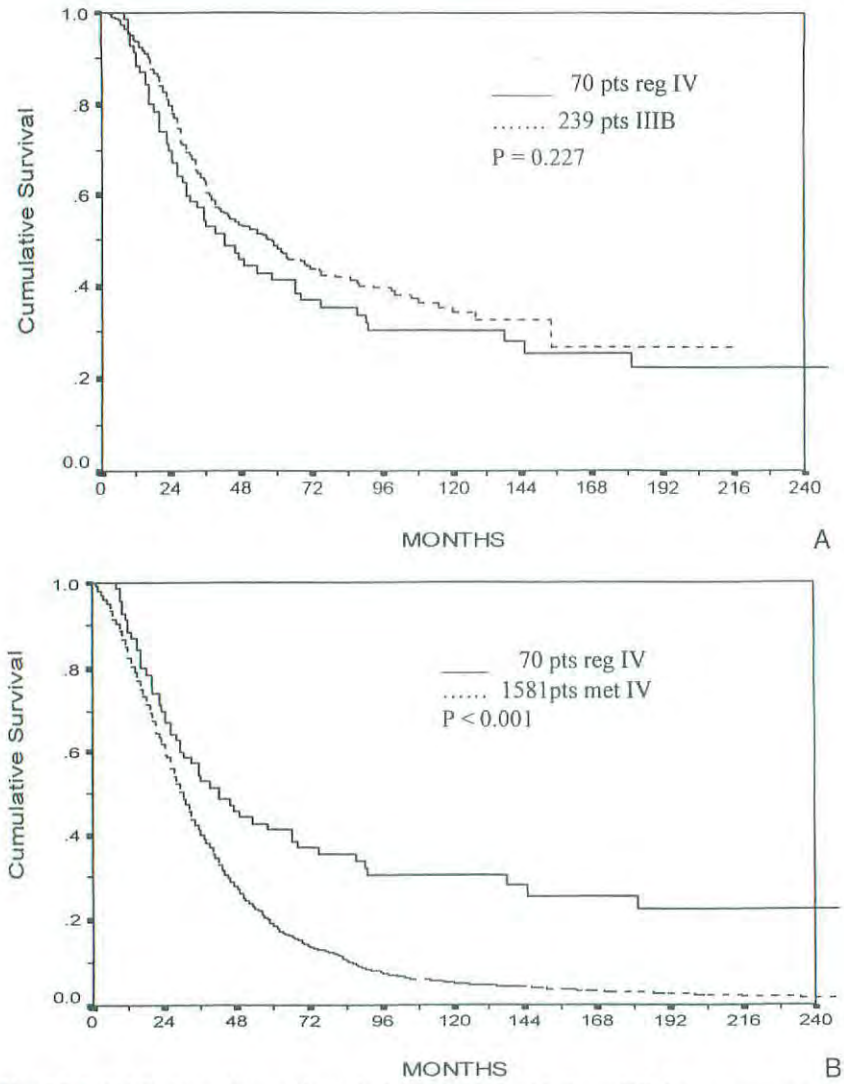


Fig. 25.4. (A) Estimated overall survival for patients with Stage IIIB breast cancer compared with regional Stage IV breast cancer (ipsilateral supraclavicular adenopathy without evidence of distant disease). (B) Estimated overall survival for patients with regional Stage IV breast cancer (ipsilateral supraclavicular adenopathy without evidence of distant disease) compared with patients with Stage IV breast cancer (distant metastases). (Reprinted from Brito et al: Long-term results of combined-modality therapy for locally advanced breast cancer with ipsilateral supraclavicular metastases: The University of Texas M. D. Anderson Cancer Center experience. J Clin Oncol 19(3):628–633, 2001 with permission.)

these factors. These studies should also contribute to the standardization of assay systems and analytic approaches that will be required to achieve reproducibility among different researchers and different institutions. Such studies of promising new prognostic factors should simultaneously measure and report proven factors—particularly size, nodal status, and histologic grade—to indicate how much the new factors reflect the classic ones.

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HISTOLOGIES—BREAST

8010/2	Carcinoma *in situ*, NOS
8010/3	Carcinoma, NOS
8020/3	Carcinoma undifferentiated, NOS
8070/3	Squamous cell carcinoma, NOS
8200/3	Adenoid cystic carcinoma
8201/2	Cribriform carcinoma *in situ*
8201/3	Cribriform carcinoma, NOS
8211/3	Tubular adenocarcinoma
8480/3	Mucinous adenocarcinoma
8500/2	Intraductal carcinoma, noninfiltrating, NOS
8500/3	Infiltrating duct carcinoma, NOS
8501/2	Comedocarcinoma, noninfiltrating
8502/3	Secretory carcinoma of breast
8503/2	Noninfiltrating intraductal papillary adenocarcinoma
8510/3	Medullary carcinoma, NOS
8520/2	Lobular carcinoma *in situ*, NOS
8520/3	Lobular carcinoma, NOS
8522/2	Intraductal carcinoma and lobular carcinoma *in situ*
8530/3	Inflammatory carcinoma
8540/3	Paget's disease, mammary
8541/3	Paget's disease and infiltrating duct carcinoma of breast
8543/2	Paget's disease and intraductal carcinoma of breast
8980/3	Carcinosarcoma, NOS
9020/3	Phyllodes tumor, malignant

BREAST

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____ Laterality: ☐ Bilateral ☐ Left ☐ Right

DEFINITIONS

Clinical	*Pathologic*	Primary Tumor (T)	
☐	☐	TX	Primary tumor cannot be assessed
☐	☐	T0	No evidence of primary tumor
☐	☐	Tis	Carcinoma *in situ*
☐	☐	Tis	(DCIS) Ductal carcinoma *in situ*
☐	☐	Tis	(LCIS) Lobular carcinoma *in situ*
☐	☐	Tis	(Paget's) Paget's disease of the nipple with no tumor *Note:* Paget's disease associated with a tumor is classified according to the size of the tumor.
☐	☐	T1	Tumor 2 cm or less in greatest dimension
☐	☐	T1mic	Microinvasion 0.1 cm or less in greatest dimension
☐	☐	T1a	Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
☐	☐	T1b	Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
☐	☐	T1c	Tumor more than 1 cm but not more than 2 cm in greatest dimension
☐	☐	T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
☐	☐	T3	Tumor more than 5 cm in greatest dimension
☐	☐	T4	Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below.
☐	☐	T4a	Extension to chest wall, not including pectoralis muscle
☐	☐	T4b	Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
☐	☐	T4c	Both T4a and T4b
☐	☐	T4d	Inflammatory carcinoma

Notes

1. *Clinically apparent* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

2. Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," e.g., pN0(i+)(sn).

3. Isolated tumor cells (ITC) are defined as single tumor cells or small cell clusters not greater than 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods but which may be verified on H&E stains. ITCs do not usually show evidence of metastatic activity (e.g., proliferation or stromal reaction.)

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

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

6. If associated with greater than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden.

7. T1 includes T1mic

(continued on reverse side)

Clinical	Regional Lymph Nodes (N)	
☐	NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
☐	N0	No regional lymph node metastasis
☐	N1	Metastasis in movable ipsilateral axillary lymph node(s)
☐	N2	Metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent[1] ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastasis
☐	N2a	Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
☐	N2b	Metastasis only in clinically apparent[1] ipsilateral internal mammary nodes and in the *absence* of clinically evident axillary lymph node metastasis
☐	N3	Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent[1] ipsilateral internal mammary lymph node(s) and in the *presence* of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
☐	N3a	Metastasis in ipsilateral infraclavicular lymph node(s) and axillary lymph node(s)
☐	N3b	Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
☐	N3c	Metastasis in ipsilateral supraclavicular lymph node(s)

Pathologic	Regional Lymph Nodes (pN)[2]	
☐	pNX	Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
☐	pN0	No regional lymph node metastasis histologically, no additional examination for isolated tumor cells (ITC)[3]
☐	pN0(i-)	No regional lymph node metastasis histologically, negative IHC
☐	pN0(i+)	No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm
☐	pN0(mol-)	No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)[4]
☐	pN0(mol+)	No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)[4]
☐	pN1	Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[5]
☐	pN1mi	Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)
☐	pN1a	Metastasis in 1 to 3 axillary lymph nodes
☐	pN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[5]
☐	pN1c	Metastasis in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[5,6]
☐	pN2	Metastasis in 4 to 9 axillary lymph nodes, or in clinically apparent[1] internal mammary lymph nodes in the *absence* of axillary lymph node metastasis
☐	pN2a	Metastasis in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
☐	pN2b	Metastasis in clinically apparent[1] internal mammary lymph nodes in the *absence* of axillary lymph node metastasis
☐	pN3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent[1] ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
☐	pN3a	Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0mm), or metastasis to the infraclavicular lymph nodes
☐	pN3b	Metastasis in clinically apparent[1] ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[5]
☐	pN3c	Metastasis in ipsilateral supraclavicular lymph nodes

Clinical	*Pathologic*	**Distant Metastasis (M)**	
☐	☐	MX	Distant metastasis cannot be assessed
☐	☐	M0	No distant metastasis
☐	☐	M1	Distant metastasis

Biopsy of metastatic site performed.... ☐Y..... ☐N

Source of pathologic metastatic specimen

_____

		Stage Grouping			
☐	☐	0	Tis	N0	M0
☐	☐	I	T1[(7)]	N0	M0
☐	☐	IIA	T0	N1	M0
			T1[(7)]	N1	M0
			T2	N0	M0
☐	☐	IIB	T2	N1	M0
			T3	N0	M0
☐	☐	IIIA	T0	N2	M0
			T1[(7)]	N2	M0
			T2	N2	M0
			T3	N1	M0
			T3	N2	M0
☐	☐	IIIB	T4	N0	M0
			T4	N1	M0
			T4	N2	M0
☐	☐	IIIC	Any T	N3	M0
☐	☐	IV	Any T	Any N	M1

Note: Stage designation may be changed if post-surgical 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.

Histologic Grade (G)

All invasive breast carcinomas with the exception of medullary carcinoma should be graded. The Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom-Richardson grading system) is recommended. The grade for a tumor is determined by assessing morphologic features (tubule formation, nuclear pleomorphism, and mitotic count), assigning a value of 1 (favorable) to 3 (unfavorable) for each feature, and adding together the scores for all three categories. A combined score of 3–5 points is designated as grade 1; a combined score of 6–7 points is grade 2; a combined score of 8–9 points is grade 3.

Histologic Grade *(Nottingham combined histologic grade is recommended)*

☐ GX	Grade cannot be assessed
☐ G1	Low combined histologic grade (favorable)
☐ G2	Intermediate combined histologic grade (moderately favorable)
☐ G3	High combined histologic grade (unfavorable)

Residual Tumor (R)

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

Additional Descriptors

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 multi-modality 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.

Prognostic Indicators (if applicable)

Notes

Additional Descriptors

Lymphatic Vessel Invasion (L)

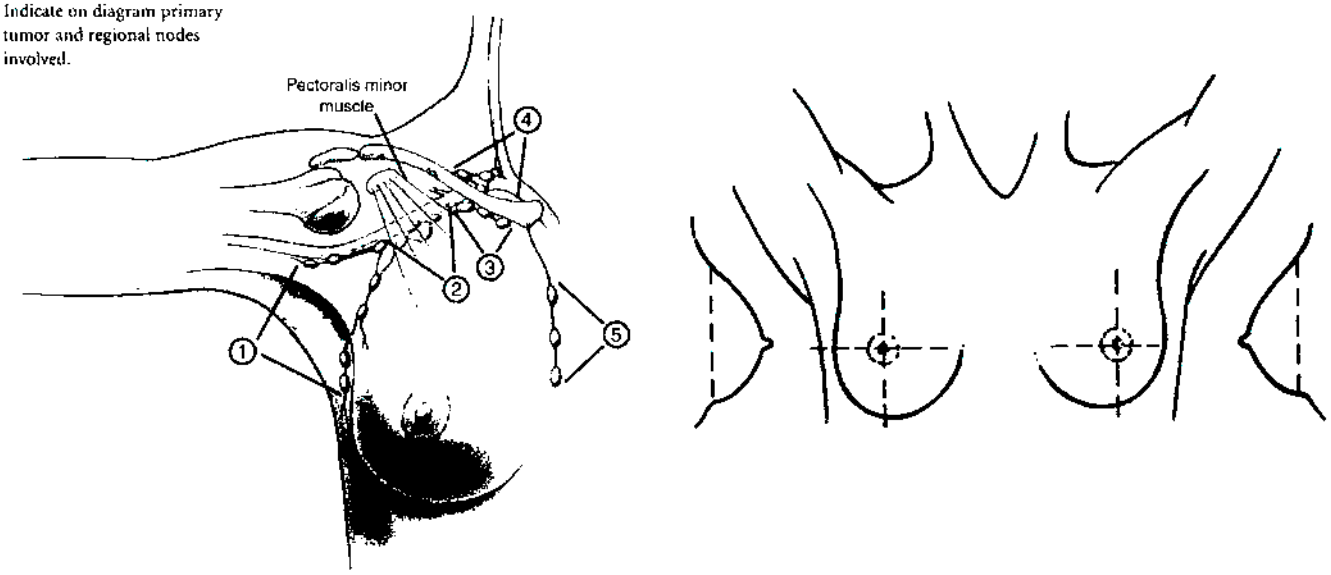
- LX Lymphatic vessel invasion cannot be assessed
- L0 No lymphatic vessel invasion
- L1 Lymphatic vessel invasion

Venous Invasion (V)

- VX Venous invasion cannot be assessed
- V0 No venous invasion
- V1 Microscopic venous invasion
- V2 Macroscopic venous invasion

ILLUSTRATION

Indicate on diagram primary tumor and regional nodes involved.



Schematic diagram of breast and regional lymph nodes:
1. Low axillary, Level I
2. Mid-axillary, Level II
3. High axillary, apical, Level III
4. Supraclavicular
5. Internal mammary nodes

Physician's Signature _____ Date _____

PART VIII
Gynecologic Sites

Cervix uteri, corpus uteri, ovary, vagina, vulva, fallopian tube, and gestational trophoblastic tumors are the sites included in this section. Cervix uteri and corpus uteri were among the first sites to be classified by the TNM system. The League of Nations stages for carcinoma of the cervix were first introduced more than 70 years ago, and since 1937 the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) has continued to modify these staging systems and collect outcomes data from throughout the world. The TNM categories have therefore been defined to correspond to the FIGO stages. Some amendments have been made in collaboration with FIGO, and the classifications now published have the approval of FIGO, the American Joint Committee on Cancer (AJCC), and all other national TNM committees of the International Union Against Cancer (UICC).

26

Vulva

(Mucosal malignant melanoma is not included.)

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

SUMMARY OF CHANGES

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

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.

Regional Lymph Nodes. The femoral and inguinal nodes are the sites of regional spread. For pN, histologic examination of an inguinal lymphadenectomy specimen will ordinarily include six or more lymph nodes. Negative pathologic examination of a lesser number of nodes still mandates a pN0 designation. The concept of sentinel lymph node mapping where only one or two key nodes are removed is currently being investigated.

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.

DEFINITION 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	0	Carcinoma *in situ* (preinvasive carcinoma)
T1	I	Tumor confined to the vulva or vulva and perineum, 2 cm or less in greatest dimension
T1a	IA	Tumor confined to the vulva or vulva and perineum, 2 cm or less in greatest dimension, and with stromal invasion no greater than 1 mm*
T1b	IB	Tumor confined to the vulva or vulva and perineum, 2 cm or less in greatest dimension, and with stromal invasion greater than 1 mm*

T2	II	Tumor confined to the vulva or vulva and perineum, more than 2 cm in greatest dimension
T3	III	Tumor of any size with contiguous spread to the lower urethra and/or vagina or anus
T4	IVA	Tumor invades any of the following: upper urethra, bladder mucosa, rectal mucosa, or is fixed to the pubic bone

**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.

Regional Lymph Nodes (N)

NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	III	Unilateral regional lymph node metastasis
N2	IVA	Bilateral regional lymph node metastasis

Every effort should be made to determine the site and laterality of lymph node metastases. However, if "regional lymph node metastases, NOS" is the final diagnosis, then the patient should be staged as N1.

Distant Metastasis (M)

MX		Distant metastasis cannot be assessed
M0		No distant metastasis
M1	IVB	Distant metastasis (including pelvic lymph node metastasis)

STAGE GROUPING

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 III	T1	N1	M0
	T2	N1	M0
	T3	N0	M0
	T3	N1	M0
Stage IVA	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4	Any N	M0
Stage IVB	Any T	Any N	M1

HISTOPATHOLOGIC TYPE

Squamous cell carcinoma is the most frequent form of cancer of the vulva. This classification does not apply to malignant melanoma.

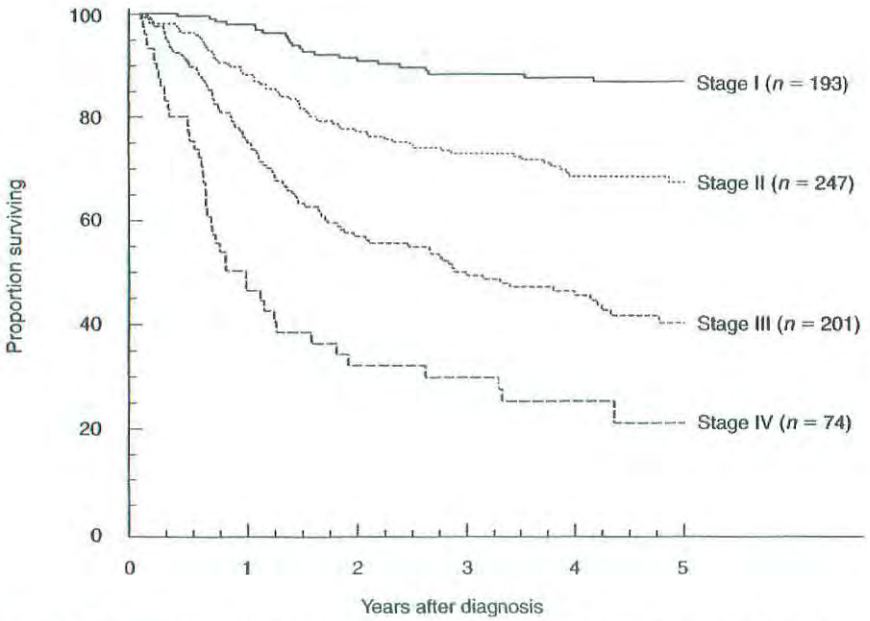


FIG. 26.1. Carcinoma of the vulva, patients treated in 1993–1995. Survival by FIGO stage (epidermoid invasive cancer only), $n = 715$. (Reprinted with permission from Beller U, Sideri M, Maisonneuve P et al: Carcinoma of the vulva. FIGO Annual Report. J Epid Biostat 2001; 6(1):153–174, 2001.)

The common histopathologic types are:

Vulvar intraepithelial neoplasia, grade III
Squamous cell carcinoma *in situ*
Squamous cell carcinoma
Verrucous carcinoma
Paget's disease of vulva
Adenocarcinoma, NOS
Basal cell carcinoma, NOS
Bartholin's gland carcinoma

HISTOLOGIC GRADE (G)

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

PROGNOSTIC FACTORS

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.

OUTCOMES RESULTS

Overall survival data from the FIGO Annual Report for patients treated mostly with radical surgery are shown in Fig. 26.1.

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Moore DH, Thomas GM, Montana GS, et al: Preoperative chemoradiation for advanced vulvar cancer: a phase II study of the Gynecologic Oncology Group. Int J Rad Oncol Biol Phys 42:79–85, 1998

Nash JD, Curry S. Vulvar cancer. Surg Oncol Clinics North Am 7:335–346, 1998

HISTOLOGIES—VULVA

8010/3	Bartholin's gland carcinoma
8051/3	Verrucous carcinoma, NOS
8070/2	Squamous cell carcinoma *in situ*, NOS
8070/3	Squamous cell carcinoma, NOS
8077/2	Squamous intraepithelial neoplasia, grade III
8090/3	Basal cell carcinoma, NOS
8140/3	Adenocarcinoma, NOS
8542/3	Paget's disease of vulva
8560/3	Adenosquamous carcinoma

VULVA

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____

DEFINITIONS

Clinical	Pathologic	Primary Tumor (T) TNM Categories	FIGO Stages	
☐	☐	TX		Primary tumor cannot be assessed
☐	☐	T0		No evidence of primary tumor
☐	☐	Tis	0	Carcinoma *in situ* (preinvasive carcinoma)
☐	☐	T1	I	Tumor confined to the vulva or vulva and perineum, 2 cm or less in greatest dimension
☐	☐	T1a	IA	Tumor confined to the vulva or vulva and perineum, 2 cm or less in greatest dimension, and with stromal invasion no greater than 1 mm[1]
☐	☐	T1b	IB	Tumor confined to the vulva or vulva and perineum, 2 cm or less in greatest dimension, and with stromal invasion greater than 1 mm[1]
☐	☐	T2	II	Tumor confined to the vulva or vulva and perineum, more than 2 cm in greatest dimension
☐	☐	T3	III	Tumor of any size with contiguous spread to the lower urethra and/or vagina or anus
☐	☐	T4	IVA	Tumor invades any of the following: upper urethra, bladder mucosa, rectal mucosa, or is fixed to the pubic bone

Regional Lymph Nodes (N)

☐	☐	NX	Regional lymph nodes cannot be assessed
☐	☐	N0	No regional lymph node metastasis
☐	☐	N1	III Unilateral regional lymph node metastasis
☐	☐	N2	IVA Bilateral regional lymph node metastasis

Distant Metastasis (M)

☐	☐	MX	Distant metastasis cannot be assessed
☐	☐	M0	No distant metastasis
☐	☐	M1	IVB Distant metastasis (including pelvic lymph node metastasis)

Biopsy of metastatic site performed .... ☐Y ..... ☐N

Source of pathologic metastatic specimen _____

Stage Grouping (AJCC/UICC/FIGO)

☐	☐	0	Tis	N0 M0
☐	☐	I	T1	N0 M0
☐	☐	IA	T1a	N0 M0
☐	☐	IB	T1b	N0 M0
☐	☐	II	T2	N0 M0
☐	☐	III	T1	N1 M0
			T2	N1 M0
			T3	N0 M0
			T3	N1 M0
☐	☐	IVA	T1	N2 M0
			T2	N2 M0
			T3	N2 M0
			T4	Any N M0
☐	☐	IVB	Any T	Any N M1

Notes

1. 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.

(continued on reverse side)

Histologic Grade (G)

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

Residual Tumor (R)

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

Additional Descriptors

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.

Prognostic Indicators (if applicable)

Notes

Additional Descriptors

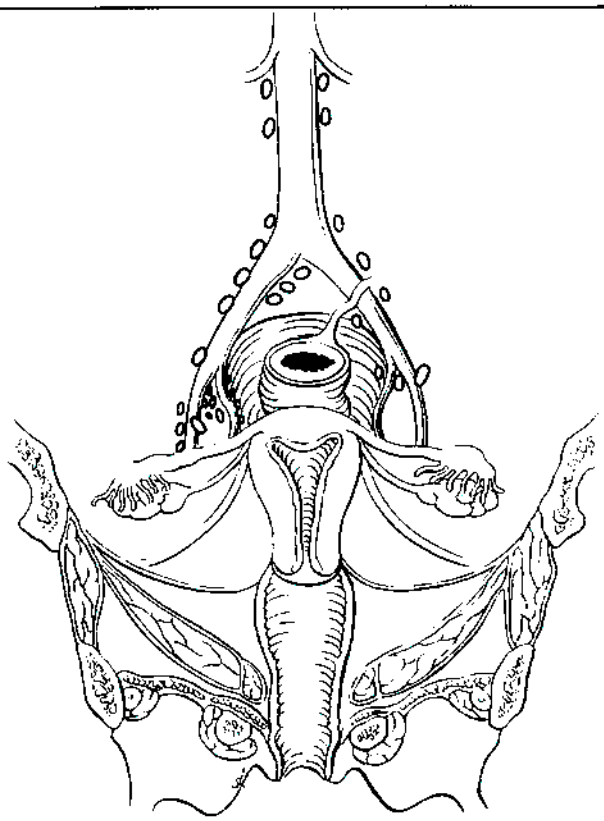
Lymphatic Vessel Invasion (L)

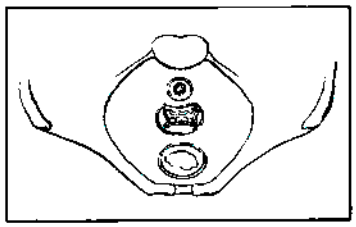
LX Lymphatic vessel invasion cannot be assessed
L0 No lymphatic vessel invasion
L1 Lymphatic vessel invasion

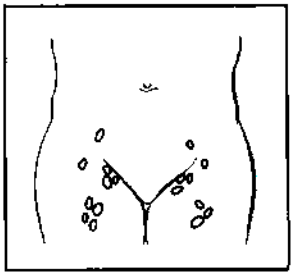
Venous Invasion (V)

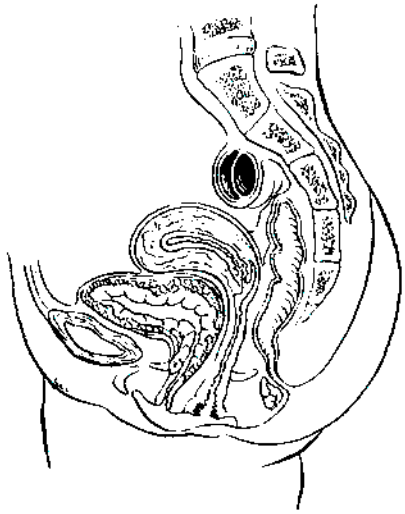
VX Venous invasion cannot be assessed
V0 No venous invasion
V1 Microscopic venous invasion
V2 Macroscopic venous invasion

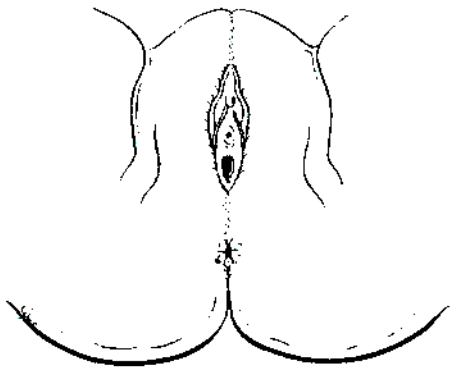
ILLUSTRATION
Indicate on diagram primary tumor and regional nodes involved.











Physician's Signature _____ Date _____

27

Vagina

C52.9 Vagina, NOS

SUMMARY OF CHANGES

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

ANATOMY

Primary Site. The vagina extends from the vulva upward to the uterine cervix. It is lined by squamous epithelium with only rare glandular structures. The vagina is drained by lymphatics toward the pelvic nodes in its upper two-thirds and toward the inguinal nodes in its lower third.

Regional Lymph Nodes. The upper two-thirds of the vagina is drained by lymphatics to the pelvic nodes, including

Obturator
Internal iliac (hypogastric)
External iliac
Pelvic, NOS

The lower third of the vagina is drained to the groin nodes, including:

Inguinal
Femoral

Metastatic Sites. The most common sites of distant spread include the aortic lymph nodes, lungs, and skeleton.

RULES FOR CLASSIFICATION

There should be histologic verification of the disease. The classification applies to primary carcinoma only. Cases should be classified as carcinoma of the vagina when the primary site of the growth is in the vagina. Tumors present in the vagina as secondary growths from either genital or extragenital sites should not be included. A growth that involves the cervix, including the external os, should always be assigned to carcinoma of the cervix. A growth limited to the urethra should be classified as carcinoma of the urethra. Tumor involving the vulva and extending to the vagina should be classified as carcinoma of the vulva.

Clinical Staging. FIGO uses clinical staging for cancer of the vagina. All data available prior to first definitive treatment should be used. The results of biopsy or fine-needle aspiration of inguinal/femoral or other nodes may be included in the clinical staging. The rules of staging are similar to those for carcinoma of the cervix.

Pathologic Staging. In addition to data used for clinical staging, information available from examination of the resected specimen, including pelvic and retroperitoneal lymph nodes, is to be used. The pT, pN, and pM categories correspond to the T, N, and M categories.

8

DEFINITION 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	0	Carcinoma *in situ*
T1	I	Tumor confined to vagina
T2	II	Tumor invades paravaginal tissues but not to pelvic wall
T3	III	Tumor extends to pelvic wall*
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)

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

Regional Lymph Nodes (N)

NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IVB	Pelvic or inguinal lymph node metastasis

Distant Metastasis (M)

MX		Distant metastasis cannot be assessed
M0		No distant metastasis
M1	IVB	Distant metastasis

STAGE GROUPING

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

HISTOPATHOLOGIC TYPE

Squamous cell carcinoma is the most common type of cancer occurring in the vagina. Approximately 10% of vaginal cancers are adenocarcinoma; melanoma and sarcoma occur rarely.

HISTOLOGIC GRADE (G)

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

PROGNOSTIC FACTORS

The most significant prognostic factor is anatomic staging, which reflects the extent of invasion into the surrounding tissue or of metastatic spread.

OUTCOMES RESULTS

Overall survival data from large series are not available because of the rarity of this malignancy. However, FIGO 5-year survival data by clinical stage in patients managed with a variety of modalities are shown in Fig. 27.1.

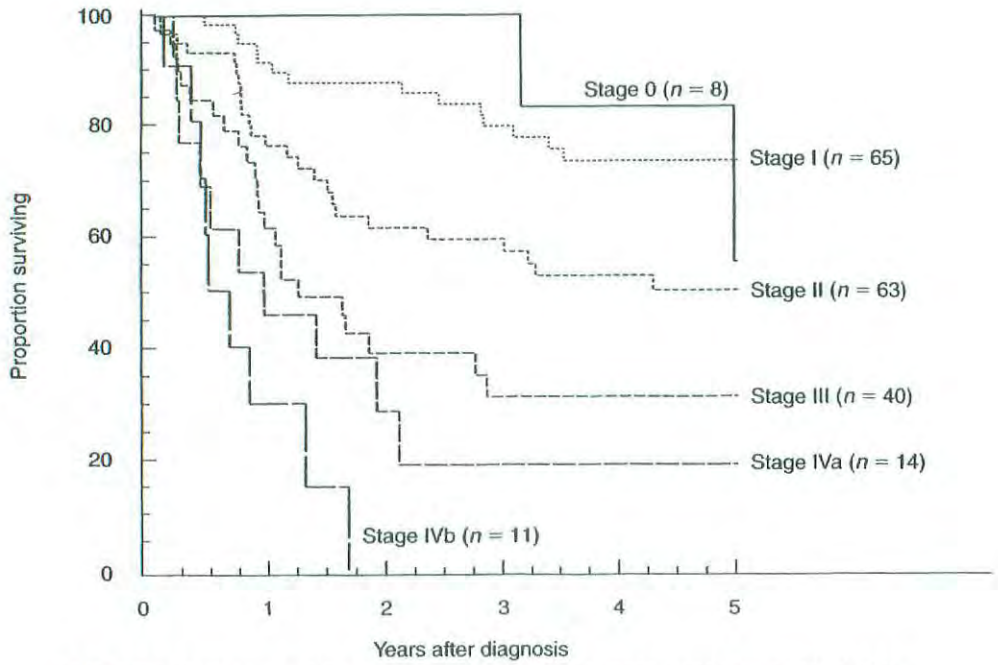


FIG. 27.1. Carcinoma of the vagina, patients treated in 1993–1995. Survival by FIGO stage, $n = 201$. (Reprinted with permission from Beller U, Sideri M, Maisonneuve P et al: Carcinoma of the vagina. FIGO Annual Report. J Epid Biostat 6(1):141–152 2001.)

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HISTOLOGIES—VAGINA

8010/2	Carcinoma *in situ*, NOS
8010/3	Carcinoma, NOS
8052/2	Papillary squamous cell carcinoma, non-invasive
8052/3	Papillary squamous cell carcinoma
8070/2	Squamous cell carcinoma *in situ*, NOS
8070/3	Squamous cell carcinoma, NOS
8071/3	Squamous cell carcinoma, keratinizing, NOS
8072/3	Squamous cell carcinoma, large cell, non-keratinizing, NOS
8076/2	Squamous cell carcinoma *in situ* with questionable stromal invasion
8076/3	Squamous cell carcinoma, microinvasive
8077/2	Squamous intraepithelial neoplasia, grade III
8082/3	Lymphoepithelial carcinoma
8084/3	Squamous cell carcinoma, clear cell type
8140/2	Adenocarcinoma *in situ*, NOS
8140/3	Adenocarcinoma, NOS
8570/3	Adenocarcinoma with squamous metaplasia
8572/3	Adenocarcinoma with spindle cell metaplasia
8800/3	Sarcoma, NOS
8801/3	Spindle cell sarcoma

VAGINA

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____

DEFINITIONS

Primary Tumor (T)

Clinical	*Pathologic*	*TNM Categories*	*FIGO Stages*	*Definitions*
☐	☐	TX		Primary tumor cannot be assessed
☐	☐	T0		No evidence of primary tumor
☐	☐	Tis	0	Carcinoma *in situ*
☐	☐	T1	I	Tumor confined to vagina
☐	☐	T2	II	Tumor invades paravaginal tissues but not to pelvic wall
☐	☐	T3	III	Tumor extends to pelvic wall[1]
☐	☐	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)

Regional Lymph Nodes (N)

☐	☐	NX	Regional lymph nodes cannot be assessed
☐	☐	N0	No regional lymph node metastasis
☐	☐	N1	Pelvic or inguinal lymph node metastasis

Distant Metastasis (M)

☐	☐	MX		Distant metastasis cannot be assessed
☐	☐	M0		No distant metastasis
☐	☐	M1	IVB	Distant metastasis

Biopsy of metastatic site performed ..... ☐Y ..... ☐N

Source of pathologic metastatic specimen _____

Stage Grouping (A)JCC/UICC/FIGO

☐	☐	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

Histologic Grade (G)

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

Residual Tumor (R)

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

Notes

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

8

(continued on reverse side)

Additional Descriptors

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.

Prognostic Indicators (if applicable)

Notes

Additional Descriptors

Lymphatic Vessel Invasion (L)

LX Lymphatic vessel invasion cannot be assessed

L0 No lymphatic vessel invasion

L1 Lymphatic vessel invasion

Venous Invasion (V)

VX Venous invasion cannot be assessed

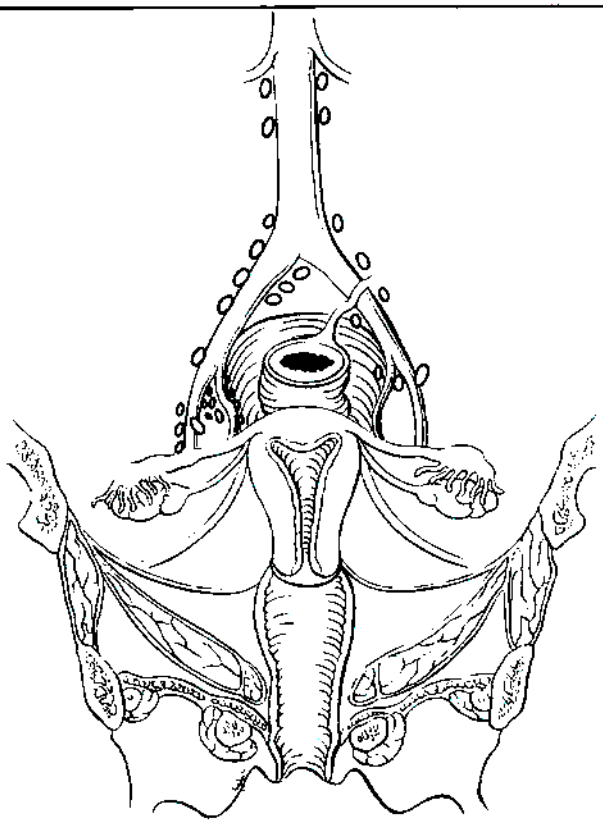
V0 No venous invasion

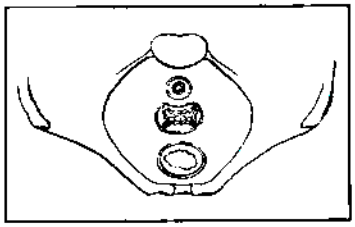
V1 Microscopic venous invasion

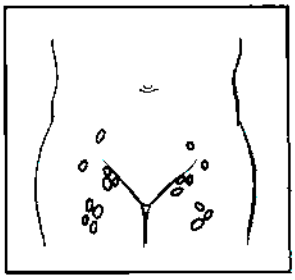
V2 Macroscopic venous invasion

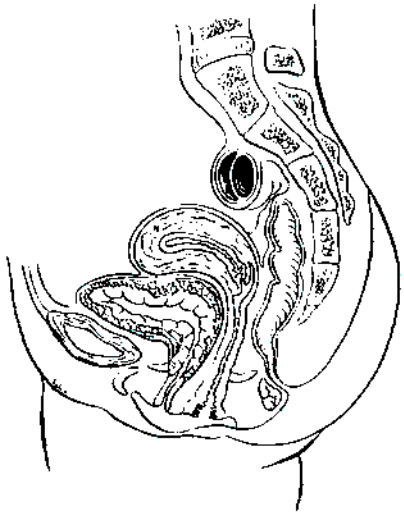
ILLUSTRATION

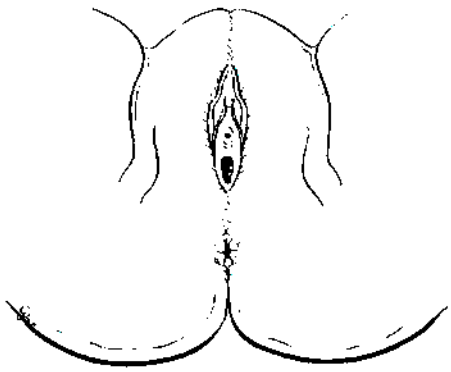
Indicate on diagram primary tumor and regional nodes involved.











Physician's Signature _____ Date _____

28

Cervix Uteri

C53.0 Endocervix
C53.1 Exocervix
C53.8 Overlapping lesion of cervix uteri
C53.9 Cervix uteri

SUMMARY OF CHANGES

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

ANATOMY

Primary Site. The cervix is the lower third of the uterus. It is roughly cylindrical in shape and projects into the upper vagina. The endocervical canal is lined by glandular or columnar epithelium. Through the cervix runs the endocervical canal, which is the passageway connecting the vagina with the uterine cavity. The vaginal portion of the cervix, known as the exocervix, is covered by squamous epithelium. The squamocolumnar junction is usually located at the external cervical os, where the endocervical canal begins. Cancer of the cervix may originate from the squamous epithelium of the exocervix or the glandular epithelium of the canal.

Regional Lymph Nodes. The cervix is drained by parametrial, cardinal and uterosacral ligament routes into the following regional lymph nodes:

Parametrial
Paracervical
Obturator
Internal iliac (hypogastric)
External iliac
Common iliac
Sacral
Presacral

Metastatic Sites. The most common sites of distant spread include the aortic and mediastinal nodes, lungs, and skeleton. Para-aortic node involvement is considered distant metastasis and is coded M1.

RULES FOR CLASSIFICATION

The classification applies only to carcinoma. There should be histologic confirmation of the disease.

Clinical Staging. Because many patients with cervical cancer are treated by radiation and never undergo surgical-pathologic staging, clinical staging of all patients provides uniformity and is therefore preferred. FIGO staging of cervical cancer is clinical.

The clinical stage should be determined prior to the start of definitive therapy. The clinical stage must not be changed because of subsequent findings once treatment has started. When there is doubt about to which stage a particular cancer should be allocated, the lesser stage should be utilized. Careful clinical examination should be performed in all cases, preferably by an experienced examiner and with the patient under anesthesia. The following examinations are recommended for staging purposes: palpation, inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, and X-ray examination of the lungs and skeleton. Suspected involvement of the bladder mucosa or rectal mucosa must be confirmed by biopsy and histology. Fine-needle aspiration cytology of palpable nodes or masses may be used, but laparoscopic or radiologically guided biopsy or aspiration is not to be used for clinical staging. The results of additional examinations such as computerized tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), lymphangiography, arteriography, and venography may *not* be used to determine clinical staging because these techniques are not universally available. They may, however, be used to develop a treatment plan.

Pathologic Staging. In cases treated by surgical procedures, the pathologist's findings in the removed tissues can be the basis for extremely accurate statements on the extent of disease. These findings should not be allowed to change the clinical staging but should be recorded in the manner described for the pathologic staging of disease. The pTNM nomenclature is appropriate for this purpose and corresponds to the T, N, and M categories. Infrequently,

hysterectomy is carried out in the presence of unsuspected invasive cervical carcinoma. Such cases cannot be clinically staged or included in therapeutic statistics; they should be reported separately.

DEFINITION 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	0	Carcinoma *in situ*
T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
*T1a	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification
T1a1	IA1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumor without parametrial invasion
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina, and/or causes hydronephrosis or non-functioning kidney
T3a	IIIA	Tumor involves lower third of vagina, no extension to pelvic wall
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or non-functioning kidney
T4	IVA	Tumor invades mucosa of bladder or rectum, and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)

*All macroscopically visible lesions—even with superficial invasion—are T1b/IB.

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)

MX		Distant metastasis cannot be assessed
M0		No distant metastasis
M1	IVB	Distant metastasis

STAGE GROUPING

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 IIB	T2b	N0	M0
Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T1	N1	M0
	T2	N1	M0
	T3a	N1	M0
	T3b	Any N	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

HISTOPATHOLOGIC TYPE

Cases should be classified as carcinoma of the cervix if the primary growth is in the cervix. All carcinomas should be included. Grading is encouraged but is not a basis for modifying the stage groupings. When surgery is the primary treatment, the histologic findings permit the case to have pathologic staging, and the pTNM nomenclature is to be used. The histopathologic types are

Cervical intraepithelial neoplasia, grade III
Squamous cell carcinoma *in situ*
Squamous cell carcinoma
  Invasive
  Keratinizing
  Non-keratinizing
  Verrucous
Adenocarcinoma *in situ*
Adenocarcinoma, invasive
Endometrioid adenocarcinoma
Clear cell adenocarcinoma
Adenosquamous carcinoma
Adenoid cystic carcinoma
Adenoid basal cell carcinoma
Small cell carcinoma
Neuroendocrine
Undifferentiated carcinoma

HISTOLOGIC GRADE (G)

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

PROGNOSTIC FACTORS

Current data suggest that more than 90% of squamous cervical cancer contains human papilloma virus (HPV) DNA, most frequently types 16 and 18. In addition to extent or stage of disease, prognostic factors include histology and tumor differentiation. Small cell, neuroendocrine, and clear cell lesions have a worse prognosis, as do poorly differentiated cancers. Women with cervical cancer who are infected with human immunodeficiency virus (HIV) are defined as having autoimmune deficiency syndrome (AIDS), and they have a very poor prognosis, often with rapidly progressive cancer.

OUTCOMES RESULTS

The overall survival by stage of more than 11,000 patients treated from 1993 to 1995 is shown in Figure 28.1.

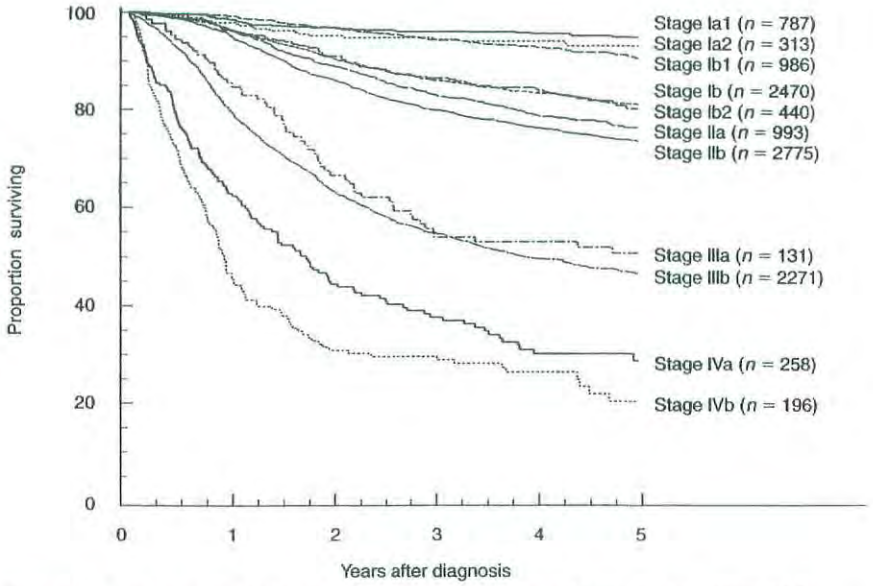


FIG. 28.1. Carcinoma of the cervix uteri: patients treated in 1993–1995. Survival by FIGO stage, $n = 11{,}620$. (Reprinted with permission from Benedet JL, Odicino F, Maisonneuve P et al: Carcinoma of the cervix. FIGO Annual Report. J Epid Biostat 6:5–44, 2001.)

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HISTOLOGIES—CERVIX UTERI

8020/3	Carcinoma, undifferentiated, NOS
8041/3	Small cell carcinoma, NOS
8051/3	Verrucous carcinoma, NOS
8070/2	Squamous cell carcinoma *in situ*, NOS
8070/3	Squamous cell carcinoma, NOS
8071/3	Squamous cell carcinoma, keratinizing, NOS
8072/3	Squamous cell carcinoma, large cell, non-keratinizing, NOS
8073/3	Squamous cell carcinoma, small cell, non-keratinizing
8077/2	Squamous intraepithelial neoplasia, grade III
8098/3	Adenoid basal carcinoma
8140/2	Adenocarcinoma *in situ*, NOS
8140/3	Adenocarcinoma, NOS
8200/3	Adenoid cystic carcinoma
8246/3	Neuroendocrine carcinoma, NOS
8310/3	Clear cell adenocarcinoma, NOS
8380/3	Endometrioid adenocarcinoma, NOS
8560/3	Adenosquamous carcinoma

CERVIX UTERI

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____

DEFINITIONS

Primary Tumor (T)

Clinical	Pathologic	TNM Categories	FIGO Stages	Definitions
☐	☐	TX		Primary tumor cannot be assessed
☐	☐	T0		No evidence of primary tumor
☐	☐	Tis	0	Carcinoma *in situ*
☐	☐	T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
☐	☐	T1a	IA	Invasive carcinoma diagnosed only by microscopy.[1] All macroscopically visible lesions – even with superficial invasion – are T1b/IB. Stromal invasion with a maximal depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification
☐	☐	T1a1	IA1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
☐	☐	T1a2	IA2	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less
☐	☐	T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a2/IA2
☐	☐	T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
☐	☐	T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
☐	☐	T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
☐	☐	T2a	IIA	Tumor without parametrial invasion
☐	☐	T2b	IIB	Tumor with parametrial invasion
☐	☐	T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or non-functioning kidney
☐	☐	T3a	IIIA	Tumor involves lower third of vagina, no extension to pelvic wall
☐	☐	T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or non-functioning kidney
☐	☐	T4	IVA	Tumor invades mucosa of bladder or rectum and/ or extends beyond true pelvis (bullous edema is not sufficient evidence to classify a tumor as T4)

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)

☐	☐	MX	Distant metastasis cannot be assessed
☐	☐	M0	No distant metastasis
☐	☐	M1	IVB Distant metastasis

Biopsy of metastatic site performed..... ☐Y ..... ☐N

Source of pathologic metastatic specimen _____

Notes

1. 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.

(continued on reverse side)

8

Clinical	Pathologic	Stage Grouping (AJCC/UICC/FIGO)			
☐	☐	0	Tis	N0	M0
☐	☐	I	T1	N0	M0
☐	☐	IA	T1a	N0	M0
☐	☐	IA1	T1a1	N0	M0
☐	☐	IA2	T1a2	N0	M0
☐	☐	IB	T1b	N0	M0
☐	☐	IB1	T1b1	N0	M0
☐	☐	IB2	T1b2	N0	M0
☐	☐	II	T2	N0	M0
☐	☐	IIA	T2a	N0	M0
☐	☐	IIB	T2b	N0	M0
☐	☐	III	T3	N0	M0
☐	☐	IIIA	T3a	N0	M0
☐	☐	IIIB	T1	N1	M0
			T2	N1	M0
			T3a	N1	M0
			T3b	Any N	M0
☐	☐	IVA	T4	Any N	M0
☐	☐	IVB	Any T	Any N	M1

Histologic Grade (G)

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

Residual Tumor (R)

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

Additional Descriptors

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.

Prognostic Indicators (if applicable)

Notes

Additional Descriptors

Lymphatic Vessel Invasion (L)

LX Lymphatic vessel invasion cannot be assessed

L0 No lymphatic vessel invasion

L1 Lymphatic vessel invasion

Venous Invasion (V)

VX Venous invasion cannot be assessed

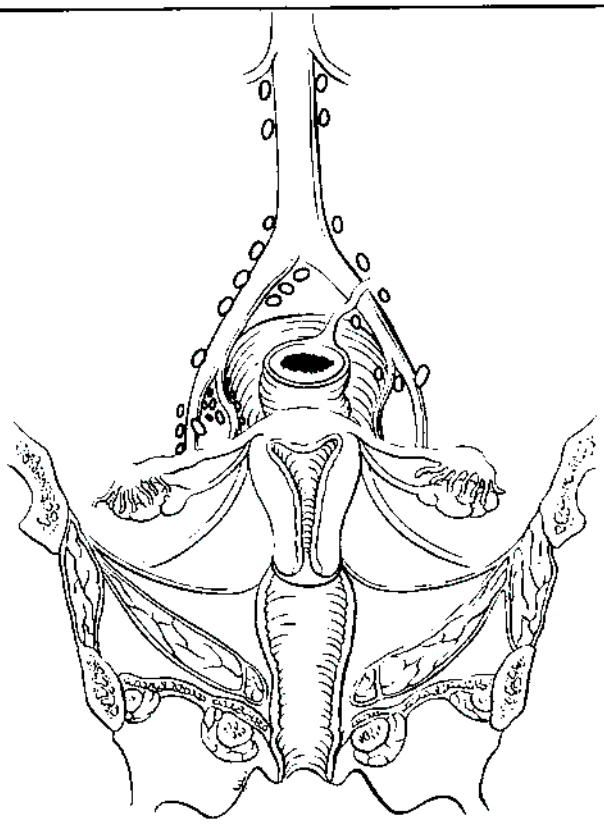
V0 No venous invasion

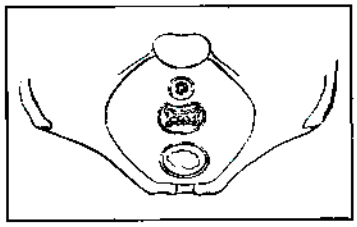
V1 Microscopic venous invasion

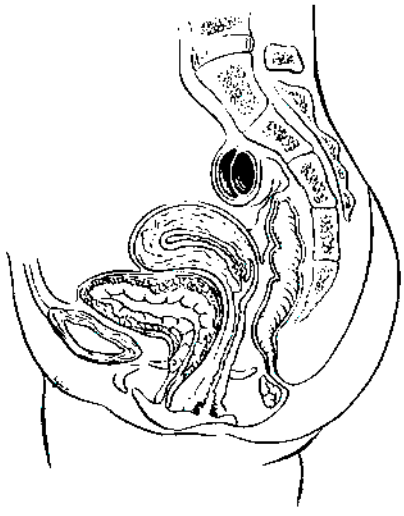
V2 Macroscopic venous invasion

ILLUSTRATION

Indicate on diagram primary tumor and regional nodes involved.







Physician's Signature _____ Date _____

29

Corpus Uteri

C54.0 Isthmus uteri
C54.1 Endometrium
C54.2 Myometrium
C54.3 Fundus uteri
C54.8 Overlapping lesion of corpus uteri
C54.9 Corpus uteri
C55.9 Uterus, NOS

SUMMARY OF CHANGES

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

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 endocervical mucosa and/or the stroma of the endocervix is prognostically important and affects staging (T2). 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. Extension of the tumor through the myometrial wall of the uterus into the parametrium occurs on occasion and constitutes regional extension (T3a). Involvement of the ovaries (T3a) by direct extension or metastases or extension to the vagina (T3b) occurs relatively infrequently.

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

Obturator
Internal iliac (hypogastric)
External iliac
Common iliac
Para-aortic
Presacral
Parametrial
Pelvic lymph nodes, NOS

For adequate evaluation of the regional lymph nodes, sampling of para-aortic and bilateral obturator nodes and at least one other regional node group should be documented in either or both of 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.

Metastatic Sites. The vagina and lung are the common metastatic sites. Intra-abdominal metastases occur frequently in advanced disease.

RULES FOR CLASSIFICATION

The classification applies only to carcinoma and malignant mixed mesodermal tumors. There should be histologic verification and grading of the tumor.

Clinical Staging. If the surgeon feels that systematic regional lymph node sampling imposes an unfavorable risk-to-benefit ratio, clinical assessment of the pertinent node groups (obturator, para-aortic groups, internal iliac, common iliac, and external iliac) should be performed and specifically annotated in the operative report and recorded as cN.

A small number of patients may be treated with primary radiation therapy. In such cases, patients should be staged with the clinical staging system adopted by FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) in 1971. The designation of that staging system must be recorded (cT).

Pathologic Staging. FIGO uses surgical/pathologic staging for corpus uteri cancer. Stage should be assigned at the time of definitive surgical treatment or prior to radiation or chemotherapy if those are the initial modes of therapy. The stage should not 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 resections. Ideally, the depth of myometrial invasion (in millimeters) should be recorded, along with the thickness of the myometrium at that level (recorded as a percentage of myometrial invasion).

The presence of carcinoma in the regional lymph nodes is a clinically critical prognostic variable. Multiple studies have confirmed the inaccuracy of clinical assessment of regional nodal metastasis in many anatomic sites. For this

reason, surgical/pathologic assessment of the regional lymph nodes is strongly advocated for all patients with corpus uteri cancer. This is also the recommendation of FIGO.

Fractional curettage is not adequate to establish cervical involvement or to distinguish between Stages I and II. That distinction can best be made by histologic verification of clinically suspicious cervical involvement or histopathologic examination of the removed uterus.

The pT, pN, and pM categories correspond to the T, N, and M categories and are used to designate cases where adequate pathologic specimens are available for accurate stage groupings. When there are insufficient surgical-pathologic findings, the clinical cT, cN, cM categories should be used on the basis of clinical evaluation.

DEFINITION OF TNM

The definitions of the T categories correspond to the stages accepted by FIGO. FIGO stages are further subdivided by histologic grade of tumor—for example, Stage IC G2. Both systems are included for comparison.

Primary Tumor (T) (Surgical-Pathologic findings)

TNM Categories	*FIGO Stages*	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis	0	Carcinoma *in situ*
T1	I	Tumor confined to corpus uteri
T1a	IA	Tumor limited to endometrium
T1b	IB	Tumor invades less than one-half of the myometrium
T1c	IC	Tumor invades one-half or more of the myometrium
T2	II	Tumor invades cervix but does not extend beyond uterus
T2a	IIA	Tumor limited to the glandular epithelium of the endocervix. There is no evidence of connective tissue stromal invasion
T2b	IIB	Invasion of the stromal connective tissue of the cervix
T3	III	Local and/or regional spread as defined below
T3a	IIIA	Tumor involves serosa and/or adnexa (direct extension or metastasis) and/or cancer cells in ascites or peritoneal washings
T3b	IIIB	Vaginal involvement (direct extension or metastasis)
T4	IVA	Tumor invades bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)

Regional Lymph Nodes (N)

NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC	Regional lymph node metastasis to pelvic and/or para-aortic nodes

Distant Metastasis (M)

MX		Distant metastasis cannot be assessed
M0		No distant metastasis
M1	IVB	Distant metastasis (includes metastasis to abdominal lymph nodes other than para-aortic, and/or inguinal lymph nodes; excludes metastasis to vagina, pelvic serosa, or adnexa)

STAGE GROUPING

Stage 0	Tis	N0	M0
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 III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

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 of the uterus should not be included.

HISTOLOGIC GRADE (G)

GX	Grade cannot be assessed
G1	Well differentiated

G2 Moderately differentiated
G3–4 Poorly differentiated or undifferentiated

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 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 to 3.
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.

PROGNOSTIC FACTORS

The presence or absence of metastatic disease in the regional lymph nodes is the most important prognostic factor in carcinomas clinically confined to the uterus. The AJCC strongly advocates the use of surgical/pathologic assessment of nodal status whenever possible. Palpation of regional nodes is well recognized to be much less accurate than pathologic evaluation of the nodes.

Historically, the factors of grade of the tumor and depth of myometrial invasion have been recognized as important prognostic factors. In surgically staged patients, using multivariate analysis, these factors are surrogates for the probability of nodal metastasis. Preoperative endometrial biopsy does not accurately correlate with tumor grade and depth of myometrial invasion.

The presence or absence of lymphovascular space involvement of the myometrium is important in most, but not all, series. When present, lymphovascular space involvement increases the probability of metastatic involvement of the regional lymph nodes.

The importance of tumor cells in peritoneal "washings" and the presence of metastatic foci in adnexal structures may have an adverse impact on prognosis, but they remain controversial and require further study.

Serous papillary and clear cell adenocarcinomas have a higher incidence of extrauterine disease at detection than endometrioid adenocarcinomas. The risk of extrauterine disease does not correlate with the depth of myometrial invasion, because widespread abdominal mestastases can be found even when there is no myometrial invasion. For this reason, they are classified as Grade 3 tumors.

In malignancies with squamous elements, the aggressiveness of the tumor seems to be related to the degree of differentiation of the glandular component rather than the squamous element. Clinicopathologic and immunohistochemical studies support classifying malignant mixed mesodermal tumors as high-grade (G3) malignancies of epithe-

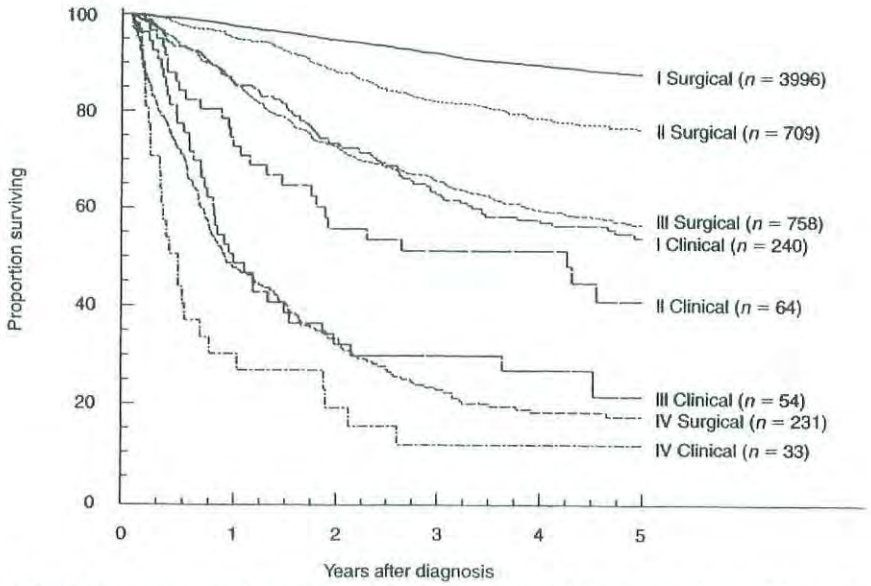


FIG. 29.1. Carcinoma of the corpus uteri, patients treated 1993–1995. Survival by mode of staging, $n = 6085$. (Reprinted with permission from Creasman W, Odicino F, Maisonneuve P et al: Carcinoma of the corpus uteri. FIGO Annual Report. J Epid Biostat 6:45–86, 2001.)

lial origin rather than as sarcomas with mixed epithelial and mesenchymal differentiation, as in earlier classification systems.

The data regarding the impact of DNA ploidy, estrogen and progesterone receptor status, and tumor suppressor gene and oncogene expression are not sufficiently mature to incorporate into the stage grouping at this time.

OUTCOMES RESULTS

The significance of clinical compared with surgical/pathologic staging is shown in Figure 29.1. 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.

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HISTOLOGIES—CORPUS UTERI

8020/3	Carcinoma, undifferentiated, NOS
8070/3	Squamous cell carcinoma, NOS
8263/3	Villoglandular adenocarcinoma
8310/3	Clear cell adenocarcinoma, NOS
8380/3	Endometrioid adenocarcinoma, NOS
8383/3	Endometrioid adenocarcinoma, ciliated cell variant
8441/3	Serous cystadenocarcinoma, NOS
8460/3	Serous adenocarcinoma (papillary serous)
8480/3	Mucinous adenocarcinoma
8560/3	Adenosquamous carcinoma
8570/3	Adenocarcinoma with squamous metaplasia
8951/3	Malignant mixed mesodermal tumors

CORPUS UTERI

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____

DEFINITIONS

Clinical — Primary Tumor (T)

FIGO recommends surgical/pathologic staging. Clinical staging is done with 1971 FIGO as follows:

	TNM	FIGO	Definitions
☐	(c)Tis	0	Carcinoma *in situ*. Histological findings suspicious of malignancy
☐	(c)T1	I	Carcinoma is confined to the corpus including the isthmus
☐	(c)T1a	IA	Length of the uterine cavity is 8 cm or less
☐	(c)T1b	IB	Length of the uterine cavity is more than 8 cm

Stage I cases should be subgrouped with regard to the histological type of the adenocarcinoma as follows:

☐	G1	Highly differentiated adenomatous carcinoma
☐	G2	Moderately differentiated adenomatous carcinoma with partly solid areas
☐	G3	Predominately solid or entirely undifferentiated carcinoma
☐	(c)T2 II	Carcinoma has involved the corpus and the cervix, but has not extended outside the uterus
☐	(c)T3 III	Carcinoma has extended outside the uterus, but not outside the true pelvis
☐	(c)T4 IV	Carcinoma has extended outside the true pelvis or has obviously involved the mucosa of the bladder or rectum (Bullous edema as such does not permit a case to be allotted to stage IV)
☐	(c)T4a IVA	Spread of the growth to adjacent organs as urinary bladder, rectum, sigmoid colon, or small bowel

Stage 0 cases should not be included in any therapeutic statistics.

Pathologic — Primary Tumor (T)

	TNM	FIGO	Definitions
☐	TX		Primary tumor cannot be assessed
☐	T0		No evidence of primary tumor
☐	Tis	0	Carcinoma *in situ*
☐	T1	I	Tumor confined to corpus uteri
☐	T1a	IA	Tumor limited to endometrium
☐	T1b	IB	Tumor invades less than one-half of the myometrium
☐	T1c	IC	Tumor invades one-half or more of the myometrium
☐	T2	II	Tumor invades cervix but does not extend beyond uterus
☐	T2a	IIA	Tumor limited to the glandular epithelium of the endocervix. There is no evidence of connective tissue stromal invasion
☐	T2b	IIB	Invasion of the stromal connective tissue of the cervix
☐	T3	III	Local and/or regional spread as defined below
☐	T3a	IIIA	Tumor involves serosa and/or adnexa (direct extension or metastasis) and/or cancer cells in ascites or peritoneal washings
☐	T3b	IIIB	Vaginal involvement (direct extension or metastasis)
☐	T4	IVA	Tumor invades bladder mucosa and/or bowel mucosa (bullous edema is not sufficient evidence to classify a tumor as T4)

Clinical / Pathologic — Regional Lymph Nodes (N)

Clinical	Pathologic			
☐	☐	NX		Regional lymph nodes cannot be assessed
☐	☐	N0		No regional lymph node metastasis
☐	☐	N1	IIIC	Regional lymph node metastases to pelvic and/or para-aortic lymph nodes

Distant Metastasis (M)

☐	☐	MX		Distant metastasis cannot be assessed
☐	☐	M0		No distant metastasis
☐	☐	M1	IVB	Distant metastasis includes metastasis to intra-abdominal lymph nodes other than para-aortic, and/or inguinal lymph nodes; excludes metastasis to vagina, pelvic serosa, or adnexa

Biopsy of metastatic site performed ..... ☐ Y ..... ☐ N

Source of pathologic metastatic specimen _____ *(continued on reverse side)*

Clinical	*Pathologic*	**Stage Grouping** (AJCC/UICC/FIGO)			
☐	☐	0	Tis	N0	M0
☐	☐	I	T1	N0	M0
☐	☐	IA	T1a	N0	M0
☐	☐	IB	T1b	N0	M0
☐	☐	IC	T1c	N0	M0
☐	☐	II	T2	N0	M0
☐	☐	IIA	T2a	N0	M0
☐	☐	IIB	T2b	N0	M0
☐	☐	III	T3	N0	M0
☐	☐	IIIA	T3a	N	M0
☐	☐	IIIB	T3b	N0	M0
☐	☐	IIIC	T1	N1	M0
			T2	N1	M0
			T3	N1	M0
☐	☐	IVA	T4	Any N	M0
☐	☐	IVB	Any T	Any N	M1

Histologic Grade (G)

- ☐ GX Grade cannot be assessed
- ☐ G1 Well differentiated
- ☐ G2 Moderately differentiated
- ☐ G3-G4 Poorly differentiated or undifferentiated

Histopathology—Degree of Differentiation

Cases of carcinoma of the corpus should be grouped with regard 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

Residual Tumor (R)

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

Additional Descriptors

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.

Prognostic Indicators (if applicable)

Notes

Additional Descriptors

Lymphatic Vessel Invasion (L)

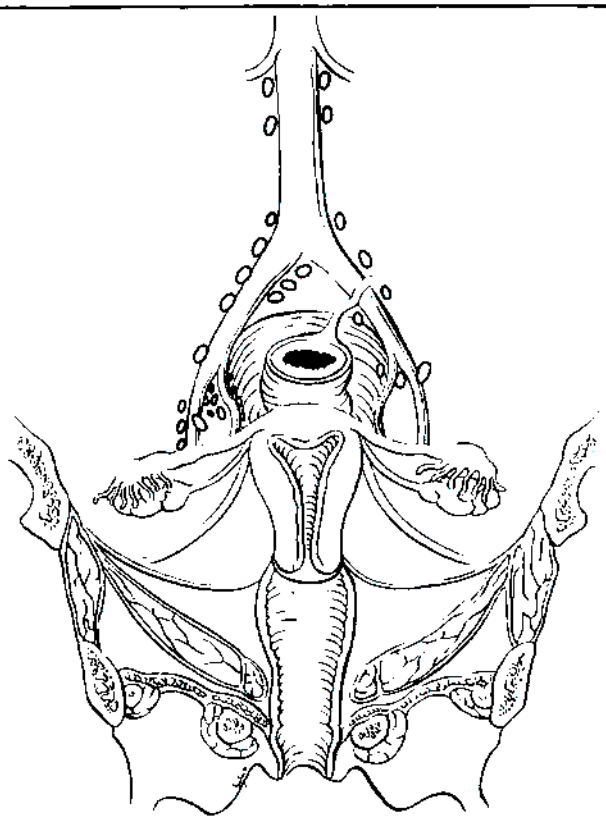
- LX Lymphatic vessel invasion cannot be assessed
- L0 No lymphatic *vessel invasion*
- L1 Lymphatic vessel invasion

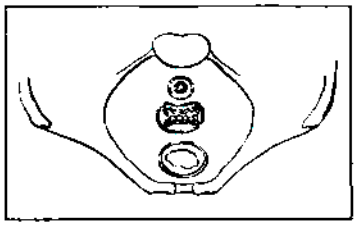
Venous Invasion (V)

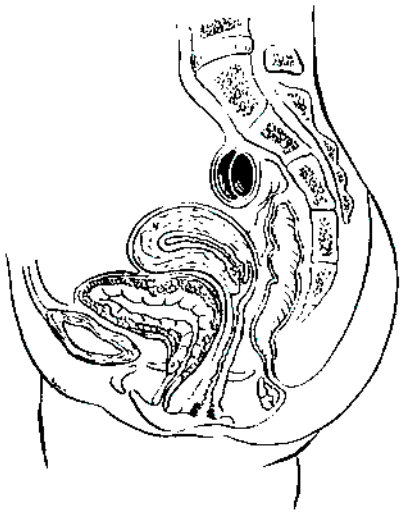
- VX Venous invasion cannot be assessed
- V0 No venous invasion
- V1 Microscopic venous invasion
- V2 Macroscopic venous invasion

ILLUSTRATION

Indicate on diagram primary tumor and regional nodes involved.







Physician's Signature _____ Date _____

30

Ovary

C56.9 Ovary

SUMMARY OF CHANGES

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

ANATOMY

Primary Site. The ovaries are a pair of solid, flattened ovoids 2 to 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 to 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 utero-ovarian and round ligament trunks and an external iliac accessory route into the following regional nodes:

External iliac
Internal iliac (hypogastric)
Obturator
Sacral
Common iliac
Para-aortic
Inguinal
Pelvic, NOS
Retroperitoneal, NOS

For pN0, histologic examination should include both pelvic and para-aortic lymph nodes.

Metastatic Sites. The peritoneum, including the omentum and the pelvic and abdominal visceral and parietal peritoneum, comprises common sites for seeding. Diaphragmatic and liver surface involvement are also common. However, to be consistent with FIGO staging, these implants within the abdominal cavity (T3) are not considered distant metastases. Primary peritoneal adenocarcinoma is always metastatic at diagnosis (M1). Extraperitoneal sites, including parenchymal liver, lung, skeletal metastases, and supraclavicular and axillary nodes, are M1.

RULES FOR CLASSIFICATION

Ovarian cancer is surgically/pathologically staged. There should be histologic confirmation of the ovarian disease. Laparotomy and resection of the ovarian mass, as well as hysterectomy, form the basis for staging. Biopsies of all frequently involved sites, such as omentum, mesentery, diaphragm, peritoneal surfaces, pelvic nodes, and para-aortic nodes, are required for ideal staging of early disease. For example, in order to stage a patient confidently as Stage IA (T1 N0 M0), negative biopsies of all of the above sites should be obtained to exclude microscopic metastases. On the other hand, a single biopsy showing metastatic adenocarcinoma in the omentum is adequate to classify a patient as Stage IIIC, thus making other biopsies unnecessary from a staging standpoint. The final histologic and cytologic findings after surgery are to be considered in the staging. Operative findings prior to tumor debulking determine stage, which may be modified by histopathologic as well as clinical or radiologic evaluation (palpable supraclavicular node or pulmonary metastases on chest X-ray, for example).

Clinical Staging. Although clinical studies similar to those for other sites may be used, surgical-pathologic evaluation of the abdomen and pelvis is necessary to establish a definitive diagnosis of ovarian cancer and rule out other primary malignancies (such as bowel, uterine, and pancreatic cancers or occasionally lymphoma) that may present with similar preoperative findings. A laparotomy is the most

widely accepted procedure used for surgical-pathologic staging, but occasionally laparoscopy can be used. Occasionally, patients with advanced disease and/or women who are medically unsuitable candidates for surgery may be presumed to have ovarian cancer on the basis of cytology of ascites or pleural effusion showing typical adenocarcinoma, combined with imaging studies demonstrating enlarged ovaries. Such patients are usually considered as unstaged (TX), although positive cytology of a pleural effusion or supraclavicular lymph node occasionally allows designation of M1 or FIGO Stage IV disease.

Imaging studies are often done in conjunction with definitive abdominal-pelvic surgery, and chest X-ray, bone scans, computerized scanning (CT), or positron emission tomography (PET) may identify lung, bone, or brain metastases that should be considered in the final stage. Pleural effusions should be evaluated with cytology.

As with all gynecologic cancers, the final stage should be established at the time of initial treatment. It should not be modified or changed on the basis of subsequent findings.

Second-look laparotomies and laparoscopy after initial chemotherapy are being evaluated because of the limitation of routine examinations in detecting early recurrence. Findings related to these procedures do not change the patient's original stage.

Pathologic Staging. Laparotomy and biopsy of all suspected sites of involvement provide the basis for staging. Histologic and cytologic data are required. This is the preferred method of staging for ovarian cancer. The operative note and/or the pathology report should describe the location and size of metastatic lesions and the primary tumors for optimal staging. In addition, the determination of tumor size outside of the pelvis must be noted and documented in the operative report. This is reported in centimeters and represents the largest implant, whether resected or not at the time of surgical exploration.

DEFINITION 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
T1	I	Tumor limited to ovaries (one or both)
T1a	IA	Tumor limited to one ovary; capsule intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings*
T1b	IB	Tumor limited to both ovaries; capsules intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings*
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
T2	II	Tumor involves one or both ovaries with pelvic extension and/or implants
T2a	IIA	Extension and/or implants on uterus and/or tube(s). No malignant cells in ascites or peritoneal washings
T2b	IIB	Extension to and/or implants on other pelvic tissues. No malignant cells in ascites or peritoneal washings
T2c	IIC	Pelvic extension and/or implants (T2a or T2b) with malignant cells in ascites or peritoneal washings
T3	III	Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis
T3a	IIIA	Microscopic peritoneal metastasis beyond pelvis (no macroscopic tumor)
T3b	IIIB	Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension
T3c	IIIC	Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis

**Note:* The presence of non-malignant ascites is not classified. The presence of ascites does not affect staging unless malignant cells are present.

Note: Liver capsule metastasis T3/Stage III; liver parenchymal metastasis M1/Stage IV. Pleural effusion must have positive cytology for M1/Stage IV.

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)

MX		Distant metastasis cannot be assessed
M0		No distant metastasis
M1	IV	Distant metastasis (excludes peritoneal metastasis)

pTNM Pathologic Classification. The pT, pN, and pM categories correspond to the T, N, and M categories.

STAGE GROUPING

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

HISTOPATHOLOGIC TYPE

The American Joint Committee on Cancer (AJCC) endorses the histologic typing of malignant ovarian tumors as endorsed by the World Health Organization (WHO) and recommends that all ovarian epithelial tumors be subdivided according to a simplified version of this classification. The three main histologic types, which include nearly all ovarian cancers, are epithelial tumors, sex-cord stromal tumors, and germ cell tumors. Non-epithelial primary ovarian cancers may be staged using this classification but should be reported separately.

I. Epithelial tumors
   A. Serous tumors
      1. Benign serous cystadenoma
      2. Of borderline malignancy: Serous cystadenoma with proliferating activity of the epithelial cells and nuclear abnormalities, but with no infiltrative destructive growth (carcinomas of low potential malignancy)
      3. Serous cystadenocarcinoma
   B. Mucinous tumors
      1. Benign mucinous cystadenoma
      2. Of borderline malignancy: Mucinous cystadenoma with proliferating activity of the epithelial cells and nuclear abnormalities, but with no infiltrative destructive growth (carcinomas of low potential malignancy)
      3. Mucinous cystadenocarcinoma
   C. Endometrioid tumors
      1. Benign endometrioid cystadenoma
      2. Endometrioid tumors with proliferating activity of the epithelial cells and nuclear abnormalities, but with no infiltrative destructive growth (carcinomas of low potential malignancy)
      3. Endometrioid adenocarcinoma
   D. Clear cell tumors
      1. Benign clear cell tumors
      2. Clear cell tumors with proliferating activity of the epithelial cells and nuclear abnormalities, but with no infiltrative destructive growth (low potential malignancy)
      3. Clear cell cystadenocarcinoma
   E. Brenner (transitional cell tumors)
      1. Benign Brenner
      2. Borderline malignancy
      3. Malignant
      4. Transitional cell
   F. Squamous cell tumor
   G. Undifferentiated carcinoma
      1. A malignant tumor of epithelial structure that is too poorly differentiated to be placed in any other group
   H. Mixed epithelial tumor
      1. Tumors composed of two or more of the five major cell types of common epithelial tumors (types should be specified)

Cases with intraperitoneal carcinoma in which the ovaries appear to be incidentally involved and not the primary origin should be labeled as extraovarian peritoneal carcinoma. They are usually staged with the ovarian staging classification. Because the peritoneum is essentially always involved throughout the abdomen, the peritoneal tumors are usually within the Stage III (T3) or Stage IV (M1) categories.

HISTOLOGIC GRADE (G)

GX	Grade cannot be assessed
GB	Borderline malignancy
G1	Well differentiated
G2	Moderately differentiated
G3–4	Poorly differentiated or undifferentiated

PROGNOSTIC FACTORS

Histology and grade are important prognostic factors. Women with borderline tumors (low malignant potential) have an excellent prognosis, even when extraovarian disease is found. In patients with invasive ovarian cancer, well-differentiated lesions have a better prognosis than poorly differentiated tumors, stage for stage. Histologic type is also extremely important, because some stromal tumors (theca cell, granulosa) have an excellent prognosis, whereas epithelial tumors in general have a less favorable outcome. For this reason, epithelial cell types are generally reported together, and sex-cord stromal tumors and germ cell tumors are reported separately. Tumor cell type also helps to guide the type of chemotherapy that is recommended.

In advanced disease, the most important prognostic factor is the residual disease after the initial surgical management. Even with advanced stage, patients with no gross residual after the surgical debulking have a considerably better

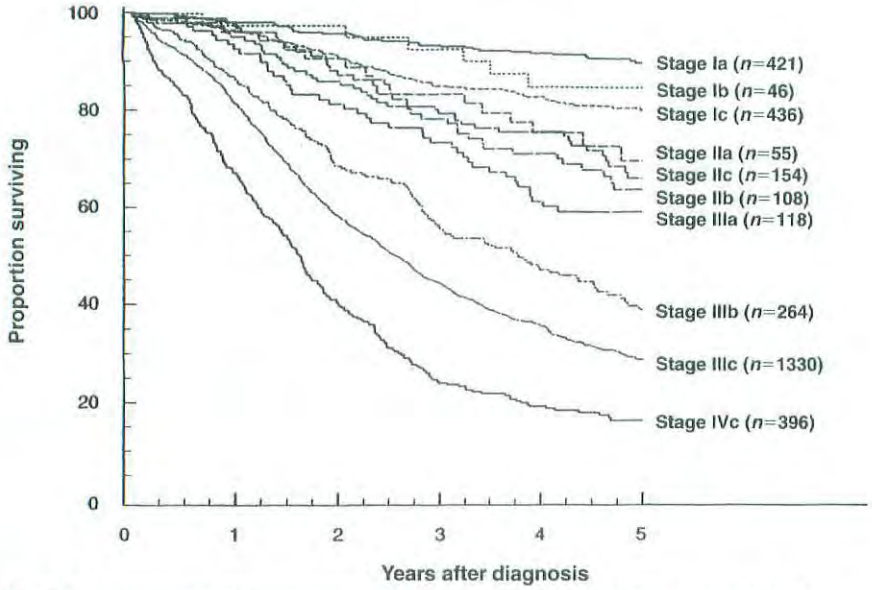


Fig 30.1. Carcinoma of the ovary, patient treated in 1993–1995. Survival by FIGO stage, obviously malignant, $n = 3328$. From Heintz APM, Odicino F, Maisonneuve P, et al: Carcinoma of the ovary. FIGO Annual Report. J Epid Biostat 6:107–138, 2001.

prognosis than those with minimal or extensive residual. Not only is the size of the residual important, but the number of sites of residual tumor also appears to be important (tumor volume).

The tumor marker CA-125 is useful for following the response to therapy in patients with epithelial ovarian cancer who have elevated levels of this marker. The rate of regression during chemotherapy treatment may have prognostic significance. Women with germ cell tumors may also have elevated serum tumor markers—alpha fetoprotein (AFP) or human chorionic gonadotropin (β-hCG). Other factors, such as growth factors and oncogene amplification, are currently under investigation.

OUTCOMES RESULTS

Epithelial carcinoma accounts for approximately 80% of all patients with cancer of the ovary. Because of the difficulty of diagnosing this cancer at an early stage, the overall prognosis of women with epithelial ovarian cancer is poor, despite the fact that patients with early stage disease have a favorable outlook. The prognostic significance of stage is shown in Figure 30.1.

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HISTOLOGIES—OVARY

8020/3	Undifferentiated carcinoma
8070/3	Squamous cell tumor
8140/2	Adenocarcinoma *in situ*, NOS
8140/3	Adenocarcinoma, NOS
8310/3	Clear cell adenocarcinoma, NOS
8323/3	Mixed epithelial tumor
8380/0	Benign endometrioid cystadenoma
8380/1	Endometrioid cystadenoma of low malignant potential
8380/3	Endometrioid adenocarcinoma, NOS
8381/1	Endometrioid adenofibroma of borderline malignancy
8381/3	Endometrioid adenofibroma, malignant
8382/3	Endometrioid adenocarcinoma, secretory variant
8383/3	Endometrioid adenocarcinoma, ciliated cell variant
8440/3	Cystadenocarcinoma, NOS
8441/0	Benign serous adenoma
8441/3	Serous cystadenocarcinoma, NOS
8442/1	Serous cystadenoma of low malignant potential
8444/1	Clear cell cystadenoma of low malignant potential
8450/3	Clear cell cystadenocarcinoma
8460/3	Papillary serous cystadenocarcinoma
8461/3	Serous surface papillary carcinoma
8470/0	Benign mucinous cystadenoma
8470/2	Mucinous cystadenocarcinoma, non-invasive
8470/3	Mucinous cystadenocarcinoma, NOS
8472/1	Mucinous cystadenoma of low malignant potential
8480/3	Mucinous adenocarcinoma

HISTOLOGIES—OVARY (CONT.)

8480/6	Pseudomyxoma peritonei
8481/3	Mucin-producing adenocarcinoma
8482/3	Mucinous adenocarcinoma, endocervical type
8490/3	Signet ring cell carcinoma
8560/3	Adenosquamous carcinoma
8562/3	Epithelial-myoepithelial carcinoma
8570/3	Adenocarcinoma with squamous metaplasia
8600/3	Thecoma, malignant
8620/3	Granulosa cell tumor, malignant
8630/3	Androblastoma, malignant
8631/3	Sertoli-Leydig cell tumor, poorly differentiated
8634/3	Sertoli-Leydig cell tumor, poorly differentiated, with heterologous elements
8640/3	Sertoli cell carcinoma
8650/3	Leydig cell tumor, malignant
8670/3	Steroid cell tumor, malignant
8930/3	Endometrial stromal sarcoma, NOS
8931/3	Endometrial stromal sarcoma, low grade
8933/3	Adenosarcoma
8935/3	Stromal sarcoma, NOS
8950/3	Mullerian mixed tumor
8951/3	Mesodermal mixed tumor
9000/0	Benign Brenner tumor
9000/1	Brenner tumor of borderline malignancy
9000/3	Brenner tumor, malignant
9014/3	Serous adenocarcinofibroma
9015/3	Mucinous adenocarcinofibroma
9050/3	Mesothelioma, malignant
9051/3	Fibrous mesothelioma, malignant
9052/3	Epithelioid mesothelioma, malignant
9053/3	Mesothelioma, biphasic, malignant
9060/3	Dysgerminoma
9064/3	Germinoma
9065/3	Germ cell tumor, nonseminomatous
9070/3	Embryonal carcinoma, NOS
9071/3	Yolk sac tumor
9072/3	Polyembryoma
9080/3	Teratoma, malignant, NOS
9081/3	Teratocarcinoma
9082/3	Malignant teratoma, undifferentiated
9083/3	Malignant teratoma, intermediate
9084/3	Teratoma with malignant transformation
9085/3	Mixed germ cell tumor
9090/3	Struma ovarii, malignant
9100/3	Choriocarcinoma, NOS
9101/3	Choriocarcinoma combined with other germ cell elements
9102/3	Malignant teratoma, trophoblastic
9105/3	Trophoblastic tumor, epithelioid
9110/3	Mesonephroma, malignant

OVARY

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____ Laterality: ☐ Bilateral ☐ Left ☐ Right

DEFINITIONS

Primary Tumor (T)

Clinical	*Pathologic*	*TNM Categories*	*FIGO Stages*	*Definitions*
☐	☐	TX		Primary tumor cannot be assessed
☐	☐	T0		No evidence of primary tumor
☐	☐	T1	I	Tumor limited to ovaries (one or both)
☐	☐	T1a	IA	Tumor limited to one ovary; capsule intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings[1]
☐	☐	T1b	IB	Tumor limited to both ovaries; capsule intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings[1]
☐	☐	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
☐	☐	T2	II	Tumor involves one or both ovaries with pelvic extension
☐	☐	T2a	IIA	Extension and/or implants on uterus and/or tube(s). No malignant cells in ascites or peritoneal washings
☐	☐	T2b	IIB	Extension to and/or implants on other pelvic tissues. No malignant cells in ascites or peritoneal washings
☐	☐	T2c	IIC	Pelvic extension and/or implants (T2a or T2b) with malignant cells in ascites or peritoneal washings
☐	☐	T3	III	Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis[2]
☐	☐	T3a	IIIA	Microscopic peritoneal metastasis beyond pelvis (no macroscopic tumor)[2]
☐	☐	T3b	IIIB	Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension[2]
☐	☐	T3c	IIIC	Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis[2]

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)

☐	☐	MX		Distant metastasis cannot be assessed
☐	☐	M0		No distant metastasis
☐	☐	M1	IV	Distant metastasis (excludes peritoneal metastasis)[2]

Biopsy of metastatic site performed ..... ☐Y ..... ☐N

Source of pathologic metastatic specimen _____

Notes

1. The presence of non-malignant ascites is not classified. The presence of ascites does not affect staging unless malignant cells are present.

2. Liver capsule metastasis T3/III, liver parenchymal metastasis M1/Stage IV. Pleural effusion must have positive cytology for M1/Stage IV.

8

(continued on reverse side)

Clinical	Pathologic	Stage Grouping (AJCC/UICC/FIGO)			
☐	☐	I	T1	N0	M0
☐	☐	IA	T1a	N0	M0
☐	☐	IB	T1b	N0	M0
☐	☐	IC	T1c	N0	M0
☐	☐	II	T2	N0	M0
☐	☐	IIA	T2a	N0	M0
☐	☐	IIB	T2b	N0	M0
☐	☐	IIC	T2c	N0	M0
☐	☐	III	T3	N0	M0
☐	☐	IIIA	T3a	N0	M0
☐	☐	IIIB	T3b	N0	M0
☐	☐	IIIC	T3c	N0	M0
			Any T	N1	M0
☐	☐	IV	Any T	Any N	M1

Notes

Additional Descriptors

Lymphatic Vessel Invasion (L)
- LX Lymphatic vessel invasion cannot be assessed
- L0 No lymphatic vessel invasion
- L1 Lymphatic vessel invasion

Venous Invasion (V)
- VX Venous invasion cannot be assessed
- V0 No venous invasion
- V1 Microscopic venous invasion
- V2 Macroscopic venous invasion

Histologic Grade (G)

- ☐ GX Grade cannot be assessed
- ☐ GB Borderline malignancy
- ☐ G1 Well differentiated
- ☐ G2 Moderately differentiated
- ☐ G3-G4 Poorly differentiated or undifferentiated

Residual Tumor (R)

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

Additional Descriptors

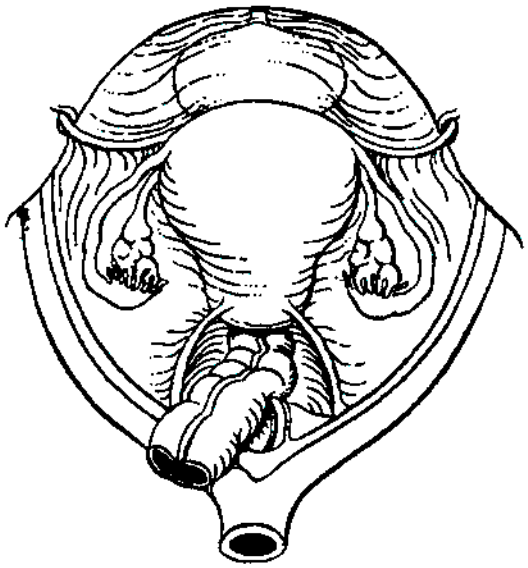
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

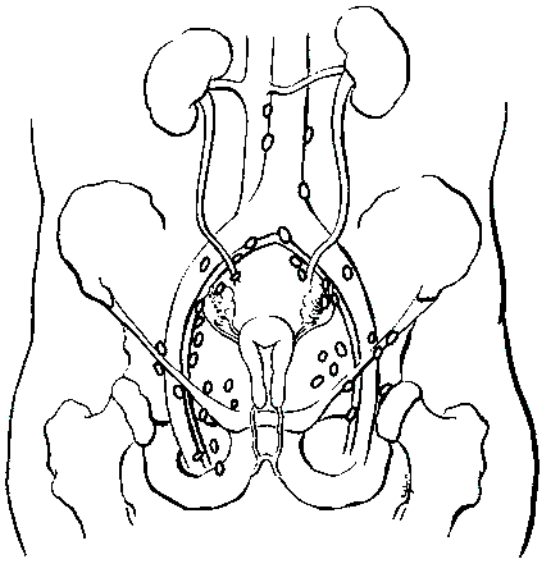
- ☐ **m suffix** indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.
- ☐ **y prefix** indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a "y" 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.

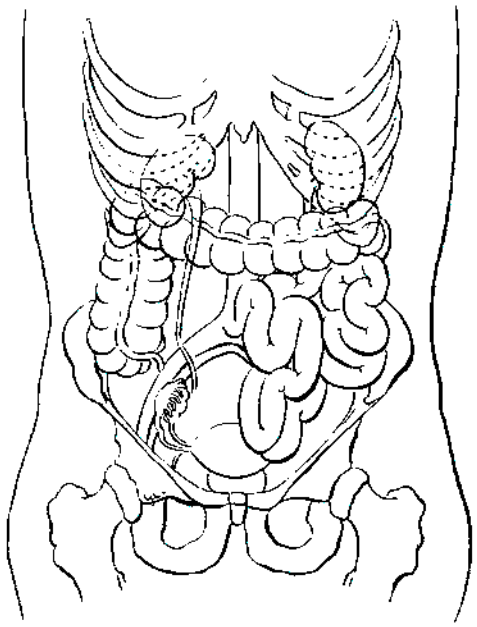
Prognostic Indicators (if applicable)

ILLUSTRATION

Indicate on diagram primary tumor and regional nodes involved.







Physician's Signature _____ Date _____

31

Fallopian Tube

C57.0 Fallopian tube

SUMMARY OF CHANGES

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

ANATOMY

Primary Site. The fallopian tube extends from the posterior superior aspect of the uterine fundus laterally and anteriorly to the ovary. Its length is approximately 10 cm. The medial end arises in the cornual portion of the uterine cavity, and the lateral end opens to the peritoneal cavity.

Carcinoma of the fallopian tube is almost always an adenocarcinoma arising from an *in situ* lesion of the tubal mucosa. It invades locally into the muscular wall of the tube and then into the peritubal soft tissue or adjacent organs such as the uterus or ovary, or through the serosa of the tube into the peritoneal cavity. Metastatic tumor implants can be found throughout the peritoneal cavity. The tumor may obstruct the tubal lumen and present as a ruptured or unruptured hydrosalpinx or hematosalpinx.

Regional Nodes. Carcinoma of the fallopian tube can also metastasize to the regional lymph nodes, which include

Common iliac
Internal iliac (hypogastric)
Obturator
Presacral
Para-aortic
Inguinal
Pelvic lymph nodes, NOS

Adequate evaluation of the regional lymph nodes usually includes aortic and pelvic nodes.

Distant Metastases. Surface implants within the pelvic cavity and the abdominal cavity are common, but these are classified as T2 and T3 disease, respectively. Parenchymal liver metastases and extraperitoneal sites, including lung and skeletal metastases, are M1.

RULES FOR CLASSIFICATION

There should be histologic confirmation of primary disease with complete evaluation of the abdomen and pelvis as outlined in the staging of ovarian malignancy (See Chapter 30). In many patients, the diagnosis may be unsuspected until the fallopian tube is examined histopathologically. Tumors may involve one or both fallopian tubes, and complete assessment of both adnexal areas affects the staging of the disease.

Clinical Staging. Perioperative imaging studies, including chest X-ray, computerized tomography scans, and magnetic resonance imaging, may identify distant metastases. Staging may be modified by imaging studies or clinical findings obtained prior to the initiation of treatment.

Pathologic Staging. Laparotomy with resection of tubal masses, usually including hysterectomy and bilateral oophorectomy, form the basis for the operative management of fallopian tube carcinoma. Widespread intra-abdominal disease is common; therefore, adequate evaluation of potentially early stage lesions requires multiple biopsies of commonly involved sites, such as omentum, pelvic peritoneum, mesentery, bowel serosa, diaphragm, and regional nodes, in order to rule out microscopic metastases to any of these sites.

Cytologic studies of ascites (if present) or of pelvic and abdominal peritoneal washings (if no ascites are present) should be included in the staging. The surgical-pathologic findings form the basis for staging. Staging is based on the findings at the time the abdomen is opened, not on the residual disease after debulking.

It may be preferable to classify a patient as TX (primary tumor cannot be assessed) if inadequate staging biopsies and/or a lack of peritoneal cytology make it inaccurate to classify the patient with confidence as early stage (Stage T3a/IIIA has not been excluded by adequate staging biopsies).

DEFINITION OF TNM

Primary Tumor (T)

TNM Categories	*FIGO Stages*	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis	0	Carcinoma *in situ* (limited to tubal mucosa)
T1	I	Tumor limited to the fallopian tube(s)
T1a	IA	Tumor limited to one tube, without penetrating the serosal surface; no ascites
T1b	IB	Tumor limited to both tubes, without penetrating the serosal surface; no ascites
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
T2	II	Tumor involves one or both fallopian tubes with pelvic extension
T2a	IIA	Extension and/or metastasis to the uterus and/or ovaries
T2b	IIB	Extension to other pelvic structures
T2c	IIC	Pelvic extension with malignant cells in ascites or peritoneal washings
T3	III	Tumor involves one or both fallopian tubes, with peritoneal implants outside the pelvis
T3a	IIIA	Microscopic peritoneal metastasis outside the pelvis
T3b	IIIB	Macroscopic peritoneal metastasis outside the pelvis 2 cm or less in greatest dimension
T3c	IIIC	Peritoneal metastasis more than 2 cm in diameter

Note: Liver capsule metastasis is T3/Stage III; liver parenchymal metastasis M1/Stage IV. Pleural effusion must have positive cytology for M1/Stage IV.

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)

MX		Distant metastasis cannot be assessed
M0		No distant metastasis
M1	IV	Distant metastasis (excludes metastasis within the peritoneal cavity)

STAGE GROUPING

Stage 0	Tis	N0	M0
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

HISTOPATHOLOGIC TYPES

Adenocarcinoma is the most frequently seen histology.

HISTOLOGIC GRADE (G)

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

PROGNOSTIC FACTORS

The surgical-pathologic stage is the most significant prognostic characteristic. Tumor differentiation is an important prognostic characteristic in all stages of disease. In patients with localized tumors, depth of invasion into the tubal musculature and rupture of the tube have prognostic importance. With advanced disease, the volume of residual tumor after surgical debulking appears to be related to prognosis.

OUTCOMES RESULTS

This is a very uncommon tumor. It is usually treated with surgery followed by chemotherapy. The 5-year survival in early disease is approximately 70%, but surgical staging is often inadequate. At 5 years, the overall survival for patients with advanced disease is about 20%.

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HISTOLOGIES—FALLOPIAN TUBE

8010/2	Carcinoma *in situ*, NOS
8010/3	Carcinoma, NOS
8140/2	Adenocarcinoma *in situ*, NOS
8140/3	Adenocarcinoma, NOS
8310/3	Clear cell adenocarcinoma, NOS
8380/3	Endometrioid adenocarcinoma, NOS
8381/3	Endometrioid adenofibroma, malignant
8382/3	Endometrioid adenocarcinoma, secretory variant
8383/3	Endometrioid adenocarcinoma, ciliated cell variant
8440/3	Cystadenocarcinoma, NOS
8441/3	Serous cystadenocarcinoma, NOS
8460/3	Papillary serous cystadenocarcinoma
8461/3	Serous surface papillary carcinoma
8470/2	Mucinous cystadenocarcinoma, non-invasive
8470/3	Mucinous cystadenocarcinoma, NOS
8480/3	Mucinous adenocarcinoma
8481/3	Mucin-producing adenocarcinoma
8482/3	Mucinous adenocarcinoma, endocervical type
8490/3	Signet ring cell carcinoma
8560/3	Adenosquamous carcinoma
8562/3	Epithelial-myoepithelial carcinoma
8570/3	Adenocarcinoma with squamous metaplasia

FALLOPIAN TUBE

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____ Laterality: ☐ Bilateral ☐ Left ☐ Right

DEFINITIONS

Clinical	*Pathologic*	**Primary Tumor (T)** *TNM Categories*	*FIGO Stages*	
☐	☐	TX		Primary tumor cannot be assessed
☐	☐	T0		No evidence of primary tumor
☐	☐	Tis	0	Carcinoma *in situ* (limited to tubal mucosa)
☐	☐	T1	I	Tumor limited to the fallopian tube(s)
☐	☐	T1a	IA	Tumor limited to one tube, without penetrating the serosal surface; no ascites
☐	☐	T1b	IB	Tumor limited to both tubes, without penetrating the serosal surface; no ascites
☐	☐	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
☐	☐	T2	II	Tumor involves one or both fallopian tubes with pelvic extension
☐	☐	T2a	IIA	Extension and/or metastasis to the uterus and/or ovaries
☐	☐	T2b	IIB	Extension to other pelvic structures
☐	☐	T2c	IIC	Pelvic extension with malignant cells in ascites or peritoneal washings
☐	☐	T3	III	Tumor involves one or both fallopian tubes, with peritoneal implants outside the pelvis
☐	☐	T3a	IIIA	Microscopic peritoneal metastasis outside the pelvis
☐	☐	T3b	IIIB	Macroscopic peritoneal metastasis outside the pelvis 2 cm or less in greatest dimension
☐	☐	T3c	IIIC	Peritoneal metastasis more than 2 cm in diameter
		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)		
☐	☐	MX		Distant metastasis cannot be assessed
☐	☐	M0		No distant metastasis
☐	☐	M1	IV	Distant metastasis (excludes metastasis within the peritoneal cavity)

Biopsy of metastatic site performed ..... ☐Y ..... ☐N

Source of pathologic metastatic specimen _____

(continued on reverse side)

Clinical	*Pathologic*	**Stage Grouping** (AJCC/UICC/FIGO)			
☐	☐	0	Tis	N0	M0
☐	☐	I	T1	N0	M0
☐	☐	IA	T1a	N0	M0
☐	☐	IB	T1b	N0	M0
☐	☐	IC	T1c	N0	M0
☐	☐	II	T2	N0	M0
☐	☐	IIA	T2a	N0	M0
☐	☐	IIB	T2b	N0	M0
☐	☐	IIC	T2c	N0	M0
☐	☐	III	T3	N0	M0
☐	☐	IIIA	T3a	N0	M0
☐	☐	IIIB	T3b	N0	M0
☐	☐	IIIC	T3c	N0	M0
			Any T	N1	M0
☐	☐	IV	Any T	Any N	M1

Histologic Grade (G)

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

Residual Tumor (R)

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

Additional Descriptors

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.

Prognostic Indicators (if applicable)

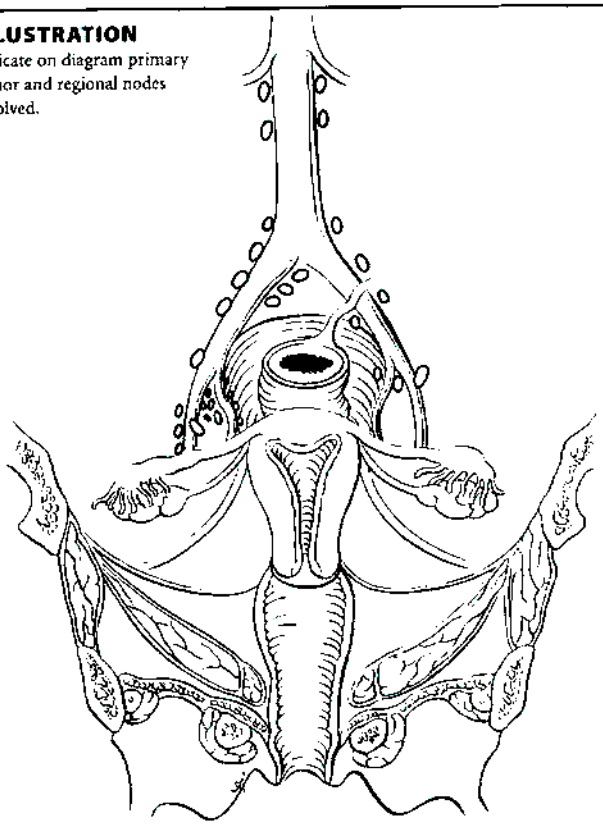
Notes

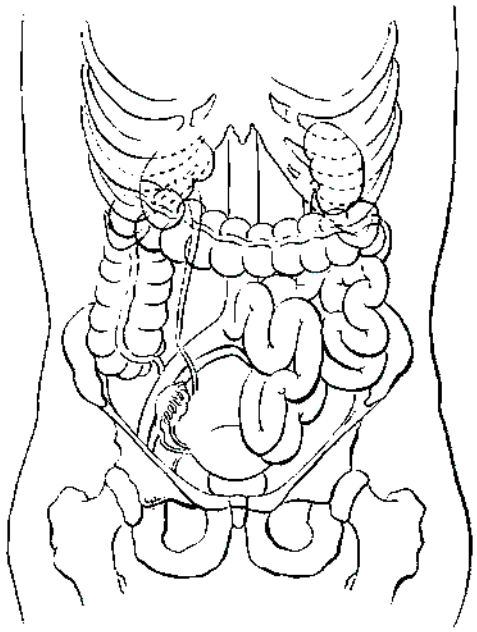
Additional Descriptors

Lymphatic Vessel Invasion (L)
- LX Lymphatic vessel invasion cannot be assessed
- L0 No lymphatic vessel invasion
- L1 Lymphatic vessel invasion

Venous Invasion (V)
- VX Venous invasion cannot be assessed
- V0 No venous invasion
- V1 Microscopic venous invasion
- V2 Macroscopic venous invasion

ILLUSTRATION
Indicate on diagram primary tumor and regional nodes involved.





Physician's Signature _____ Date _____

32

Gestational Trophoblastic Tumors

C58.9 Placenta

SUMMARY OF CHANGES

- Gestational trophoblastic tumors are effectively treated with chemotherapy even when widely metastatic so that traditional anatomic staging parameters do not adequately provide different prognostic categories. For this reason, although the anatomic categories are preserved, a scoring system of other non-anatomic risk factors has been added. This risk factor score provides the basis for substaging patients into A (low risk, score of 7 or less) or B (high risk, score of 8 or greater).
- The "Risk Factors" portion of the stage grouping has been revised to reflect the new scoring system.

INTRODUCTION

Gestational trophoblastic tumors are uncommon (1 in 1,000 pregnancies) malignancies that arise from the placenta. Usually as a result of a genetic accident in the developing egg, the maternal chromosomes are lost, and the paternal chromosomes duplicate (46xx). The resulting tumor is known as a *complete* hydatidiform mole: There are no fetal parts, the tumor is composed of dilated, avascular, "grape-like" vesicles that may grow as large as, or larger than, the normal pregnancy that it replaces. There is obviously no heartbeat detected, and the patient may have vaginal bleeding similar to a miscarriage. Many times, the diagnosis is not made until a dilatation and curettage is done and the tissue is examined pathologically. In some patients, fetal parts will be found in association with mild proliferative trophoblastic (placental) tissue. Such patients have a *partial* hydatidiform mole, which has a 69xxx or 69xxy chromosomal complement resulting from twice the normal number of paternal chromosomes. Both of these tumors usually follow a benign course, resolving completely after evacuation by dilatation and suction or curettage, but approximately 20% of complete moles and 5% of partial moles persist locally or metastasize and thus require chemotherapy.

Much less frequently (about 1 in 20,000 pregnancies in the United States), a highly malignant, rapidly growing metastatic form of gestational trophoblastic disease called choriocarcinoma is encountered. This solid, anaplastic, vascular, and aggressively proliferative tumor is easily recognized microscopically and may present with symptoms of vaginal bleeding (as with a hydatidiform mole). However, metastatic lesions may be the first sign of this lesion, which can follow any pregnancy event, including an incomplete abortion or a full-term pregnancy.

The trophoblastic tissue that makes up these tumors produces a serum tumor marker, beta-human chorionic gonadotropin (β-hCG), which is very helpful in the diagnosis and monitoring of therapy in these patients. Gestational trophoblastic tumors are very responsive to chemotherapy, with cure rates approaching 100%.

8

ANATOMY

Because of the responsiveness of this tumor to treatment and the accuracy of the serum tumor marker hCG in reflecting the status of disease, the traditional anatomic staging system used in most solid tumors has little prognostic significance. Trophoblastic tumors not associated with pregnancy (ovarian teratomas) are not included in this classification.

Primary Site. By definition, gestational trophoblastic tumors arise from placental tissue in the uterus. Although most of these tumors are non-invasive and are removed by dilatation and suction evacuation, local invasion of the myometrium can occur. When this is diagnosed on a hysterectomy specimen (rarely done these days), it may be reported as an *invasive* hydatidiform mole.

Regional lymph nodes. Nodal involvement in gestational trophoblastic tumors is rare but has a very poor

prognosis when diagnosed. There is no regional nodal designation in the staging of these tumors. Nodal metastases should be classified as metastatic (M1) disease.

Metastatic sites. This is a highly vascular tumor that results in frequent, widespread metastases when these lesions become malignant. The cervix and vagina are common pelvic sites of metastases (T2), and the lungs are often involved by distant metastases (M1a). Other, less frequently encountered metastatic sites include kidney, gastrointestinal tract, and spleen (M1b). The liver and brain are occasionally involved and may harbor metastatic sites that are difficult to treat with chemotherapy.

RULES FOR CLASSIFICATION

Gestational trophoblastic tumors have a very high cure rate, and as a result, the ultimate goal of staging is to identify patients who are likely to respond to less intensive chemotherapeutic protocols and distinguish these individuals from patients who will require more intensive chemotherapy in order to achieve remission. In 1991, the International Federation of Gynecology and Obstetrics (FIGO) added non-anatomic risk factors to the traditional staging system. Further modifications have been made in an attempt to merge several prognostic classification systems. The current staging classification is still evolving.

Indications for Treatment. The following criteria are suggested for the diagnosis of trophoblastic tumors requiring chemotherapy:

- Three or more values of hCG showing no significant change (a plateau) over 4 weeks, or
- Rise of hCG of 10% or greater for 2 values over 3 weeks or longer, or
- Persistence of elevated hCG 6 months after evacuation of molar pregnancy, or
- Histologic diagnosis of choriocarcinoma

Diagnosis of Metastasis

- For the diagnosis of lung metastasis, chest X-ray is appropriate and should be used to count metastases for risk scoring. Lung CT scan may be used.
- For the diagnosis of intra-abdominal metastasis, CT scanning is preferred, although many institutions still use ultrasound to detect liver metastasis.
- For the diagnosis of brain metastasis, MRI is superior to CT scan, even with 1-cm cuts.

Prognostic Index Scores. The score on the Prognostic Scoring Index is used to substage patients (Table 32.1). Each stage is anatomically defined, but substage A (low risk) and B (high risk) are assigned on the basis of a non-anatomic risk 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 7 or less, and high risk is a score of 8 or greater.

DEFINITION 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)

MX		Metastasis cannot be assessed
M0		No distant metastasis
M1		Distant metastasis
M1a	III	Lung metastasis
M1b	IV	All other distant metastasis

STAGE GROUPING

Stage	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

HISTOPATHOLOGIC TYPE

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

TABLE 32.1. Prognostic Scoring Index

	Risk Score			
Prognostic Factor	*0*	*1*	*2*	*4*
Age	<40	≥40		
Antecedent Pregnancy	Hydatidiform mole	Abortion	Term pregnancy	
Interval months from index pregnancy	<4	4–<7	7–12	>12
Pretreatment hCG (IU/ml)	$<10^3$	$\geq 10^3$–$<10^4$	10^4–$<10^5$	$\geq 10^5$
Largest tumor size, including uterus	<3 cm	3–<5 cm	≥5 cm	
Site of metastases	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases identified		1–4	5–8	>8
Previous failed chemotherapy			Single drug	Two or more drugs
Total Score				

Low risk is a score of 7 or less. High risk is a score of 8 or greater.

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.

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Ngan HYS, Odicino F, Maisonneuve P, et al: Gestational trophoblastic diseases. FIGO Annual Report. J Epidem Biostat 6: 175–184, 2001

HISTOLOGIES—GESTATIONAL TROPHOBLASTIC TUMORS

9100/0	Hydatidiform mole, NOS
9100/1	Invasive hydatidiform mole
9100/3	Choriocarcinoma, NOS
9101/3	Choriocarcinoma combined with other germ cell elements
9102/3	Malignant teratoma, trophoblastic
9103/0	Partial hydatidiform mole
9104/1	Placental site trophoblastic tumor
9105/3	Trophoblastic tumor, epithelioid

GESTATIONAL TROPHOBLASTIC TUMORS

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____

DEFINITIONS

Primary Tumor (T)[1]

Clinical	Pathologic	TNM* Categories	FIGO Stages	
☐	☐	TX		Primary tumor cannot be assessed
☐	☐	T0		No evidence of primary tumor
☐	☐	T1	I	Disease limited to uterus
☐	☐	T2	II	Disease outside of uterus but limited to genital structures (ovary, tube, vagina, broad ligaments)

Distant Metastasis (M)

☐ ☐	MX		Metastasis cannot be assessed
☐ ☐	M0		No distant metastasis
☐ ☐	M1		Distant metastasis
☐ ☐	M1a	III	Lung metastasis
☐ ☐	M1b	IV	All other distant metastasis

Biopsy of metastatic site performed ..... ☐Y ..... ☐N

Source of pathologic metastatic specimen _____

Note: There is no regional nodal staging for this tumor.

Stage Grouping[2]

	Stage	T	M	Risk Factors
☐ ☐	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

Notes

1. See prognostic indicator section for substage definitions.
2. See prognostic indicators for substage grouping

8

(continued on reverse side)

Histopathologic Type

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

Residual Tumor (R)

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

Additional Descriptors

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.

Prognostic Indicators Scoring Index

Prognostic Factor	*Risk Score*			
	0	1	2	4
Age	<40	≥40		
Antecedent Pregnancy	H. mole	Abortion	Term Pregnancy	
Interval months from index pregnancy	<4	4-<7	7-12	>12
Pretreatment hCG (IU/ml)	$<10^3$	$\geq 10^3$-$<10^4$	10^4-$<10^5$	$\geq 10^5$
Largest tumor size including uterus	<3cm	3-<5cm	≥5cm	
Site of metastases	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases identified		1-4	5-8	>8
Previous failed chemotherapy			Single drug	Two or more drugs
Total Score				

Low Risk is a score of 7 or less. *High risk* is a score of 8 or greater.

Notes

Additional Descriptors

Lymphatic Vessel Invasion (L)

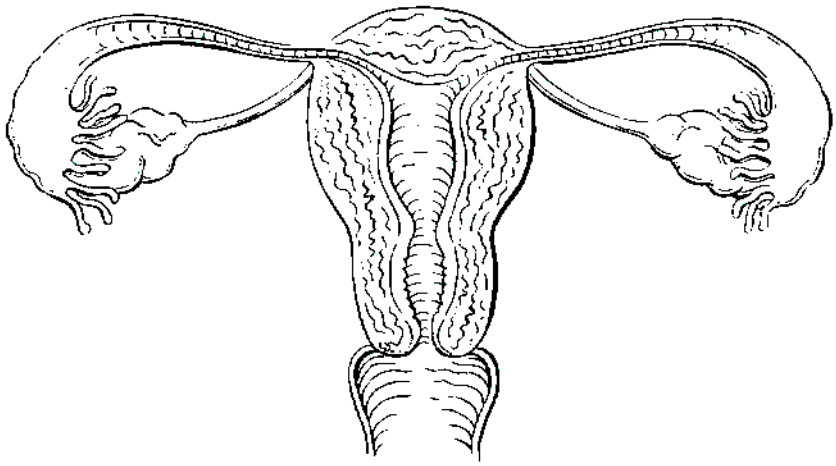
- LX Lymphatic vessel invasion cannot be assessed
- L0 No lymphatic vessel invasion
- L1 Lymphatic vessel invasion

Venous Invasion (V)

- VX Venous invasion cannot be assessed
- V0 No venous invasion
- V1 Microscopic venous invasion
- V2 Macroscopic venous invasion

ILLUSTRATION

Indicate on diagram primary tumor and regional nodes involved.



Physician's Signature _____ Date_____

PART IX
Genitourinary Sites

33

Penis

(Melanomas are not included.)

C60.0 Prepuce
C60.1 Glans penis
C60.2 Body of penis
C60.8 Overlapping lesion of penis
C60.9 Penis, NOS

SUMMARY OF CHANGES

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

INTRODUCTION

Cancers of the penis are rare in the United States, although the incidence varies in different countries of the world. Most are squamous cell carcinomas that arise in the skin or on the glans penis. Prognosis is favorable provided that the lymph nodes are not involved. Melanomas can also occur. The staging classification, however, applies to carcinomas. Melanomas are staged in Chapter 24. Some cancers of the penis may be described as verrucous. Similarly, basaloid tumors are recognized as a subtype of squamous carcinoma. These are included under this classification. An *in situ* lesion is also included and by definition should be coded as an *in situ* carcinoma of the penis.

ANATOMY

Primary Site. The penis is composed of three cylindrical masses of cavernous tissue bound together by fibrous tissue. Two masses are lateral and are known as the corpora cavernosa penis. The corpus spongiosum penis is a median mass and contains the greater part of the urethra. The penis is attached to the front and the sides of the pubic arch. The skin covering the penis is thin and loosely connected with the deeper parts of the organ. This skin at the root of the penis is continuous with that over the scrotum and perineum. Distally, the skin becomes folded upon itself to form the prepuce, or foreskin. Circumcision has been associated with a decreased incidence of cancer of the penis.

Regional Lymph Nodes. The regional lymph nodes are:

Single superficial inguinal (femoral)
Multiple or bilateral superficial inguinal (femoral)
Deep inguinal: Rosenmuller's or Cloquet's node
External iliac
Internal iliac (hypogastric)
Pelvic nodes, NOS

Metastatic Sites. Lung, liver, and bone are most often involved.

RULES FOR CLASSIFICATION

Clinical Staging. Clinical examination, endoscopy where possible, and histologic confirmation are required. Imaging techniques are indicated for metastatic disease detection.

Pathologic Staging. Complete resection of the primary site with appropriate margins is required. Where regional lymph node involvement is suspected, lymphadenectomy is usually indicated.

The definitions of Primary Tumor (T) for Ta, T1, T2, T3 and T4 are illustrated in Figures 33.1–33.5.

DEFINITION OF TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
Ta	Non-invasive verrucous carcinoma
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades corpus spongiosum or cavernosum
T3	Tumor invades urethra or prostate
T4	Tumor invades other adjacent structures

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single superficial, inguinal lymph node
N2 Metastasis in multiple or bilateral superficial inguinal lymph nodes
N3 Metastasis in deep inguinal or pelvic lymph node(s) unilateral or bilateral

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Additional Descriptor

The **m suffix** indicates the presence of multiple primary tumors and is recorded in parentheses—e.g., pTa(m)N0M0.

STAGE GROUPING

Stage 0	Tis	N0	M0
	Ta	N0	M0
Stage I	T1	N0	M0
Stage II	T1	N1	M0
	T2	N0	M0
	T2	N1	M0
Stage III	T1	N2	M0
	T2	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
Stage IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

HISTOPATHOLOGIC TYPE

Cell types are limited to carcinomas.

HISTOLOGIC GRADE (G)

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3–4 Poorly differentiated or undifferentiated

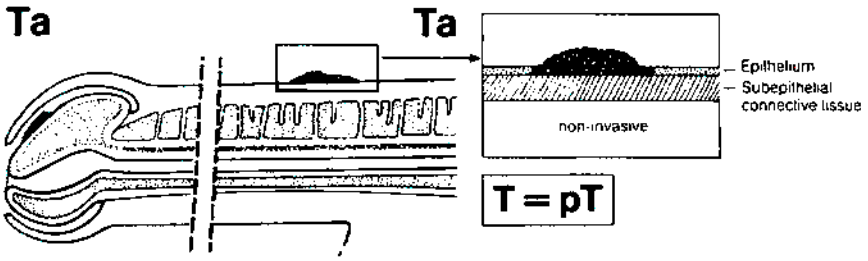


FIG. 33.1. Ta: Non-invasive verrucous carcinoma.

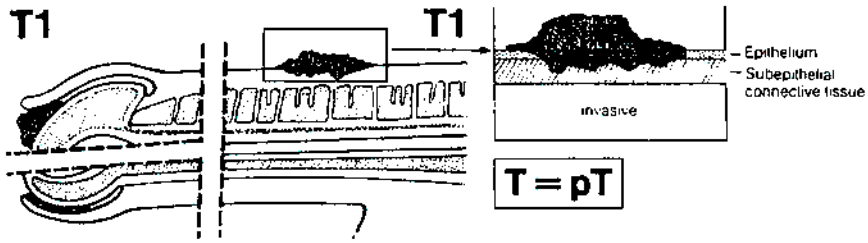


FIG. 33.2. T1: Tumor invading subepithelial connective tissue.

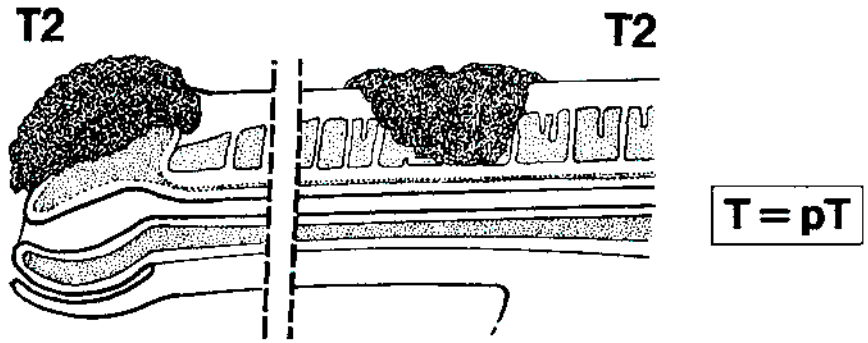


FIG. 33.3. T2: Tumor invading corpus spongiosum or cavernosum.

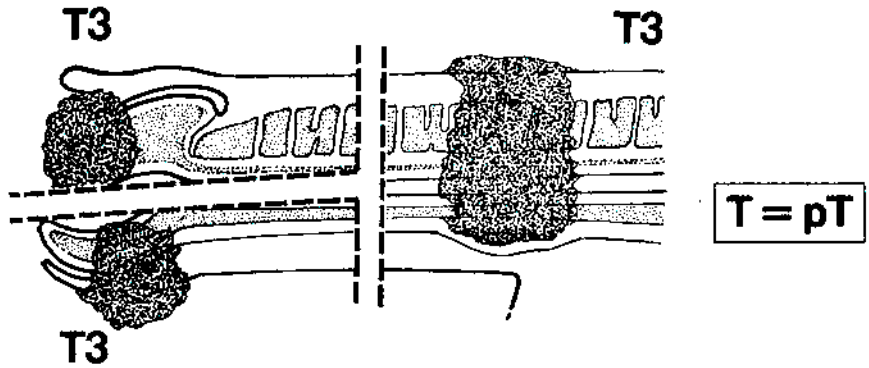


FIG. 33.4. T3: Tumor invading urethra or prostate.

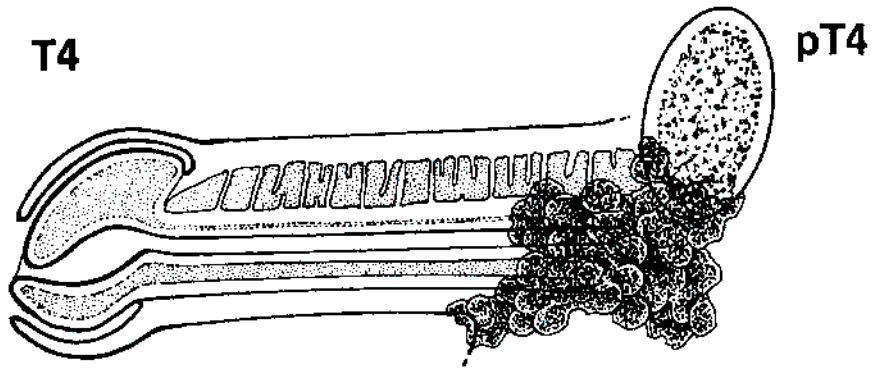


FIG. 33.5. T4: Tumor invading other adjacent structures.

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Wajsman Z, et al: Fine needle aspiration of metastatic lesions and regional lymph nodes in genitourinary cancer. Urology 19:356, 1982

HISTOLOGIES—PENIS

8010/2	Carcinoma *in situ*, NOS
8010/3	Carcinoma, NOS
8051/3	Verrucous carcinoma, NOS
8070/2	Squamous cell carcinoma *in situ*, NOS
8070/3	Squamous cell carcinoma, NOS
8081/2	Bowen disease
8090/3	Basal cell carcinoma
8140/2	Adenocarcinoma *in situ*, NOS
8140/3	Adenocarcinoma, NOS
8560/3	Adenosquamous carcinoma

PENIS

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____

DEFINITIONS

Clinical	*Pathologic*	**Primary Tumor (T)**	
☐	☐	TX	Primary tumor cannot be assessed
☐	☐	T0	No evidence of primary tumor
☐	☐	Tis	Carcinoma *in situ*
☐	☐	Ta	Non-invasive verrucous carcinoma
☐	☐	T1	Tumor invades subepithelial connective tissue
☐	☐	T2	Tumor invades corpus spongiosum or cavernosum
☐	☐	T3	Tumor invades urethra or prostate
☐	☐	T4	Tumor invades other adjacent structures

Regional Lymph Nodes (N)

☐	☐	NX	Regional lymph nodes cannot be assessed
☐	☐	N0	No regional lymph node metastasis
☐	☐	N1	Metastasis in a single superficial inguinal lymph node
☐	☐	N2	Metastasis in multiple or bilateral superficial inguinal lymph nodes
☐	☐	N3	Metastasis in deep inguinal or pelvic lymph node(s), unilateral or bilateral

Distant Metastasis (M)

☐	☐	MX	Distant metastasis cannot be assessed
☐	☐	M0	No distant metastasis
☐	☐	M1	Distant metastasis

Biopsy of metastatic site performed ..... ☐Y ..... ☐N

Source of pathologic metastatic specimen _____

Stage Grouping

☐ ☐	0	Tis	N0	M0
		Ta	N0	M0
☐ ☐	I	T1	N0	M0
☐ ☐	II	T1	N1	M0
		T2	N0	M0
		T2	N1	M0
☐ ☐	III	T1	N2	M0
		T2	N2	M0
		T3	N0	M0
		T3	N1	M0
		T3	N2	M0
☐ ☐	IV	T4	Any N	M0
		Any T	N3	M0
		Any T	Any N	M1

(continued on reverse side)

Histologic Grade (G)

- ☐ GX Grade cannot be assessed
- ☐ G1 Well differentiated
- ☐ G2 Moderately differentiated
- ☐ G3-4 Poorly differentiated or undifferentiated

Residual Tumor (R)

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

Additional Descriptors

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.

Prognostic Indicators (if applicable)

Notes

Additional Descriptors

Lymphatic Vessel Invasion (L)

LX Lymphatic vessel invasion cannot be assessed
L0 No lymphatic vessel invasion
L1 Lymphatic vessel invasion

Venous Invasion (V)

VX Venous invasion cannot be assessed
V0 No venous invasion
V1 Microscopic venous invasion
V2 Macroscopic venous invasion

Physician's Signature _____ Date_____

34

Prostate

(Sarcomas and transitional cell carcinomas are not included.)

C61.9 Prostate gland

SUMMARY OF CHANGES

- T2 lesions have been divided to include T2a, T2b, and T2c once again. These are the same subcategories found in the Fourth Edition of the manual.
- Gleason score is emphasized as the grading system of choice and using the terms *well differentiated, moderately differentiated,* and *poorly differentiated* for grading is not recommended.

INTRODUCTION

Prostate cancer is the most common 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 diagnosis is generally made using transrectal ultrasound (TRUS) guided biopsy.

ANATOMY

Primary Site. Adenocarcinoma of the prostate frequently arises within the peripheral zone of the gland, where it may be amenable to detection by digital rectal examination (DRE). A less common site of origin is the anteromedial prostate, the transition zone, which is remote from the rectal surface and is the site of origin of benign nodular hyperplasia. The central zone, which makes up most of the base of the prostate, seldom gives rise to cancer but is often invaded by the spread of large cancers. Pathologically, cancers of the prostate are often multifocal.

There is agreement that 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 DRE and TRUS to define precisely the size or local extent of disease; DRE is currently the most common modality used to define the local stage. Heterogeneity within the Tlc 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 resected tissue from a transurethral resection of the prostate (TURP) for obstructive voiding symptoms.

The histologic grade of the prostate cancer is important for prognosis. The histopathologic grading of these tumors can be complex because of the morphologic heterogeneity so often encountered in surgical specimens. Either a histologic or a pattern type of grading method can be used. The Gleason score for assessing the histologic pattern of prostate cancer is preferred.

Regional Lymph Nodes. The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries. They include the following groups:

Pelvic, NOS
Hypogastric
Obturator
Iliac (internal, external, or NOS)
Sacral (lateral, presacral, promontory [Gerota's], or NOS)

Laterality does not affect the "N" classification.

Distant Lymph Nodes. Distant lymph nodes lie outside the confines of the true pelvis. They can be imaged using

ultrasound, computed tomography, magnetic resonance imaging, or lymphangiography. Although enlarged lymph nodes can occasionally be visualized, because of a stage migration associated with PSA screening, very few patients will be found to have nodal disease, so false-positive and false-negative results are common when imaging tests are employed. In lieu of imaging, risk tables are generally used to determine individual patient risk of nodal involvement. Involvement of distant lymph nodes is classified as M1a. The distant lymph nodes include:

Aortic (para-aortic lumbar)
Common iliac
Inguinal, deep
Superficial inguinal (femoral)
Supraclavicular
Cervical
Scalene
Retroperitoneal, NOS

The significance of regional lymph node metastasis, pN, in staging prostate cancer lies in the presence of metastatic foci present within the lymph nodes.

Metastatic Sites. Osteoblastic metastases are the most common non-nodal site of prostate cancer metastasis. In addition, this tumor frequently spreads to distant lymph nodes. Lung and liver metastases are usually identified late in the course of the disease.

RULES FOR CLASSIFICATION

Clinical Staging. Primary tumor assessment includes digital rectal examination of the prostate and histologic or cytologic confirmation of prostate carcinoma. All information available 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 non-palpable 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 7–8 and PSA values < 20 ng/ml, imaging studies may not always be helpful in accurate staging.

Since publication of the Fifth Edition of the *AJCC Cancer Staging Manual*, review of the results of clinical series of patients with T2 tumors has demonstrated that recurrence-free survival following treatment was significantly different if the Fourth Edition system of T2a, T2b, and T2c stratification was used. Therefore, to enhance the characterization of palpable tumors, the Sixth Edition has reincorporated the three clinical stages T2a (palpable tumor confined to less than one-half of one lobe), T2b (palpable tumor involving more than half of one lobe but not both lobes), and T2c (tumor involving both lobes).

Pathologic Staging. In general, total prostatoseminal-vesiculectomy, including regional node specimen, and histologic confirmation are required for pathologic T 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 prostatoseminal-vesiculectomy, and (2) a biopsy revealing carcinoma in extraprostatic soft tissue permits a pT3 classification, as does a biopsy revealing adenocarcinoma infiltrating the seminal vesicles. However, there is no pT1 category because there is insufficient tissue to assess the highest pT category. Margin positivity, potentially a consequence of surgical technique rather than anatomic extent of disease, should be specified along with pathologic stage. (Positive surgical margin should be indicated by an R1 descriptor [residual microscopic disease].)

In addition to pathologic stage, independent prognostic factors for survival have been identified for prostate cancer. These include age of patient, comorbid diseases, histologic grade, Gleason score, PSA, and percent free-PSA level, surgical margin status, and ploidy.

DEFINITION 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: bladder neck, external sphincter, 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, involving one-half of one lobe or less
pT2b Unilateral involving more than one-half of one lobe but not both lobes
pT2c Bilateral disease
pT3 Extraprostatic extension
pT3a Extraprostatic extension**
pT3b Seminal vesicle invasion
pT4 Invasion of bladder, rectum

**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)*

MX Distant metastasis cannot be assessed (not evaluated by any modality)
M0 No distant metastasis
M1 Distant metastasis
M1a Non-regional 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. pMlc is most advanced.

STAGE GROUPING

Stage I	Tla	N0	M0	G1
Stage II	Tla	N0	M0	G2, 3–4
	Tlb	N0	M0	Any G
	Tlc	N0	M0	Any G
	T1	N0	M0	Any G
	T2	N0	M0	Any G
Stage III	T3	N0	M0	Any G
Stage IV	T4	N0	M0	Any G
	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

HISTOPATHOLOGIC TYPE

This classification applies to adenocarcinomas and squamous carcinomas, but not to sarcoma or transitional cell carcinoma of the prostate. Adjectives used to describe adenocarcinomas can include *mucinous, small cell, papillary, ductal,* and *neuroendocrine.* Transitional cell carcinoma of the prostate is classified as a urethral tumor (see Chapter 39). There should be histologic confirmation of the disease.

HISTOLOGIC GRADE (G)

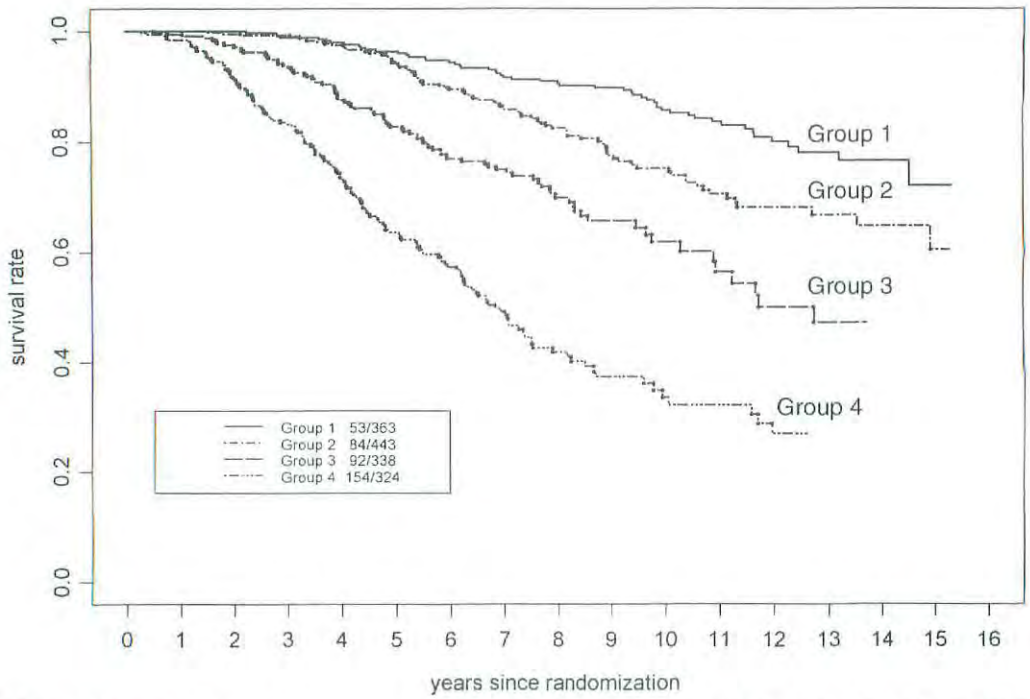
Gleason score is considered to be the optimal method of grading, because this method takes into account the inherent heterogeneity of prostate cancer, and because it has been clearly shown that this method is of great prognostic value. A primary and a secondary pattern (the range of each is 1–5) are assigned and then summed to yield a total score. Scores of 2–10 are thus possible. (If a single focus of disease is seen, it should be reported as both scores. For example, if a single focus of Gleason 3 disease is seen, it is reported as 3 + 3.)

GX Grade cannot be assessed
G1 Well differentiated (slight anaplasia) (Gleason 2–4)
G2 Moderately differentiated (moderate anaplasia) (Gleason 5–6)
G3–4 Poorly differentiated/undifferentiated (marked anaplasia) (Gleason 7–10)

PROGNOSTIC FEATURES

Prostate-specific antigen, grade, and tumor stage all have a profound relationship with prognosis. An increasing number of molecular markers (such as ploidy, p53, and bcl-2) have been identified that 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.

Recent studies have demonstrated that Gleason score provides extremely important information about prognosis.



Group 1: Gleason Score (GS) = 2–6, T1–2 NX
Group 2: GS = 2–6, T3 NX or GS = 2–6, N+ or GS = 7, T1–2 NX
Group 3: GS = 7, T3 NX or GS = 7, N+ or GS = 8–10, T1–2 NX
Group 4: GS = 8–10, T3 NX or GS = 8–10, N+

FIG. 34.1. Four prognostic groups predicting long-term survival from prostate cancer following radiotherapy alone on Radiation Therapy Oncology Group clinical trials. (Reprinted from Roach M, Lu J, Pilepich M, et al. Int J Rad Onc Bio Phys 47(3):609–615, 2000, with permission from Elsevier Science.)

In an analysis, conducted by the Radiation Therapy Oncology Group (RTOG), of nearly 1500 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 (See Fig. 34.1). 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. Other clinical features, such as the number of positive biopsies and the presence of perineural invasion, may provide additional prognostic information. However, long-term confirmatory, multi-institutional studies demonstrating the independent impact of these factors on survival from prostate cancer are not yet available.

OUTCOMES BY STAGE, GRADE, AND PSA

A number of endpoints are useful in assessing disease outcomes. 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 also useful endpoints.

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HISTOLOGIES—PROSTATE

8041/3	Small cell carcinoma, NOS
8070/3	Squamous cell carcinoma, NOS
8074/3	Squamous cell carcinoma, spindle cell
8082/3	Lymphoepithelial carcinoma
8098/3	Adenoid basal carcinoma
8120/3	Transitional cell carcinoma, NOS
8140/2	Adenocarcinoma *in situ,* NOS
8140/3	Adenocarcinoma, NOS
8148/2	Glandular intraepithelial neoplasia, grade III
8200/3	Adenoid cystic carcinoma
8240/3	Carcinoid tumor, NOS
8246/3	Neuroendocrine carcinoma, NOS
8260/3	Papillary adenocarcinoma
8480/3	Mucinous adenocarcinoma
8490/3	Signet ring cell carcinoma
8500/3	Infiltrating duct carcinoma, NOS
8560/3	Adenosquamous carcinoma

PROSTATE

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____

DEFINITIONS

Pathologic	Primary Tumor (T)[1]	
☐	pT2	Organ confined
☐	pT2a	Unilateral, one-half of one lobe or less
☐	pT2b	Unilateral, involving more than one-half of lobe but not both lobes
☐	pT2c	Bilateral disease
☐	pT3	Extraprostatic extension
☐	pT3a	Extraprostatic extension[2]
☐	pT3b	Seminal vesicle invasion
☐	pT4	Invasion of bladder, rectum

Clinical	Primary Tumor (T)	
☐	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[3]
☐	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[4]
☐	T3a	Extracapsular extension (unilateral or bilateral)
☐	T3b	Tumor invades seminal vesicle(s)
☐	T4	Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

Notes

1. There is no pathologic T1 classification.

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

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

4. Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3, but as T2.

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

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

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

Clinical	Pathologic	Distant Metastasis (M)[5]	
☐	—	MX	Distant metastasis cannot be assessed (not evaluated by any modality)
☐	☐	M0	No distant metastasis
☐	☐	M1	Distant metastasis
☐	☐	M1a	Non-regional lymph node(s)
☐	☐	M1b	Bone(s)
☐	☐	M1c	Other site(s) with or without bone disease.

Biopsy of metastatic site performed..... ☐Y..... ☐N

Source of pathologic metastatic specimen _____

(continued on reverse side)

Clinical	Pathological	Stage Grouping				
☐	☐	I	T1a	N0	M0	G1
☐	☐	II	T1a	N0	M0	G2, 3-4
			T1b	N0	M0	Any G
			T1c	N0	M0	Any G
			T1	N0	M0	Any G
			T2	N0	M0	Any G
☐	☐	III	T3	N0	M0	Any G
☐	☐	IV	T4	N0	M0	Any G
			Any T	N1	M0	Any G
			Any T	Any N	M1	Any G

Histologic Grade (G)

Gleason score = ____ + ____

- ☐ GX Grade cannot be assessed
- ☐ G1 Well differentiated (slight anaplasia) (Gleason 2-4)
- ☐ G2 Moderately differentiated (moderate anaplasia) (Gleason 5-6)
- ☐ G3-4 Poorly differentiated/undifferentiated (marked anaplasia) (Gleason 7-10)

Residual Tumor (R)

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

Additional Descriptors

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: cT(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.

Prognostic Indicators

PSA
Gleason score
Ploidy
Molecular markers (e.g., p53, bcl-2)

Notes

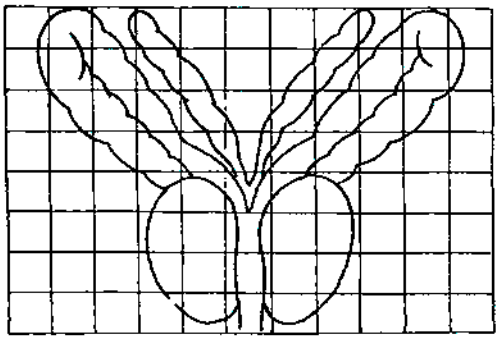
Additional Descriptors

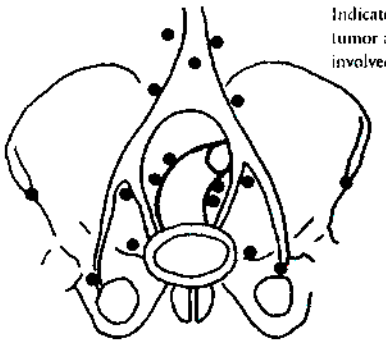
Lymphatic Vessel Invasion (L)
- LX Lymphatic vessel invasion cannot be assessed
- L0 No lymphatic vessel invasion
- L1 Lymphatic vessel invasion

Venous Invasion (V)
- VX Venous invasion cannot be assessed
- V0 No venous invasion
- V1 Microscopic venous invasion
- V2 Macroscopic venous invasion

ILLUSTRATION

This diagram is for use with the prostate diagram. Sketch in extent of tumor.





Indicate on diagram primary tumor and regional nodes involved.

Physician's Signature _____ Date _____

35

Testis

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

SUMMARY OF CHANGES

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

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 20th 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 non-seminomas. 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 serum 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. Cancer of the testis is highly curable, even in cases with advanced, metastatic disease.

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 testes 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 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 non-regional lymph nodes, and metastases to pulmonary and non-pulmonary 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 hours. 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 (for example, 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 lactate dehydrogenase (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 to complete the status of the serum tumor markers (S).

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 the tumor is intra- or extratesticular. If intratesticular, it should be determined whether the tumor extends through the tunica albuginea and whether it invades the epididymis and/or spermatic cord. Tissue sections should document these findings. The tumor should be sampled extensively, including all grossly diverse areas (hemorrhagic, mucoid, solid, cystic, etc.). The junction of tumor and non-neoplastic testis and at least one section remote from the tumor should be obtained to determine whether intratubular germ cell neoplasia (carcinoma *in situ*) is present. These sections will allow assessment of either the presence or absence of vascular invasion. If possible, most tissue sections should include overlying tunica albuginea. Small tumors (2 cm or less) may be submitted *in toto*. In larger tumors, a sufficient amount of tissue should be sampled, perhaps one section for each 1 or 2 cm of maximum tumor diameter.

The specimens from a defined node-bearing area (such as retroperitoneal lymph node dissection) must be used for the pN classification. Retroperitoneal lymph node dissection should be oriented by the surgeon. All lymph nodes should be dissected, and the diameters of the largest nodes should

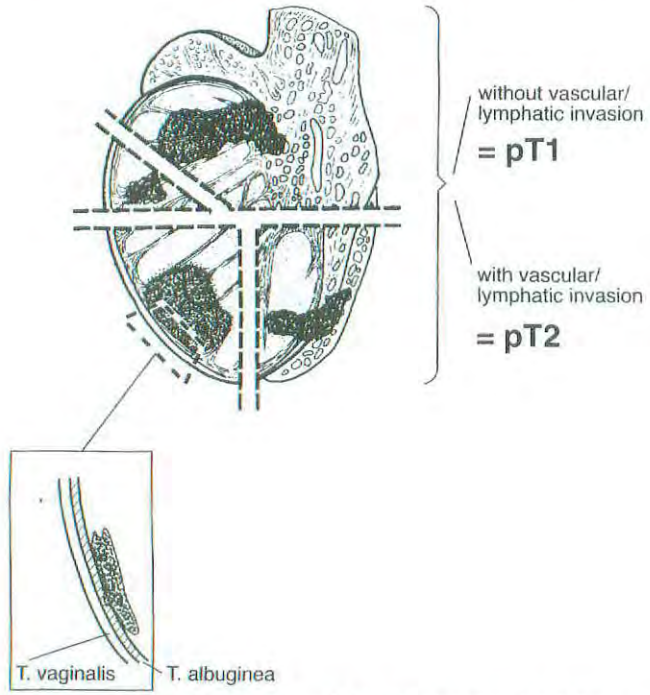


FIG. 35.1. Illustration of pT1 and pT2 showing tumor without and with vascular/lymphatic invasion.

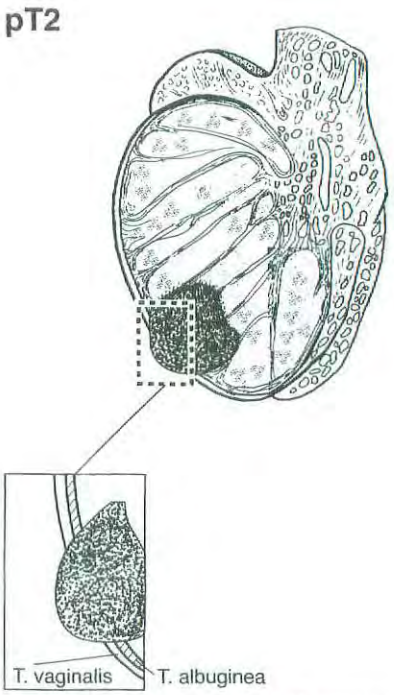


FIG. 35.2. pT2 Tumor extending through the tunica albuginea with involvement of the tunica vaginalis.

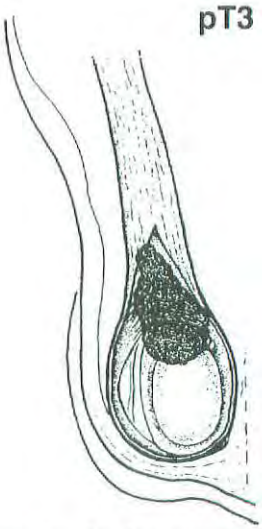


FIG. 35.3. pT3 Tumor invades the spermatic cord.

be recorded, along with the number of lymph nodes involved by tumor. Extranodal soft tissue extension of disease should be noted, if present. It is important to examine carefully and liberally sample the specimen, including cystic, fibrotic, hemorrhagic, necrotic, and solid areas. Laterality does not affect the N classification. In post-treatment specimens, it may be difficult to distinguish individual lymph nodes. The definitions for Primary Tumor (T) for pT1, pT2, and pT3 are illustrated in Figures 35.1, 35.2, and 35.3.

DEFINITION OF TNM

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
pT0	No evidence of primary tumor (e.g., histologic scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma *in situ*)
PT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade into the tunica albuginea but not the tunica vaginalis
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
PT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion

Note: 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)

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
pNl	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
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
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Mla	Non-regional nodal or pulmonary metastasis
Mlb	Distant metastasis other than to non-regional lymph nodes and lungs

Serum Tumor Markers (S)

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

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

STAGE GROUPING

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

HISTOPATHOLOGIC TYPE

Following the guidelines of the *World Health Organization Histological Classification of Tumors,* germ cell tumors may be either seminomatous or non-seminomatous. Seminomas may be classic type or with syncytiotrophoblasts. A distinct variant is spermatocytic seminoma, which is characteristically found in older patients, is often associated with intratumoral calcification, and tends not to metastasize. Non-seminomatous germ cell tumors may be pure (embryonal carcinoma, yolk sac tumor, teratoma, choriocarcinoma) or mixed. Mixtures of these types (including seminoma) should be noted, starting with the most prevalent component and ending with the least represented. Similarly, gonadal stromal. tumors should be classified according to the *World Health Organization Histological Classification of Tumours.*

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Raghavan D, Colls B, Levi J, et al: Surveillance for Stage I non-seminomatous germ cell tumours of the testis: the optimal protocol has not yet been defined. Br J Urol 61:522–526, 1988

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HISTOLOGIES—TESTIS

8590/1	Sex cord–gonadal stromal tumor, NOS
8592/1	Sex cord–gonadal stromal tumor, mixed forms
8620/1	Granulosa cell tumor, adult type
8640/3	Sertoli cell carcinoma
8650/1	Leydig cell tumor, NOS
9061/3	Seminoma, NOS
9063/3	Spermatocytic seminoma
9064/2	Intratubular malignant germ cells
9065/3	Germ cell tumor, non-seminomatous
9070/3	Embryonal carcinoma, NOS
9071/3	Yolk sac tumor
9081/3	Teratocarcinoma
9085/3	Mixed germ cell tumor
9100/3	Choriocarcinoma, NOS
9101/3	Choriocarcinoma combined with other germ cell elements

TESTIS

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____ Laterality: ☐ Bilateral ☐ Left ☐ Right

DEFINITIONS

Primary Tumor (T)[1]

Pathologic		
☐	pTX	Primary tumor cannot be assessed (if no radical orchiectomy has been performed, TX is used)
☐	pT0	No evidence of primary tumor (e.g., histologic scar in testis)
☐	pTis	Intratubular germ cell neoplasia (carcinoma *in situ*)
☐	PT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade into the tunica albuginea but not the tunica vaginalis
☐	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
☐	PT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion
☐	pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion

Notes

1. Except for pTis and pT4, extent of primary tumor is classified as radical orchiectomy. TX may be used for other categories in the absence of radical orchiectomy.

Primary Tumor (T)

Clinical	
☐	Tumor stage is generally determined after orchiectomy at which time a pathologic stage is assigned.

Regional Lymph Nodes (N)

Pathologic		
☐	pNX	Regional lymph nodes cannot be assessed
☐	pN0	No regional lymph node metastasis
☐	pNl	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
☐	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
☐	pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

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

Distant Metastasis (M)

Clinical	Pathologic		
☐	☐	MX	Distant metastasis cannot be assessed
☐	☐	M0	No distant metastasis
☐	☐	M1	Distant metastasis
☐	☐	Mla	Non-regional nodal or pulmonary metastasis
☐	☐	Mlb	Distant metastasis other than to non-regional lymph nodes and lungs

Biopsy of metastatic site performed..... ☐Y..... ☐N

Source of pathologic metastatic specimen _____

Serum Tumor Markers (S) *(N indicates the upper limit of normal for the LDH assay)*

☐	☐	SX	Marker studies not available or not performed
☐	☐	S0	Marker study levels within normal limits
☐	☐	Sl	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

(continued on reverse side)

Clinical	Pathologic	Stage Grouping				
☐	☐	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

Notes

Additional Descriptors

Lymphatic Vessel Invasion (L)

LX Lymphatic vessel invasion cannot be assessed
L0 No lymphatic vessel invasion
L1 Lymphatic vessel invasion

Venous Invasion (V)

VX Venous invasion cannot be assessed
V0 No venous invasion
V1 Microscopic venous invasion
V2 Macroscopic venous invasion

Residual Tumor (R)

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

Additional Descriptors

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.

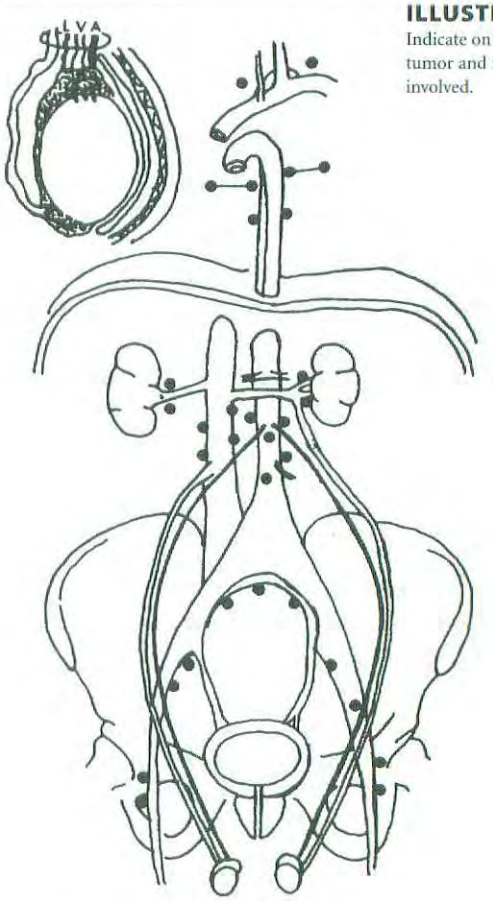
☐ **r prefix** indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

☐ **a prefix** designates the stage determined at autopsy: aTNM.

Prognostic Indicators (if applicable)

ILLUSTRATION

Indicate on diagram primary tumor and regional nodes involved.



Physician's Signature _____ Date _____

36

Kidney

(Sarcomas and adenomas are not included.)

C64.9 Kidney, NOS

SUMMARY OF CHANGES

- T1 lesions have been divided into T1a and T1b.
- T1a is defined as tumors 4 cm or less in greatest dimension, limited to the kidney.
- T1b is defined as tumors greater than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney.

INTRODUCTION

Cancers of the kidney are relatively rare, accounting for less than 3% of all malignancies. Nearly all malignant tumors are carcinomas arising from the renal tubular epithelium or, less frequently, from the renal pelvis (see Chapter 37). These tumors are more common in males. Pain and hematuria are usually the presenting features, but a majority of kidney tumors are now being detected incidentally in asymptomatic individuals. These carcinomas have a tendency to extend into the renal vein and even into the vena cava. Staging depends on the size of the primary tumor, invasion of the adjacent structures, and vascular extension.

Since publication of the Fifth Edition of the *AJCC Cancer Staging Manual*, the evidence has become compelling that the T1 category should be subdivided into stages T1a and T1b, the former being tumors of 4 cm or less and the latter being tumors of 4–7 cm. The rationale is twofold: (1) the recurrence and survival difference between the two and (2) the current practice of applying partial nephrectomy for solitary tumors 4 cm or less in diameter. In the case of partial nephrectomy for tumors < 4 cm in diameter, evidence suggests that survival outcomes are equivalent to outcomes with radical nephrectomy (Lee CT et al. 2000). In a group of 485 patients undergoing nephron-sparing surgery for renal cell carcinoma and with a mean post-operative follow-up of 47 months, the authors segregated patients into four groups based on tumor size: 1—less than 2.5 cm; 2—2.5 to 4.0 cm; 3—4 to 7 cm; 4—more than 7 cm (Hafez KS et al. 1999). The authors found no difference in survival between groups 1 and 2, but survival was significantly greater in groups 1 and 2 than in both groups 3 and 4. Similar findings were reported in a second series of 394 patients (Lerner SE et al. 1996).

ANATOMY

Primary Site. Encased by a fibrous capsule and surrounded by perirenal fat, the kidney consists of the cortex (glomeruli, convoluted tubules) and the medulla (Henle's loops, pyramids of converging tubules). Each papilla opens into the minor calices; these in turn unite in the major calices and drain into the renal pelvis. At the hilus are the pelvis, ureter, and renal artery and vein. Gerota's fascia overlies the psoas and quadratus lumborum.

Regional Lymph Nodes. The regional lymph nodes are:

Renal hilar
Paracaval
Aortic (para-aortic, periaortic, lateral aortic)
Retroperitoneal, NOS

Metastatic Sites. Common metastatic sites include bone, liver, lung, brain, and distant lymph nodes.

RULES FOR CLASSIFICATION

The classification applies only to the renal cell carcinomas. Adenoma is excluded. There should be histologic confirmation of the disease. Refer to the list of histopathologic types below.

Clinical Staging. Clinical examination, abdominal computed tomography scanning, and appropriate imaging techniques are required for assessment of the primary tumor and its extensions, both local and distant. Evaluation for distant metastases should be done by laboratory biochemical studies, chest X-rays, and, if clinically indicated, isotopic studies.

Pathologic Staging. Histologic examination and confirmation of extent are recommended. Resection of the primary tumor, kidney, Gerota's fascia, perinephric fat, renal vein, and appropriate lymph nodes is recommended. Partial nephrectomy seems to be an acceptable treatment for T1a tumors with outcomes comparable to those with radical nephrectomy for this tumor stage. Laterality does not affect the N classification.

Specimen Handling. It is recommended that the pathologic specimen be processed in such a fashion as to allow full pathologic assessment. Perinephric fat should be left intact and sectioned in such a manner so as to evaluate invasion of this structure. For specimens from partial nephrectomy, margins must be evaluated from at least two sections and should include the renal sinus for central tumors. For patients in whom an assessment of multiple tumors is required, thin sections will be needed (0.5–1.0 cm).

Figures 36.1 and 36.2 illustrate the definition of T1 and T2.

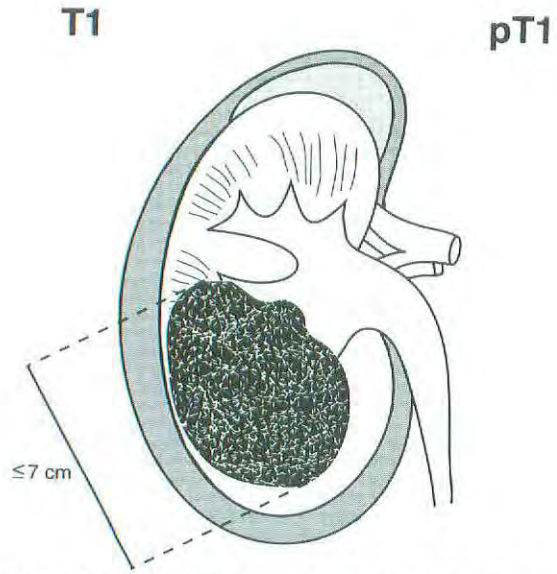


FIG. 36.1. T1 is defined as a tumor 7 cm or less in greatest dimension and limited to the kidney.

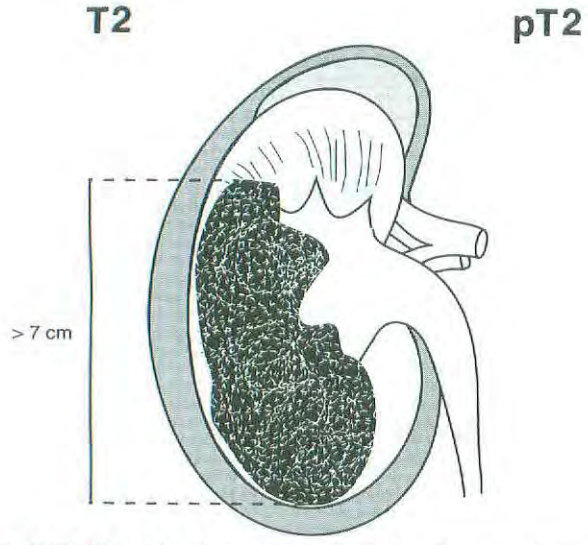


FIG. 36.2. T2 is defined as a tumor more than 7 cm in greatest dimension and limited to the kidney.

DEFINITION OF TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 7 cm or less in greatest dimension, limited to the kidney
T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney
T1b	Tumor more than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney
T2	Tumor more than 7 cm in greatest dimension, limited to the kidney
T3	Tumor extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
T3a	Tumor directly invades adrenal gland or perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or vena cava below the diaphragm
T3c	Tumor grossly extends into vena cava above diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia

*Regional Lymph Nodes (N)**

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in a single regional lymph node
N2	Metastasis in more than one regional lymph node

*Laterality does not affect the N classification.

Note: If a lymph node dissection is performed, then pathologic evaluation would ordinarily include at least eight nodes.

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

STAGE GROUPING

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N0	M0
	T3	N1	M0
	T3a	N0	M0
	T3a	N1	M0
	T3b	N0	M0
	T3b	N1	M0
	T3c	N0	M0
	T3c	N1	M0
Stage IV	T4	N0	M0
	T4	N1	M0
	Any T	N2	M0
	Any T	Any N	M1

HISTOPATHOLOGIC TYPE

The predominant cancer is adenocarcinoma; subtypes are clear cell and granular cell carcinoma. The use of the following grading system is recommended when feasible. Sarcomas and adenomas are not included. The histopathologic types are

Conventional (clear cell) renal carcinoma
Papillary renal cell carcinoma
Chromophobe renal carcinoma
Collecting duct carcinoma

HISTOLOGIC GRADE (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3–4	Poorly differentiated or undifferentiated

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HISTOLOGIES—KIDNEY

8032/3	Spindle cell carcinoma, NOS
8041/3	Small cell carcinoma, NOS
8140/3	Adenocarcinoma, NOS
8240/3	Carcinoid tumor, NOS
8260/3	Papillary adenocarcinoma, NOS
8290/3	Oxyphilic adenoma
8290/3	Oxyphilic adenocarcinoma
8310/3	Clear cell adenocarcinoma, NOS
8312/3	Renal cell carcinoma, NOS
8317/3	Renal cell carcinoma, chromophobe type
8318/3	Renal cell carcinoma, sarcomatoid
8319/3	Collecting duct carcinoma
8320/3	Granular cell carcinoma
8960/3	Nephroblastoma, NOS
8963/3	Malignant rhabdoid tumor
8966/2	Renomedullary interstitial cell tumor

KIDNEY

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____ Laterality: ☐ Bilateral ☐ Left ☐ Right

DEFINITIONS

Clinical	Pathologic		
		Primary Tumor (T)	
☐	☐	TX	Primary tumor cannot be assessed
☐	☐	T0	No evidence of primary tumor
☐	☐	T1	Tumor 7 cm or less in greatest dimension, limited to the kidney
☐	☐	T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney
☐	☐	T1b	Tumor more than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney
☐	☐	T2	Tumor more than 7 cm in greatest dimension, limited to the kidney
☐	☐	T3	Tumor extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
☐	☐	T3a	Tumor directly invades adrenal gland or perirenal and/or renal sinus fat but not beyond Gerota's fascia
☐	☐	T3b	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or vena cava below the diaphragm
☐	☐	T3c	Tumor grossly extends into vena cava above diaphragm or invades the wall of the vena cava
☐	☐	T4	Tumor invades beyond Gerota's fascia
		Regional Lymph Nodes (N)	
☐	☐	NX	Regional lymph nodes cannot be assessed
☐	☐	N0	No regional lymph node metastases
☐	☐	N1	Metastases in a single regional lymph node
☐	☐	N2	Metastasis in more than one regional lymph node
		Distant Metastasis (M)	
☐	☐	MX	Distant metastasis cannot be assessed
☐	☐	M0	No distant metastasis
☐	☐	M1	Distant metastasis

Biopsy of metastatic site performed ..... ☐Y ..... ☐N

Source of pathologic metastatic specimen _____

Stage Grouping

☐	☐	I	T1	N0	M0
☐	☐	II	T2	N0	M0
☐	☐	III	T1	N1	M0
			T2	N1	M0
			T3	N0	M0
			T3	N1	M0
			T3a	N0	M0
			T3a	N1	M0
			T3b	N0	M0
			T3b	N1	M0
			T3c	N0	M0
			T3c	N1	M0
☐	☐	IV	T4	N0	M0
			T4	N1	M0
			Any T	N2	M0
			Any T	Any N	M1

(continued on reverse side)

Histologic Grade (G)

- ☐ GX Grade cannot be assessed
- ☐ G1 Well differentiated
- ☐ G2 Moderately differentiated
- ☐ G3–4 Poorly differentiated or undifferentiated

Residual Tumor (R)

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

Additional Descriptors

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.

Prognostic Indicators (if applicable)

Notes

Additional Descriptors

Lymphatic Vessel Invasion (L)

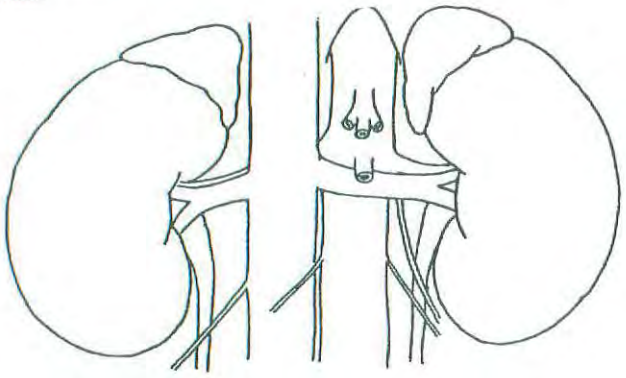
- LX Lymphatic vessel invasion cannot be assessed
- L0 No lymphatic vessel invasion
- L1 Lymphatic vessel invasion

Venous Invasion (V)

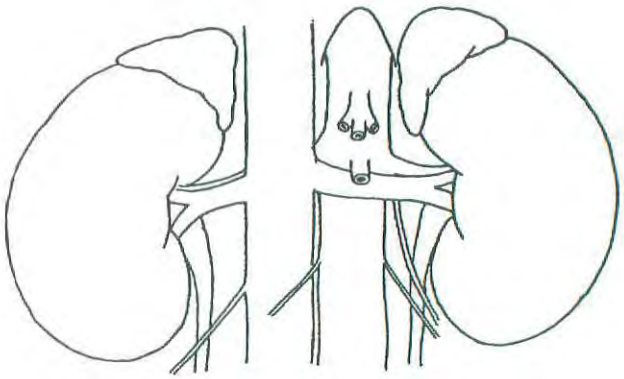
- VX Venous invasion cannot be assessed
- V0 No venous invasion
- V1 Microscopic venous invasion
- V2 Macroscopic venous invasion

ILLUSTRATION

This drawing is to be used with the checklist. Sketch in the urographic, angiographic, ultrasound, or CT extentof the tumor.



This drawing is to be used with the checklist. Sketch in the pathologic extent of tumor.



Physician's Signature _____ Date _____

37

Renal Pelvis and Ureter

C65.9 Renal pelvis C66.9 Ureter

SUMMARY OF CHANGES

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

INTRODUCTION

Urothelial (transitional cell) carcinoma may occur at any site within the upper urinary collecting system from the renal calyx to the ureterovesical junction. The tumors occur most commonly in adults and are rare before 40 years of age. There is a two- to threefold increase in incidence in men compared with women. The lesions are often multiple and are more common in patients with a history of urothelial carcinoma of the bladder. A number of analgesics (such as phenacetin) have also been associated with this disease. Local staging depends on the depth of invasion. A common staging system is used regardless of tumor location within the upper urinary collecting system, except for category T3, which differs between the pelvis or calyceal system and the ureter.

ANATOMY

Primary Site. The renal pelvis and ureter form a single unit that is continuous with the collecting ducts of the renal pyramids and comprises the minor and major calyces, which are continuous with the renal pelvis. The ureteropelvic junction is variable in position and location but serves as a "landmark" that separates the renal pelvis and the ureter, which continues caudad and traverses the wall of the urinary bladder as the intramural ureter opening in the trigone of the bladder at the ureteral orifice. The renal pelvis and ureter are composed of the following layers: epithelium, subepithelial connective tissue, and muscularis, which is continuous with a connective tissue adventitial layer. It is in this outer layer that the major blood supply and lymphatics are found.

The intrarenal portion of the renal pelvis is surrounded by renal parenchyma; the extrarenal pelvis, by perihilar fat. The ureter courses through the retroperitoneum adjacent to the parietal peritoneum and rests on the retroperitoneal musculature above the pelvic vessels. As it crosses the vessels and enters the deep pelvis, the ureter is surrounded by pelvic fat until it traverses the bladder wall.

Regional Lymph Nodes. The regional lymph nodes for the renal pelvis are:

Renal hilar
Paracaval
Aortic
Retroperitoneal, NOS

The regional lymph nodes for the ureter are:

Renal hilar
Iliac (common, internal [hypogastric], external)
Paracaval
Periureteral
Pelvic, NOS

Any amount of regional lymph node metastasis is a poor prognostic finding, and outcome is minimally influenced by the number, size, or location of the regional nodes that are involved.

Metastatic Sites. Distant spread is most commonly to lung, bone, or liver.

RULES FOR CLASSIFICATION

Clinical Staging. Primary tumor assessment includes radiographic imaging, usually by intravenous and/or retrograde pyelography. Computerized tomography scanning can be used to assess regional nodes. Ureteroscopic visualization of the tumor is desirable, and tissue biopsy through the ureteroscope may be performed if feasible. Urine cytology may help determine tumor grade if tissue is not available. Staging of tumors of the renal pelvis and ureter is not influenced by the presence of any concomitant bladder tumors that may

be identified, although it may not be possible to identify the true source of the primary tumor in the presence of metastases if both upper- and lower-tract tumors are present. In that situation, the tumor of highest grade and/or stage is most likely to have contributed to the nodal or metastatic spread.

Pathologic Staging. Pathologic staging depends on histologic determination of the extent of invasion by the primary tumor. Treatment frequently requires resection of the entire kidney, ureter, and a cuff of bladder surrounding the ureteral orifice. Appropriate regional nodes may be sampled. A more conservative surgical resection may be performed, especially with distal ureteral tumors or in the presence of compromised renal function.

Endoscopic resection through a ureteroscope or a percutaneous approach may be used in some circumstances. Submitted tissue may be insufficient for accurate histologic examination and pathologic staging. Laser or electrocautery coagulation or vaporization of the tumor may be performed, especially if the visible appearance is consistent with a low-grade and low-stage tumor. Under these circumstances, there may be no material available for histologic review.

Figures 37.1 and 37.2 illustrate the Primary Tumor (T) definition for Ta, T1, T2, and T3.

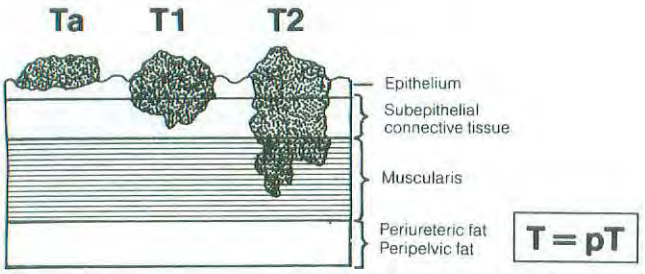


FIG. 37.1. Depth of invasion of Ta–T2 tumors.

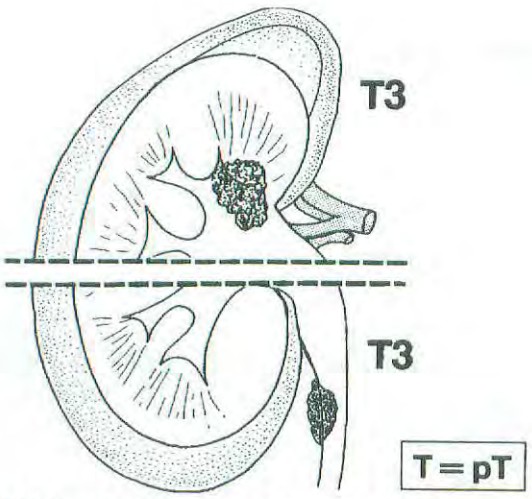


FIG. 37.2. Extent of T3 Tumor in renal pelvis and ureter.

DEFINITION OF TNM

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Ta Papillary non-invasive carcinoma
Tis Carcinoma *in situ*
T1 Tumor invades subepithelial connective tissue
T2 Tumor invades the muscularis
T3 (For renal pelvis only) Tumor invades beyond muscularis into peripelvic fat or the renal parenchyma
T3 (For ureter only) Tumor invades beyond muscularis into periureteric fat
T4 Tumor invades adjacent organs, or through the kidney into the perinephric fat.

*Regional Lymph Nodes (N)**

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

**Note:* Laterality does not affect the N classification

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

STAGE GROUPING

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IV	T4	N0	M0
	Any T	N1	M0
	Any T	N2	M0
	Any T	N3	M0
	Any T	Any N	M1

HISTOPATHOLOGIC TYPE

The histologic types are

Urothelial (transitional cell) carcinoma
Squamous cell carcinoma
Epidermoid carcinoma
Adenocarcinoma

HISTOLOGIC GRADE

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3–4	Poorly differentiated or undifferentiated

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HISTOLOGIES—RENAL PELVIS AND URETER

8010/2	Carcinoma *in situ*, NOS
8010/3	Carcinoma, NOS
8070/2	Squamous cell carcinoma *in situ*
8070/3	Squamous cell carcinoma, NOS
8120/2	Transitional cell carcinoma *in situ*
8120/3	Transitional cell carcinoma, NOS
8130/2	Papillary transitional cell carcinoma, non-invasive
8130/3	Papillary transitional cell carcinoma
8140/3	Adenocarcinoma, NOS

RENAL PELVIS AND URETER

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____ Laterality: ☐ Bilateral ☐ Left ☐ Right

DEFINITIONS

Clinical	*Pathologic*		
		Primary Tumor (T)	
☐	☐	TX	Primary tumor cannot be assessed
☐	☐	T0	No evidence of primary tumor
☐	☐	Ta	Papillary non-invasive carcinoma
☐	☐	Tis	Carcinoma *in situ*
☐	☐	T1	Tumor invades subepithelial connective tissue
☐	☐	T2	Tumor invades the muscularis
☐	☐	T3	(For renal pelvis only) Tumor invades beyond muscularis into peripelvic fat or the renal parenchyma
☐	☐	T3	(For ureter only) Tumor invades beyond muscularis into periureteric fat
☐	☐	T4	Tumor invades adjacent organs, or through the kidney into the perinephric fat
		Regional Lymph Nodes (N)	
☐	☐	NX	Regional lymph nodes cannot be assessed
☐	☐	N0	No regional lymph node metastasis
☐	☐	N1	Metastasis in a single lymph node, 2 cm or less in greatest dimension
☐	☐	N2	Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
☐	☐	N3	Metastasis in a lymph node, more than 5 cm in greatest dimension
		Distant Metastasis (M)	
☐	☐	MX	Distant metastasis cannot be assessed
☐	☐	M0	No distant metastasis
☐	☐	M1	Distant metastasis
			Biopsy of metastatic site performed ..... ☐Y ..... ☐N
			Source of pathologic metastatic specimen _____

		Stage Grouping		
☐	☐	0a	Ta	N0	M0
☐	☐	0is	Tis	N0	M0
☐	☐	I	T1	N0	M0
☐	☐	II	T2	N0	M0
☐	☐	III	T3	N0	M0
☐	☐	IV	T4	N0	M0
			Any T	N1	M0
			Any T	N2	M0
			Any T	N3	M0
			Any T	Any N	M1

(continued on reverse side)

Histologic Grade (G)

- ☐ GX Grade cannot be assessed
- ☐ G1 Well differentiated
- ☐ G2 Moderately differentiated
- ☐ G3–4 Poorly differentiated or undifferentiated

Residual Tumor (R)

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

Additional Descriptors

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.

Prognostic Indicators (if applicable)

Notes

Additional Descriptors

Lymphatic Vessel Invasion (L)

LX Lymphatic vessel invasion cannot be assessed
L0 No lymphatic vessel invasion
L1 Lymphatic vessel invasion

Venous Invasion (V)

VX Venous invasion cannot be assessed
V0 No venous invasion
V1 Microscopic venous invasion
V2 Macroscopic venous invasion

Physician's Signature _____ Date_____

38

Urinary Bladder

C67.0 Trigone of bladder
C67.1 Dome of bladder
C67.2 Lateral wall of bladder
C67.3 Anterior wall of bladder
C67.4 Posterior wall of bladder
C67.5 Bladder neck
C67.6 Ureteric orifice
C67.7 Urachus
C67.8 Overlapping lesion of bladder
C67.9 Bladder, NOS

SUMMARY OF CHANGES

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

INTRODUCTION

Bladder cancer is one of the most common malignancies in Western society, and it occurs more commonly in males. Predisposing factors include smoking, exposure to chemicals such as phenacetin and dyes, and schistosomiasis. It has also been suggested that the incidence of this disease correlates inversely with fluid intake. Hematuria is the most common presenting feature. Bladder cancer can present as a low-grade papillary lesion, as an *in situ* lesion that can occupy large areas of the mucosal surface, or as an infiltrative cancer that rapidly extends through the bladder wall and can thereafter metastasize. The papillary and *in situ* lesions may be associated with a malignant course, with sudden invasion of the bladder wall. The most common histologic variant is urothelial (transitional cell) carcinoma, although this may exhibit features of glandular or squamous differentiation. In less than 10% of cases, pure adenocarcinoma or squamous carcinoma of the bladder may occur, and less frequently, sarcoma, lymphoma, small cell anaplastic carcinoma, pheochromocytoma, or choriocarcinoma. Squamous carcinoma is associated with schistosomiasis and smoking.

ANATOMY

Primary Site. The urinary bladder consists of three layers: the epithelium and the subepithelial connective tissue, the muscularis, and the perivesical fat (peritoneum covering the superior surface and upper part). In the male, the bladder adjoins the rectum and seminal vesicle posteriorly, the prostate inferiorly, and the pubis and peritoneum anteriorly. In the female, the vagina is located posteriorly and the uterus superiorly. The bladder is located extraperitoneally.

Regional Lymph Nodes. The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries. The significance of regional lymph node metastasis in staging bladder cancer lies in the number and size, not in whether metastasis is unilateral or contralateral. One of the major prognostic determinants of ultimate cure is whether the tumor is confined to the bladder, and a major adverse prognostic feature is the presence of *any* lymph nodal metastases.

Regional nodes include:

Hypogastric
Obturator
Iliac (internal, external, NOS)
Perivesical
Pelvic, NOS
Sacral (lateral, sacral promontory [Gerota's])
Presacral

The common iliac nodes are considered sites of distant metastasis and should be coded as M1.

Metastatic Sites. Distant spread is most commonly to lymph nodes, lung, bone, and liver.

RULES FOR CLASSIFICATION

Clinical Staging. Primary tumor assessment includes bimanual examination under anesthesia before and after endoscopic surgery (biopsy or transurethral resection) and histologic verification of the presence or absence of tumor when indicated. Bimanual examination following endoscopic surgery is an indicator of clinical stage. The finding of bladder

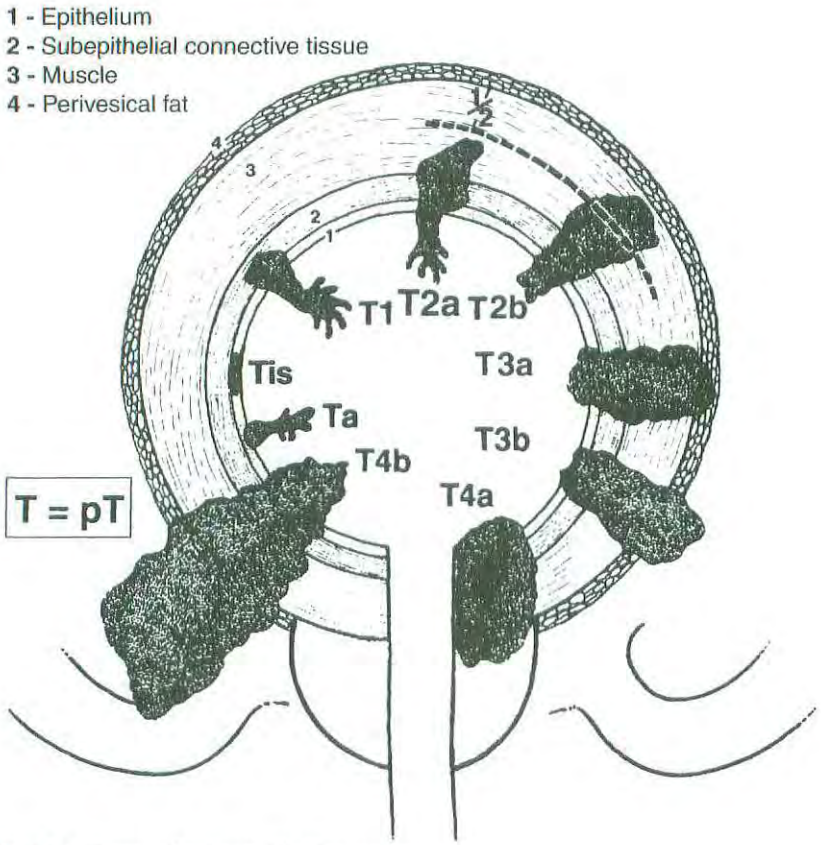

FIG. 38.1. Extent of primary bladder cancer.

wall thickening, a mobile mass, or a fixed mass suggests the presence of T3a, T3b, and T4b disease, respectively. The suffix "m" is added to denote multiple tumors. The suffix "is" is added to any T to indicate associated carcinoma *in situ.* Appropriate imaging techniques for lymph node evaluation should be used. When indicated, evaluation for distant metastases includes imaging of the chest, biochemical studies, and isotopic studies to detect common metastatic sites. Computed tomography or other modalities may subsequently be used to supply information concerning minimal requirements for staging. Evidence suggests that MRI may be another useful modality for staging locally advanced bladder cancer. As yet, the role of positron emission tomography (PET) scanning in the staging and management of bladder cancer has not been defined. The primary tumor may be superficial or invasive and can be partially or totally resected with sufficient tissue from the tumor base for evaluation of full depth of tumor invasion. Visually adjacent cystoscopically normal mucosa should be considered for biopsy, and in most cases, multiple biopsies should be taken from other sites to rule out a field effect; urinary cytology and pyelography are important. It should be recalled that bladder cancer may occur in association with malignancies of the ureters, renal pelvis, or urethra. The definitions for Primary Tumor (T) are illustrated in Figure 38.1.

Pathologic Staging. Microscopic examination and confirmation of extent are required. Total cystectomy and lymph node dissection generally are required for this staging. Laterality does not affect the N classification.

DEFINITION OF TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ:* "flat tumor"
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscle
pT2a	Tumor invades superficial muscle (inner half)
pT2b	Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue
pT3a	microscopically
pT3b	macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostate, uterus, vagina
T4b	Tumor invades pelvic wall, abdominal wall

Regional Lymph Nodes (N)

Regional lymph nodes are those within the true pelvis; all others are distant lymph nodes.

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

N1 Metastasis in a single lymph node, 2 cm or less in greatest dimension
N2 Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
N3 Metastasis in a lymph node, more than 5 cm in greatest dimension

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

STAGE GROUPING

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1	M0
	Any T	N2	M0
	Any T	N3	M0
	Any T	Any N	M1

HISTOPATHOLOGIC TYPE

The histologic types are:

Urothelial (transitional cell) carcinoma
In situ
Papillary
Flat
With squamous metaplasia
With glandular metaplasia
With squamous and glandular metaplasia
Squamous cell carcinoma
Adenocarcinoma
Undifferentiated carcinoma

The predominant cancer is urothelial (transitional cell) carcinoma.

HISTOLOGIC GRADE (G)

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3–4 Poorly differentiated or undifferentiated

PROGNOSTIC FACTORS

For primary tumors, the major established prognostic factors are grade and stage, although other factors identified in some series include hydronephrosis, anemia, size, expression of blood group substances, expression of epidermal growth factor receptor, and mutation of P53 and up-regulation of Rb and other oncogene expression. For metastatic disease, adverse prognostic factors include poor performance status, visceral metastases, and abnormal liver function tests. The expression, up-regulation, or mutation of known oncogenes, such as P53, Rb, P21, and others, are under intense investigation in order to define which are the most important prognostic indices. To date, no consensus has been achieved, and conflicting data regarding the prognostic significance of P53 have been published. However, it does seem clear that two distinct molecular events are associated with the genesis of bladder cancer. Loss of heterozygosity of chromosome 9 is associated with the genesis of superficial bladder cancer, whereas loss of heterozygosity of chromosome 17, with mutation of the P53 suppressor gene, appears to be associated with the evolution of invasive disease and/or metastatic disease. Ploidy has been investigated as a prognostic factor. In superficial disease, an aneuploid DNA content is associated with shorter disease-free survival and with an increased chance of progression to a higher stage; however, in invasive and metastatic disease, the majority of cases are aneuploid, thus reducing the role of aneuploid DNA content as a discriminant of outcome.

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HISTOLOGIES—BLADDER

8010/2	Carcinoma *in situ*, NOS
8010/3	Carcinoma, NOS
8020/3	Undifferentiated carcinoma, NOS
8051/3	Verrucous carcinoma, NOS
8070/2	Squamous cell carcinoma *in situ*, NOS
8070/3	Squamous cell carcinoma
8120/2	Transitional cell carcinoma *in situ*
8120/3	Transitional cell carcinoma, NOS
8130/2	Papillary transitional cell carcinoma, non-invasive
8130/3	Papillary transitional cell carcinoma
8131/3	Transitional cell carcinoma, micropapillary
8140/2	Adenocarcinoma *in situ*, NOS
8140/3	Adenocarcinoma, NOS
8255/3	Adenocarcinoma with mixed subtypes

URINARY BLADDER

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____

DEFINITIONS

Clinical	*Pathologic*		
		Primary Tumor (T)	
☐	☐	TX	Primary tumor cannot be assessed
☐	☐	T0	No evidence of primary tumor
☐	☐	Ta	Non-invasive papillary carcinoma
☐	☐	Tis	Carcinoma *in situ*: "flat tumor"
☐	☐	T1	Tumor invades subepithelial connective tissue
☐	☐	T2	Tumor invades muscle
☐	☐	pT2a	Tumor invades superficial muscle (inner half)
☐	☐	pT2b	Tumor invades deep muscle (outer half)
☐	☐	T3	Tumor invades perivesical tissue
☐	☐	pT3a	microscopically
☐	☐	pT3b	macroscopically (extravesical mass)
☐	☐	T4	Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
☐	☐	T4a	Tumor invades prostate, uterus, vagina
☐	☐	T4b	Tumor invades pelvic wall, abdominal wall
		Regional Lymph Nodes (N)	
☐	☐	NX	Regional lymph nodes cannot be assessed
☐	☐	N0	No regional lymph node metastasis
☐	☐	N1	Metastasis in a single lymph node, 2 cm or less in greatest dimension
☐	☐	N2	Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
☐	☐	N3	Metastasis in a lymph node, more than 5 cm in greatest dimension
		Distant Metastasis (M)	
☐	☐	MX	Distant metastasis cannot be assessed
☐	☐	M0	No distant metastasis
☐	☐	M1	Distant metastasis
			Biopsy of metastatic site performed ..... ☐Y ..... ☐N
			Source of pathologic metastatic specimen _____

Stage Grouping

☐	☐	0a	Ta	N0 M0
☐	☐	0is	Tis	N0 M0
☐	☐	I	T1	N0 M0
☐	☐	II	T2a	N0 M0
			T2b	N0 M0
☐	☐	III	T3a	N0 M0
			T3b	N0 M0
			T4a	N0 M0
☐	☐	IV	T4b	N0 M0
			Any T	N1 M0
			Any T	N2 M0
			Any T	N3 M0
			Any T	Any N M1

(continued on reverse side)

Histologic Grade (G)

- ☐ GX Grade cannot be assessed
- ☐ G1 Well differentiated
- ☐ G2 Moderately differentiated
- ☐ G3–4 Poorly differentiated or undifferentiated

Residual Tumor (R)

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

Additional Descriptors

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.

Prognostic Indicators (if applicable)

Notes

Additional Descriptors

Lymphatic Vessel Invasion (L)

- LX Lymphatic vessel invasion cannot be assessed
- L0 No lymphatic vessel invasion
- L1 Lymphatic vessel invasion

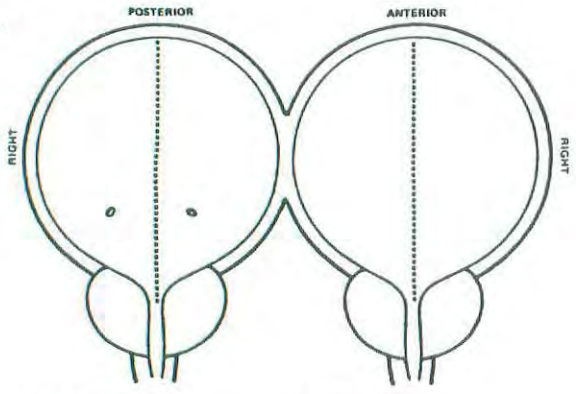
Venous Invasion (V)

- VX Venous invasion cannot be assessed
- V0 No venous invasion
- V1 Microscopic venous invasion
- V2 Macroscopic venous invasion

ILLUSTRATION

Indicate on diagram primary tumor and regional nodes involved.

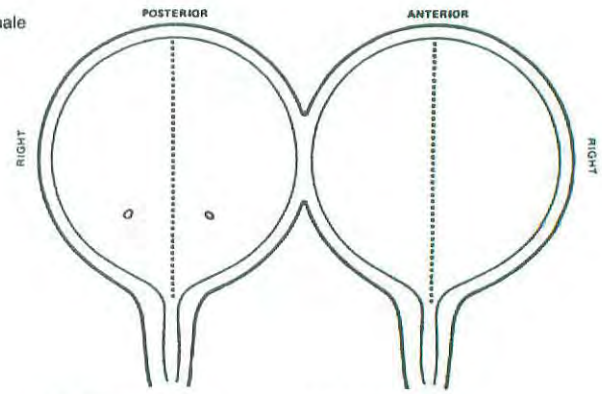
Male



PW Posterior wall
RW Right wall
LW Left wall
RU Right ureteral orifice
LU Left ureteral orifice

AW Anterior wall
TR Trigone
D Dome
N Neck
PU Prostatic urethra
PS Prostatic substance

Female



PW Posterior wall
RW Right wall
LW Left wall
RU Right ureteral orifice
LU Left ureteral orifice

AW Anterior wall
TR Trigone
D Dome
N Neck
U Urethra

Physician's Signature _____ Date _____

39

Urethra

C68.0 Urethra

SUMMARY OF CHANGES

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

INTRODUCTION

Cancer of the urethra is a rare neoplasia that is found in both sexes but more common in females. The cancer may be associated in males with chronic stricture disease and in females with urethral diverticula. Tumors of the urethra may be of primary origin from the urethral epithelium or ducts, or they may be associated with multifocal urothelial neoplasia. Histologically, these tumors may represent the spectrum of epithelial neoplasms, including squamous, adenothelial, or urothelial (transitional cell) carcinoma. Prostatic urethral neoplasms arising from the prostatic urethral epithelium or from the periurethral portion of the prostatic ducts are considered urethral neoplasms as distinct from those arising elsewhere in the prostate (see Chapter 34).

ANATOMY

Primary Site. The male urethra consists of mucosa, submucosal stroma, and the surrounding corpus spongiosum. Histologically, the meatal and parameatal urethra are lined with squamous epithelium; the penile and bulbomembranous urethra with pseudostratified or stratified columnar epithelium, and the prostatic urethra with transitional epithelium. There are scattered islands of stratified squamous epithelium and glands of Littré liberally situated throughout the entire urethra distal to the prostate portion.

The epithelium of the female urethra is supported on subepithelial connective tissue. The periurethral glands of Skene are concentrated near the meatus but extend along the entire urethra. The urethra is surrounded by a longitudinal layer of smooth muscle continuous with the bladder. The urethra is contiguous to the vaginal wall. The distal two-thirds of the urethra is lined with squamous epithelium, the proximal one-third with transitional epithelium. The periurethral glands are lined with pseudostratified and stratified columnar epithelium.

Regional Lymph Nodes. The regional lymph nodes are:

Inguinal (superficial or deep)
Iliac (common, internal [hypogastric], obturator, external)
Presacral
Sacral, NOS
Pelvic, NOS

The significance of regional lymph node metastasis in staging urethral cancer lies in the number and size, not in whether unilateral or bilateral.

Metastatic Sites. Distant spread is most commonly to lung, liver, or bone.

RULES FOR CLASSIFICATION

Clinical Staging. Radiographic imaging, cystourethroscopy, palpation, and biopsy or cytology of the tumor prior to definitive treatment are desirable. The site of origin should be confirmed to exclude metastatic disease.

Pathologic Staging. The assignment of stage for nonprostatic urethral tumors is based on depth of invasion. Prostatic urethral tumor may arise from the prostatic epithelium or from the distal portions of the prostatic ducts and will be classified as prostatic urethral neoplasms. Other prostatic malignancies will be classified under prostate.

Figures 39.1 and 39.2 illustrate Primary Tumor (T) definitions for urethral malignancies and urothelial (transitional cell) carcinoma of the prostate.

DEFINITION OF TNM

Primary Tumor (T) (male and female)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Ta Non-invasive papillary, polypoid, or verrucous carcinoma
Tis Carcinoma *in situ*
T1 Tumor invades subepithelial connective tissue
T2 Tumor invades any of the following: corpus spongiosum, prostate, periurethral muscle
T3 Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck
T4 Tumor invades other adjacent organs

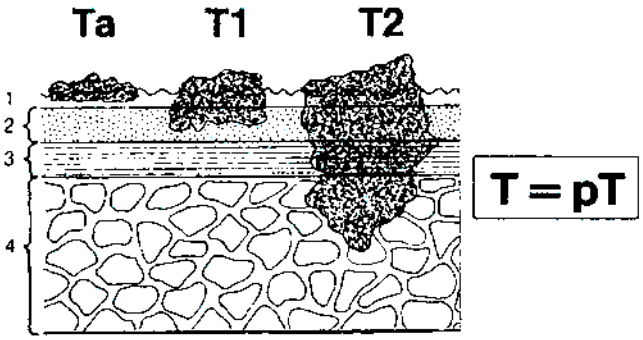


FIG. 39.1. Definition of Primary Tumor (T). 1–epithelium, 2–subepithelial connective tissue, 3–urethral muscle, 4–urogenital diaphragm.

Urothelial (Transitional Cell) Carcinoma of the Prostate

Tis pu Carcinoma *in situ*, involvement of the prostatic urethra
Tis pd Carcinoma *in situ*, involvement of the prostatic ducts
T1 Tumor invades subepithelial connective tissue
T2 Tumor invades any of the following: prostatic stroma, corpus spongiosum, periurethral muscle
T3 Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
T4 Tumor invades other adjacent organs (invasion of the bladder)

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single lymph node 2 cm or less in greatest dimension
N2 Metastasis in a single node more than 2 cm in greatest dimension, or in multiple nodes

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

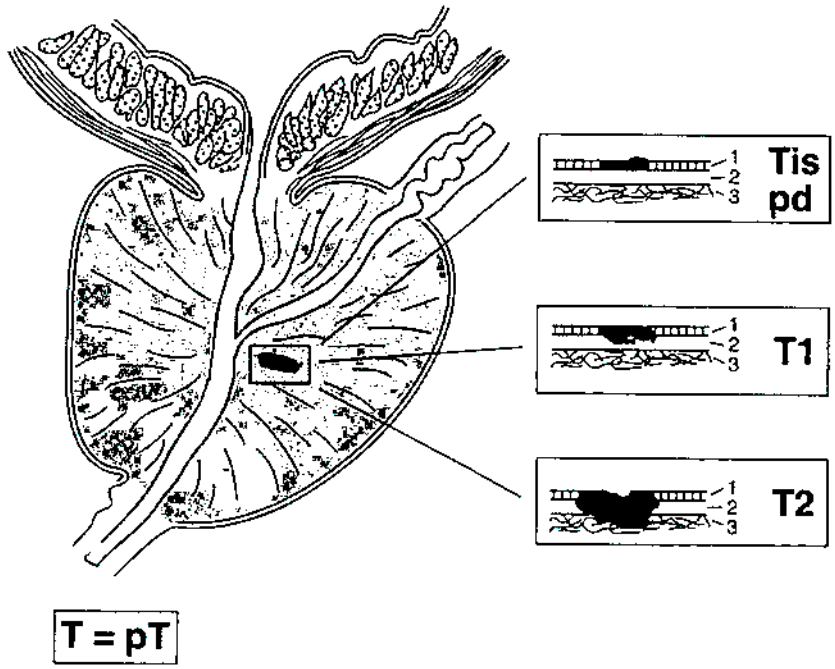


FIG. 39.2. Definition of Primary Tumor (T) for urothelial (transitional cell) carcinoma of the prostate. 1–Epithelium, 2–subepithelial connective tissue, 3–prostatic stroma.

STAGE GROUPING

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
	Tis pu	N0	M0
	Tis pd	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N0	M0
	T3	N1	M0
Stage IV	T4	N0	M0
	T4	N1	M0
	Any T	N2	M0
	Any T	Any N	M1

HISTOPATHOLOGIC TYPE

The classification applies to urothelial (transitional cell), squamous, and glandular carcinomas of the urethra and to urothelial (transitional cell) carcinomas of the prostate and prostatic urethra. There should be histologic or cytologic confirmation of the disease.

HISTOLOGIC GRADE (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3–4	Poorly differentiated or undifferentiated

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HISTOLOGIES—URETHRA

8010/2	Carcinoma *in situ*, NOS
8010/3	Carcinoma, NOS
8070/2	Squamous cell carcinoma, *in situ*
8070/3	Squamous cell carcinoma, NOS
8120/2	Transitional cell carcinoma *in situ*
8120/3	Transitional cell carcinoma, NOS
8130/2	Papillary transitional cell carcinoma, non-invasive
8130/3	Papillary transitional cell carcinoma
8140/3	Adenocarcinoma, NOS

URETHRA

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____

DEFINITIONS

Clinical	Pathologic		
		Primary Tumor (T) *(male and female)*	
☐	☐	TX	Primary tumor cannot be assessed
☐	☐	T0	No evidence of primary tumor
☐	☐	Ta	Non-invasive papillary, polypoid, or verrucous carcinoma
☐	☐	Tis	Carcinoma *in situ*
☐	☐	T1	Tumor invades subepithelial connective tissue
☐	☐	T2	Tumor invades any of the following: corpus spongiosum, prostate, periurethral muscle
☐	☐	T3	Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck
☐	☐	T4	Tumor invades other adjacent organs
		Urothelial (Transitional Cell) Carcinoma of the Prostate	
☐	☐	Tis pu	Carcinoma *in situ*, involvement of the prostatic urethra
☐	☐	Tis pd	Carcinoma *in situ*, involvement of the prostatic ducts
☐	☐	T1	Tumor invades subepithelial connective tissue
☐	☐	T2	Tumor invades any of the following: prostatic stroma, corpus spongiosum, periurethral muscle
☐	☐	T3	Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
☐	☐	T4	Tumor invades other adjacent organs (invasion of the bladder)
		Regional Lymph Nodes (N)	
☐	☐	NX	Regional lymph nodes cannot be assessed
☐	☐	N0	No regional lymph node metastasis
☐	☐	N1	Metastasis in a single lymph node 2 cm or less in greatest dimension
☐	☐	N2	Metastasis in a single node more than 2 cm in greatest dimension, or in multiple nodes
		Distant Metastasis (M)	
☐	☐	MX	Distant metastasis cannot be assessed
☐	☐	M0	No distant metastasis
☐	☐	M1	Distant metastasis
			Biopsy of metastatic site performed ☐Y ☐N
			Source of pathologic metastatic specimen _____

9

(continued on reverse side)

Stage Grouping

0a	Ta	N0	M0
0is	Tis	N0	M0
	Tis pu	N0	M0
	Tis pd	N0	M0
I	T1	N0	M0
II	T2	N0	M0
IIIA	T1	N1	M0
	T2	N1	M0
	T3	N0	M0
IIIB	T3	N1	M0
IV	T4	N0	M0
	T4	N1	M0
	Any T	N2	M0
	Any T	Any N	M1

Notes

Additional Descriptors

Lymphatic Vessel Invasion (L)

LX Lymphatic vessel invasion cannot be assessed
L0 No lymphatic vessel invasion
L1 Lymphatic vessel invasion

Venous Invasion (V)

VX Venous invasion cannot be assessed
V0 No venous invasion
V1 Microscopic venous invasion
V2 Macroscopic venous invasion

Histologic Grade (G)

- ☐ GX Grade cannot be assessed
- ☐ G1 Well differentiated
- ☐ G2 Moderately differentiated
- ☐ G3–4 Poorly differentiated or undifferentiated

Residual Tumor (R)

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

Additional Descriptors

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.

Prognostic Indicators (if applicable)

Physician's Signature _____ Date _____

PART X
Ophthalmic Sites

40

Carcinoma of the Eyelid

C44.1 Eyelid

SUMMARY OF CHANGES

- A listing of site-specific categories is now included in T4.

INTRODUCTION

The tumors of the eyelid can be broadly categorized under epithelial tumors originating from the skin and conjunctival surfaces and glandular tumors originating from sebaceous, sweat, and apocrine glands as well as hair follicles. Lymphoproliferative and melanocytic malignancies and occasionally soft tissue sarcomas (Kaposi's sarcoma, fibrous histiocytoma, leiomyosarcoma, etc.) are also encountered.

ANATOMY

Primary Site. The eyelid is covered externally by epidermis and internally by tarsal conjunctiva, which are continuous with the bulbar conjunctiva that covers the eyeball. Basal cell carcinoma and squamous cell carcinoma arise from the epidermal surface. Sebaceous carcinoma arises from the meibomian glands in the tarsus, the glands of Zeis at the lid margin, and the sebaceous glands of the caruncle. Other tumors arise from the skin appendages and mesenchymal tissues of the lid.

Regional Lymph Nodes. The eyelids contain a network of lymphatics that can be divided primarily into pre- and post-tarsal plexuses, which are anastamosed. The lymphatics of the lateral two-thirds of the upper eyelid and the lateral one-third of the lower eyelid drain into the preauricular nodes. The remaining lymphatics of the eyelids drain into the submandibular lymph nodes.

If performed for pN, histologic examination of the regional lymphadenectomy specimen would ordinarily include one or more lymph nodes.

Local Invasion. Malignancies of the eyelid may directly extend into the adjacent structures including the soft tissues of the orbit, the lacrimal gland, and the globe. Therefore, local tumor invasion (T4) should include extension to the bulbar conjunctiva, sclera and globe, soft tissues of the orbit, perineural space, bone/periosteum of the orbit, nasal cavity and paranasal sinuses, and central nervous system.

Metastatic Sites. Eyelid malignancies metastasize to distant sites, including cervical, axillary, and mediastinal lymph nodes, as well as to lungs, liver, and other viscera.

RULES FOR CLASSIFICATION

There should be histopathologic identification of the neoplasm to permit classification of the tumor into a given histopathologic type, such as basal cell carcinoma, sebaceous carcinoma, or Merkel cell tumor. In addition to criteria used for identification of the tumor, other histopathologic prognostic criteria, including the type and differentiation of the tumor, tumor presence or absence at surgical margins, perineural invasion, and vascular invasion, should be noted.

Any histopathologically unverified case should be categorized separately. Any unspecified case (malignant sarcoma, type unspecified) must be categorized separately.

Clinical Staging. The assessment of the malignancy should be based on inspection, palpation, biomicroscopic examination, ultrasonic biomicroscopy, and, when indicated, radiologic (ultrasonography, computed tomography, magnetic resonance imaging) examination of the orbit, nasal cavity and paranasal sinuses, and central nervous system.

Pathologic Staging. The nature of the histopathologic specimen (fine-needle aspiration biopsy, excisional biopsy, lumpectomy, or total excision) should be noted. In total excision specimens, histopathologic study of the surgical margins is mandatory. If the specimen includes the globe, then conjunctival margins and the resection margin of the optic nerve need to be examined.

DEFINITION OF TNM

The following definitions apply to clinical and pathologic staging.

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ*
T1 Tumor of any size, not invading the tarsal plate or, at the eyelid margin, 5 mm or less in greatest dimension
T2 Tumor invades tarsal plate or, at the eyelid margin, more than 5 mm but not more than 10 mm in greatest dimension
T3 Tumor involves full eyelid thickness or, at the eyelid margin, more than 10 mm in greatest dimension
T4 Tumor invades adjacent structures, which include bulbar conjunctiva, sclera and globe, soft tissues of the orbit, perineural space, bone and periosteum of the orbit, nasal cavity and paranasal sinuses, and central nervous system

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)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

STAGE GROUPING

No stage grouping is presently recommended.

HISTOPATHOLOGIC TYPE

Basal cell carcinoma
Squamous cell carcinoma
Sebaceous carcinoma
Merkel cell tumor
Skin appendage carcinoma
Sarcoma

HISTOLOGIC GRADE (G)

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated or differentiation is not applicable

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Shields CL: Basal cell carcinoma of the eyelids. Int Ophthalmol Clin 33:1–4, 1993

HISTOLOGIES—CARCINOMA OF THE EYELID

8010/2 Carcinoma *in situ*, NOS
8010/3 Carcinoma, NOS
8013/3 Large cell neuroendocrine carcinoma
8015/3 Glassy cell carcinoma
8020/3 Carcinoma, undifferentiated, NOS
8021/3 Carcinoma, anaplastic, NOS
8032/3 Spindle cell carcinoma, NOS
8033/3 Pseudosarcomatous carcinoma
8070/2 Squamous cell carcinoma *in situ*, NOS
8070/3 Squamous cell carcinoma, NOS
8071/3 Squamous cell carcinoma, keratinizing, NOS
8074/3 Squamous cell carcinoma, spindle cell
8076/2 Squamous cell carcinoma *in situ* with questionable stromal invasion
8076/3 Squamous cell carcinoma, microinvasive
8077/2 Squamous intraepithelial neoplasia, grade III
8081/2 Bowen disease
8082/3 Lymphoepithelial carcinoma
8083/3 Basaloid squamous cell carcinoma
8084/3 Squamous cell carcinoma, clear cell type
8090/3 Basal cell carcinoma
8091/3 Multifocal superficial basal cell carcinoma
8094/3 Basosquamous carcinoma
8095/3 Metatypical carcinoma
8098/3 Adenoid basal carcinoma
8102/3 Trichilemmocarcinoma
8110/3 Pilomatrix carcinoma
8120/3 Transitional cell carcinoma, NOS
8121/3 Schneiderian carcinoma
8140/2 Adenocarcinoma *in situ*, NOS
8140/3 Adenocarcinoma, NOS
8141/3 Scirrhous adenocarcinoma
8147/3 Basal cell adenocarcinoma
8190/3 Trabecular adenocarcinoma
8200/3 Adenoid cystic carcinoma
8240/3 Carcinoid tumor, NOS
8241/3 Enterochromaffin cell carcinoid
8242/3 Enterochromaffin-like cell tumor, malignant
8246/3 Neuroendocrine carcinoma, NOS
8247/3 Merkel cell carcinoma
8249/3 Atypical carcinoid tumor
8260/3 Papillary adenocarcinoma, NOS

HISTOLOGIES—CARCINOMA OF THE EYELID (CONT.)

8390/3 Skin appendage carcinoma
8400/3 Sweat gland adenocarcinoma
8401/3 Apocrine adenocarcinoma
8402/3 Nodular hidradenoma, malignant
8403/3 Malignant eccrine spiradenoma
8407/3 Sclerosing sweat duct carcinoma
8408/3 Eccrine papillary adenocarcinoma
8409/3 Eccrine poroma, malignant
8410/3 Sebaceous adenocarcinoma
8413/3 Eccrine adenocarcinoma
8430/3 Mucoepidermoid carcinoma
8480/3 Mucinous adenocarcinoma
8550/3 Acinar cell carcinoma
8560/3 Adenosquamous carcinoma
8562/3 Epithelial-myoepithelial carcinoma
8570/3 Adenocarcinoma with squamous metaplasia
8940/3 Mixed tumor, malignant, NOS
8941/3 Carcinoma in pleomorphic adenoma

CARCINOMA OF THE EYELID

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____ Laterality: ☐ Bilateral ☐ Left ☐ Right

DEFINITIONS

Clinical	*Pathologic*	**Primary Tumor (T)**	
☐	☐	TX	Primary tumor cannot be assessed
☐	☐	T0	No evidence of primary tumor
☐	☐	Tis	Carcinoma *in situ*
☐	☐	T1	Tumor of any size, not invading the tarsal plate or, at the eyelid margin, 5 mm or less in greatest dimension
☐	☐	T2	Tumor invades tarsal plate or, at the eyelid margin, more than 5 mm but not more than 10 mm in greatest dimension
☐	☐	T3	Tumor involves full eyelid thickness or, at the eyelid margin, more than 10 mm in greatest dimension
☐	☐	T4	Tumor invades adjacent structures, which include bulbar conjunctiva, sclera and globe, soft tissues of the orbit, perineural space, bone and periosteum of the orbit, nasal cavity and paranasal sinuses, and central nervous system

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)

☐	☐	MX	Distant metastasis cannot be assessed
☐	☐	M0	No distant metastasis
☐	☐	M1	Distant metastasis

Biopsy of metastatic site performed ..... ☐Y ..... ☐N

Source of pathologic metastatic specimen _____

Stage Grouping

No stage grouping is presently recommended

Histologic Grade (G)

☐	GX	Grade cannot be assessed
☐	G1	Well differentiated
☐	G2	Moderately differentiated
☐	G3	Poorly differentiated
☐	G4	Undifferentiated or differentiation is not applicable

Residual Tumor (R)

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

(continued on reverse side)

Additional Descriptors

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.

Prognostic Indicators (if applicable)

Notes

Additional Descriptors

Lymphatic Vessel Invasion (L)

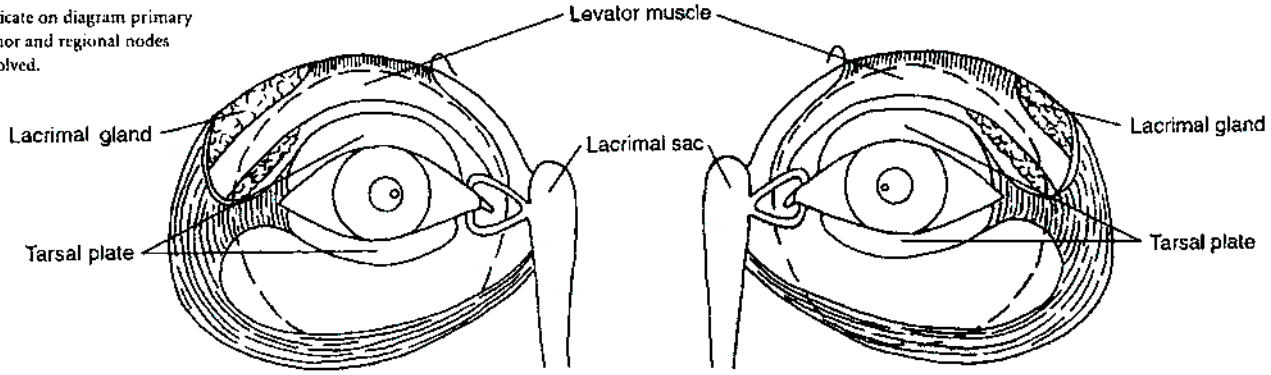
LX Lymphatic vessel invasion cannot be assessed
L0 No lymphatic vessel invasion
L1 Lymphatic vessel invasion

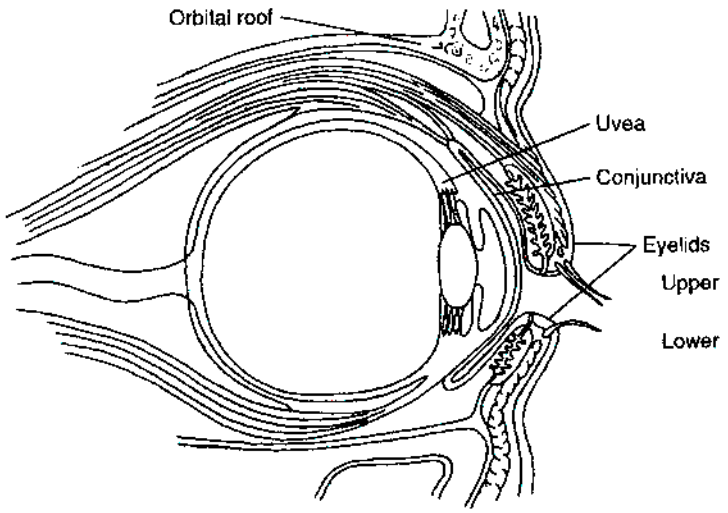
Venous Invasion (V)

VX Venous invasion cannot be assessed
V0 No venous invasion
V1 Microscopic venous invasion
V2 Macroscopic venous invasion

ILLUSTRATION

Indicate on diagram primary tumor and regional nodes involved.





Physician's Signature _____ Date _____

41

Carcinoma of the Conjunctiva

C69.0 Conjunctiva

SUMMARY OF CHANGES

- Specific categories of extension were added to T4.

ANATOMY

Primary Site. The conjunctiva consists of stratified epithelium that contains mucus-secreting goblet cells; these cells are most numerous in the fornices. Palpebral conjunctiva lines the eyelid; bulbar conjunctiva covers the eyeball. Conjunctival epithelium merges with that of the cornea at the limbus. It is at this exposed site, particularly at the temporal limbus, that carcinoma is most likely to arise. Conjunctival intraepithelial neoplasia (C.I.N.) embraces all forms of intraepithelial dysplasia, including *in situ* squamous cell carcinoma.

Regional Lymph Nodes. The regional lymph nodes are:

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. Tumors of the conjunctiva, in addition to spreading by way of regional lymphatics, may also involve the eyelid proper, the eye, orbit, adjacent paranasal sinus structures, and the brain.

RULES FOR CLASSIFICATION

Clinical Staging. The assessment of cancer is based on inspection, slit-lamp examination, palpation of the regional lymph nodes, and, when indicated, radiologic examination (including computed tomography and magnetic resonance imaging) and ultrasonographic examination of the orbit, paranasal sinuses, brain, and chest.

Pathologic Staging. Complete resection of the primary site is indicated if possible. Cryotherapy and/or topical chemotherapy may be considered as adjunctive therapies. Extensive tumor involvement of orbital soft tissues requires exenteration. The specimen should be thoroughly sampled for histologic study of surgical margins, type of tumor, and grade of malignancy.

DEFINITION OF TNM

These definitions apply to both clinical and pathologic staging.

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor 5 mm or less in greatest dimension
T2	Tumor more than 5 mm in greatest dimension, without invasion of adjacent structures
T3	Tumor invades adjacent structures, excluding the orbit
T4	Tumor invades the orbit with or without further extension
T4a	Tumor invades orbital soft tissues, without bone invasion
T4b	Tumor invades bone
T4c	Tumor invades adjacent paranasal sinuses
T4d	Tumor invades brain

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)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

STAGE GROUPING

No stage grouping is presently recommended.

HISTOPATHOLOGIC TYPE

This classification applies only to carcinoma of the conjunctiva.

Conjunctival intraepithelial neoplasia (C.I.N.) including *in situ* squamous cell carcinoma.
Squamous cell carcinoma
Mucoepidermoid carcinoma
Basal cell carcinoma

HISTOLOGIC GRADE (G)

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

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HISTOLOGIES—CARCINOMA OF THE CONJUNCTIVA

8010/2 Carcinoma *in situ*, NOS
8010/3 Carcinoma, NOS
8013/3 Large cell neuroendocrine carcinoma
8015/3 Glassy cell carcinoma
8020/3 Carcinoma, undifferentiated, NOS
8021/3 Carcinoma, anaplastic, NOS
8032/3 Spindle cell carcinoma, NOS
8033/3 Pseudosarcomatous carcinoma
8070/2 Squamous cell carcinoma *in situ*, NOS
8070/3 Squamous cell carcinoma, NOS
8071/3 Squamous cell carcinoma, keratinizing, NOS
8074/3 Squamous cell carcinoma, spindle cell
8076/2 Squamous cell carcinoma *in situ* with questionable stromal invasion
8076/3 Squamous cell carcinoma, microinvasive
8077/2 Squamous intraepithelial neoplasia, grade III
8081/2 Bowen disease
8082/3 Lymphoepithelial carcinoma
8083/3 Basaloid squamous cell carcinoma
8084/3 Squamous cell carcinoma, clear cell type
8090/3 Basal cell carcinoma
8091/3 Multifocal superficial basal cell carcinoma
8094/3 Basosquamous carcinoma
8095/3 Metatypical carcinoma
8098/3 Adenoid basal carcinoma
8120/3 Transitional cell carcinoma, NOS
8121/3 Schneiderian carcinoma
8140/2 Adenocarcinoma *in situ*, NOS
8140/3 Adenocarcinoma, NOS
8141/3 Scirrhous adenocarcinoma
8246/3 Neuroendocrine carcinoma, NOS
8247/3 Merkel cell carcinoma
8249/3 Atypical carcinoid tumor
8260/3 Papillary adenocarcinoma, NOS
8390/3 Skin appendage carcinoma
8400/3 Sweat gland adenocarcinoma
8401/3 Apocrine adenocarcinoma
8402/3 Nodular hidradenoma, malignant
8403/3 Malignant eccrine spiradenoma
8407/3 Sclerosing sweat duct carcinoma
8408/3 Eccrine papillary adenocarcinoma
8409/3 Eccrine poroma, malignant
8430/3 Mucoepidermoid carcinoma
8480/3 Mucinous adenocarcinoma
8550/3 Acinar cell carcinoma
8560/3 Adenosquamous carcinoma
8562/3 Epithelial-myoepithelial carcinoma
8570/3 Adenocarcinoma with squamous metaplasia
8940/3 Mixed tumor, malignant, NOS
8941/3 Carcinoma in pleomorphic adenoma

CARCINOMA OF THE CONJUNCTIVA

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____ Laterality: ☐ Bilateral ☐ Left ☐ Right

DEFINITIONS

Clinical	*Pathologic*	**Primary Tumor (T)**	
☐	☐	TX	Primary tumor cannot be assessed
☐	☐	T0	No evidence of primary tumor
☐	☐	Tis	Carcinoma *in situ*
☐	☐	T1	Tumor 5 mm or less in greatest dimension
☐	☐	T2	Tumor more than 5 mm in greatest dimension, without invasion of adjacent structures
☐	☐	T3	Tumor invades adjacent structures, excluding the orbit
☐	☐	T4	Tumor invades the orbit with or without further extension
☐	☐	T4a	Tumor invades orbital soft tissues without bone invasion
☐	☐	T4b	Tumor invades bone
☐	☐	T4c	Tumor invades adjacent paranasal sinuses
☐	☐	T4d	Tumor invades brain

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)

☐	☐	MX	Distant metastasis cannot be assessed
☐	☐	M0	No distant metastasis
☐	☐	M1	Distant metastasis

Biopsy of metastatic site performed ..... ☐Y ..... ☐N

Source of pathologic metastatic specimen _____

Stage Grouping

No stage grouping is presently recommended.

Histologic Grade (G)

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

Residual Tumor (R)

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

(continued on reverse side)

Additional Descriptors

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.

Prognostic Indicators (if applicable)

Notes

Additional Descriptors

Lymphatic Vessel Invasion (L)

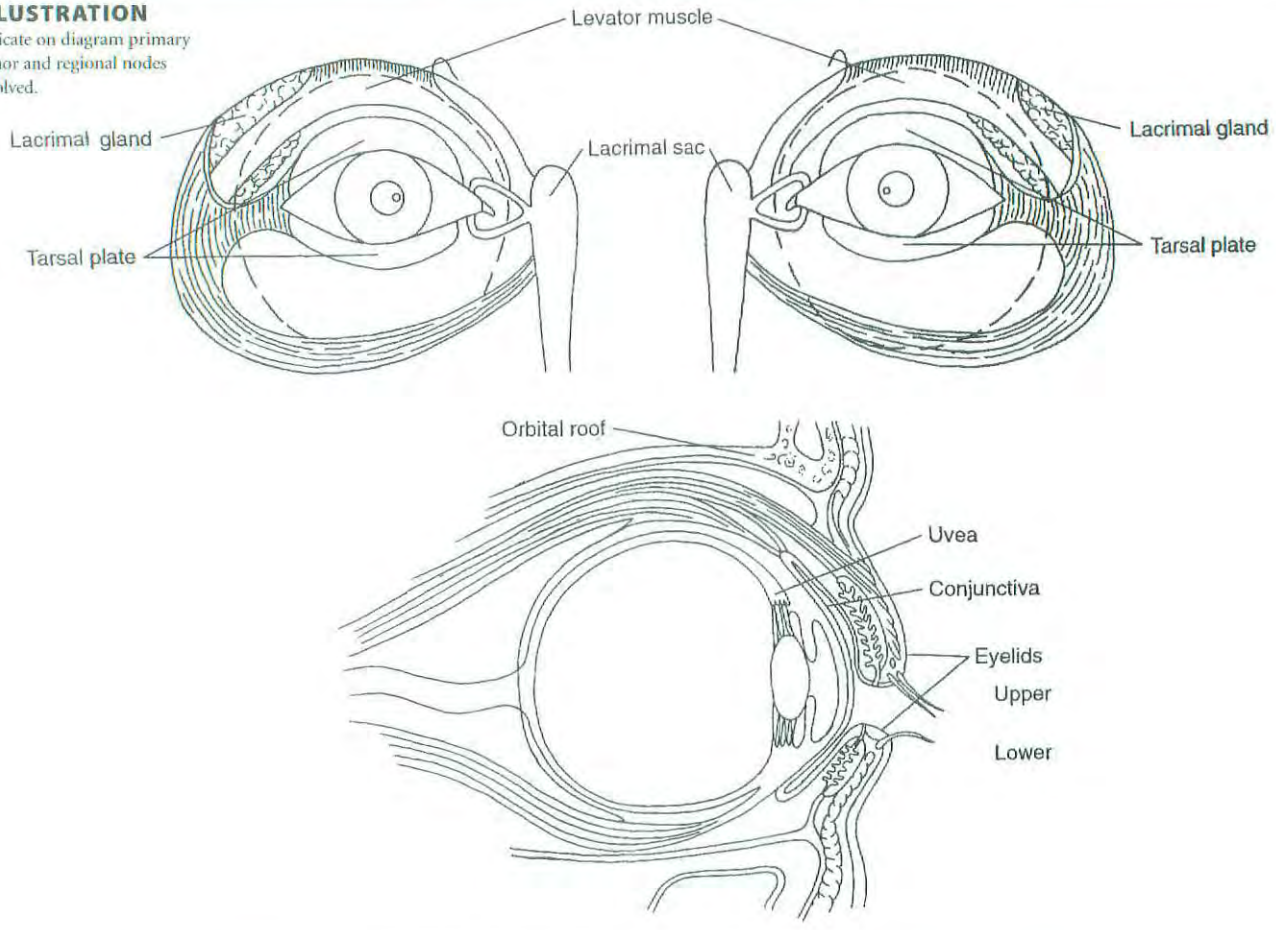
LX Lymphatic vessel invasion cannot be assessed
L0 No lymphatic vessel invasion
L1 Lymphatic vessel invasion

Venous Invasion (V)

VX Venous invasion cannot be assessed
V0 No venous invasion
V1 Microscopic venous invasion
V2 Macroscopic venous invasion

ILLUSTRATION

Indicate on diagram primary tumor and regional nodes involved.



Physician's Signature _____ Date _____

42

Malignant Melanoma of the Conjunctiva

C69.0 Conjunctiva

SUMMARY OF CHANGES

- Definitions of T classification have changed to describe depth of tumor penetration.

ANATOMY

Primary Site. Melanocytes have been noted to exist in the basal layer of the conjunctival epithelium. These melanocytes can be the source of acquired melanosis, malignant melanoma, and junctional and compound nevi. Melanocytic conjunctival tumors range from melanocytic hypertrophy and melanoma *in situ* to invasive malignant melanoma. Local clinically relevant classifications divide these tumors by conjunctival location, uni- or multifocality, and tumor thickness. Factors that influence both treatment and prognosis include local invasion, nodal spread, and distant metastasis.

Regional Lymph Nodes. The regional lymph nodes are:

Preauricular (parotid)
Submandibular
Cervical

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

Metastatic Sites. In addition to spread by lymphatics and the bloodstream, direct extension into the orbit, eyelids, and sinuses occurs.

RULES FOR CLASSIFICATION

The classification applies only to conjunctival melanoma. In general, there should be a histologic evaluation of the tumor.

Clinical Staging. The clinical assessment of a melanocytic conjunctival tumor is based on inspection, slit-lamp examination, and palpation of the regional lymph nodes. All conjunctival surfaces should be inspected (including eversion of the upper lid). Inspection of the ipsilateral sinuses is indicated if punctal involvement has been noted.

Radiologic evaluations to stage local disease may include computed tomography, magnetic resonance imaging, and/or ultrasonography of the orbits and sinuses. Complete metastatic surveys may include hematology screening as well as radiologic evaluations of the head, chest, and abdomen. Bone scans may be employed.

Pathologic Staging. Complete resection of the primary site is indicated. Cryotherapy, chemotherapy, and radiation therapy have been employed when complete resection is not possible or have been employed as an adjunctive treatment. Histopathologic evaluations for negative peripheral and deep margins should be performed. To best judge the depth of penetration of the tumor, sections should be made perpendicular to the epithelial surface. Perpendicular sections can be facilitated if the surgeon places the specimen epithelial side superior on a moist filter paper. The role of sentinel node biopsy is unknown.

10

DEFINITION OF TNM

Clinical

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Tumor of the bulbar conjunctiva
T2 Tumor of the bulbar conjunctiva with corneal extension
T3 Tumor extending into the conjunctival fornix, palpebral conjunctiva, or caruncle
T4 Tumor invades the eyelid, globe, orbit, sinuses, or central nervous system

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)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Pathologic

Primary Tumor (pT)

pTX Primary tumor cannot be assessed
pT0 No evidence of primary tumor
pT1 Tumor of the bulbar conjunctiva confined to the epithelium
pT2 Tumor of the bulbar conjunctiva not more than 0.8 mm in thickness with invasion of the substantia propria
pT3 Tumor of the bulbar conjunctiva more than 0.8 mm in thickness with invasion of the substantia propria or tumors involving the palpebral or caruncular conjunctiva
pT4 Tumor invades the eyelid, globe, orbit, sinuses, or central nervous system

Regional Lymph Nodes (pN)

pNX Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastasis
pN1 Regional lymph node metastasis present

Distant Metastasis (pM)

pMX Distant metastasis cannot be assessed
pM0 No distant metastasis
pM1 Distant metastasis

STAGE GROUPING

No stage grouping is presently recommended.

HISTOPATHOLOGIC TYPE

This categorization applies only to melanoma of the conjunctiva.

HISTOLOGIC GRADE (G)

Histologic grade represents the origin of the primary tumor.

GX Origin cannot be assessed
G0 Primary acquired melanosis without cellular atypia
G1 Conjunctival nevus
G2 Primary acquired melanosis with cellular atypia (epithelial disease only)
G3 *De novo* malignant melanoma

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Paridaens AD, Minassian DC, McCartney AC, et al: Prognostic factors in primary malignant melanoma of the conjunctiva: a clinicopathologic study of 256 cases. Br J Ophthalmol 78:252–259, 1994

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HISTOLOGIES—MALIGNANT MELANOMA OF THE CONJUNCTIVA

8720/2 Melanoma *in situ*
8720/3 Malignant melanoma, NOS
8723/3 Malignant melanoma, regressing
8730/3 Amelanotic melanoma
8740/3 Malignant melanoma in junctional nevus
8741/2 Precancerous melanosis, NOS
8741/3 Malignant melanoma in precancerous melanosis
8742/2 Lentigo maligna
8742/3 Lentigo maligna melanoma
8743/3 Superficial spreading melanoma
8744/3 Acral lentiginous melanoma, malignant
8745/3 Desmoplastic melanoma, malignant
8761/3 Malignant melanoma in giant pigmented nevus
8770/3 Mixed epithelioid and spindle cell melanoma
8771/3 Epithelioid cell melanoma
8772/3 Spindle cell melanoma

MALIGNANT MELANOMA OF THE CONJUNCTIVA

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____ Laterality: ☐ Bilateral ☐ Left ☐ Right

DEFINITIONS

Clinical	**Primary Tumor (T)**	
☐	TX	Primary tumor cannot be assessed
☐	T0	No evidence of primary tumor
☐	T1	Tumor of the bulbar conjunctiva
	T2	Tumor of the bulbar conjunctiva with corneal extension
☐	T3	Tumor extending into the conjunctival fornix, palpebral conjunctiva, or caruncle
☐	T4	Tumor invades the eyelid, globe, orbit, sinuses, or central nervous system

Pathologic	**Primary Tumor (T)**	
☐	pTX	Primary tumor cannot be assessed
☐	pT0	No evidence of primary tumor
☐	pT1	Tumor of the bulbar conjunctiva confined to the epithelium
☐	pT2	Tumor of the bulbar conjunctiva not more than 0.8 mm in thickness with invasion of the substantia propria
☐	pT3	Tumor of the bulbar conjunctiva more than 0.8 mm in thickness with invasion of the substantia propria or tumors involving palpebral or caruncular conjunctiva
☐	pT4	Tumor invades the eyelid, globe, orbit, sinuses, or central nervous system

Clinical	*Pathologic*	**Regional Lymph Nodes (N)**	
☐	☐	pNX	Regional lymph nodes cannot be assessed
☐	☐	pN0	No regional lymph node metastasis
☐	☐	pN1	Regional lymph node metastasis present

Distant Metastasis (M)

☐	☐	pMX	Distant metastasis cannot be assessed
☐	☐	pM0	No distant metastasis
		pM1	Distant metastasis
			Biopsy of metastatic site performed ..... ☐Y ..... ☐N
			Source of pathologic metastatic specimen _____

Stage Grouping

No stage grouping is presently recommended.

Histologic Grade (G)

Histopathologic grade represents the origin of the primary tumor.

☐	GX	Origin cannot be assessed
☐	G0	Primary acquired melanosis without cellular atypia
☐	G1	Conjunctival nevus
☐	G2	Primary acquired melanosis with cellular atypia (epithelial disease only)
☐	G3	*De novo* malignant melanoma

Residual Tumor (R)

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

(continued on reverse side)

Additional Descriptors

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.

Prognostic Indicators (if applicable)

Notes

Additional Descriptors

Lymphatic Vessel Invasion (L)

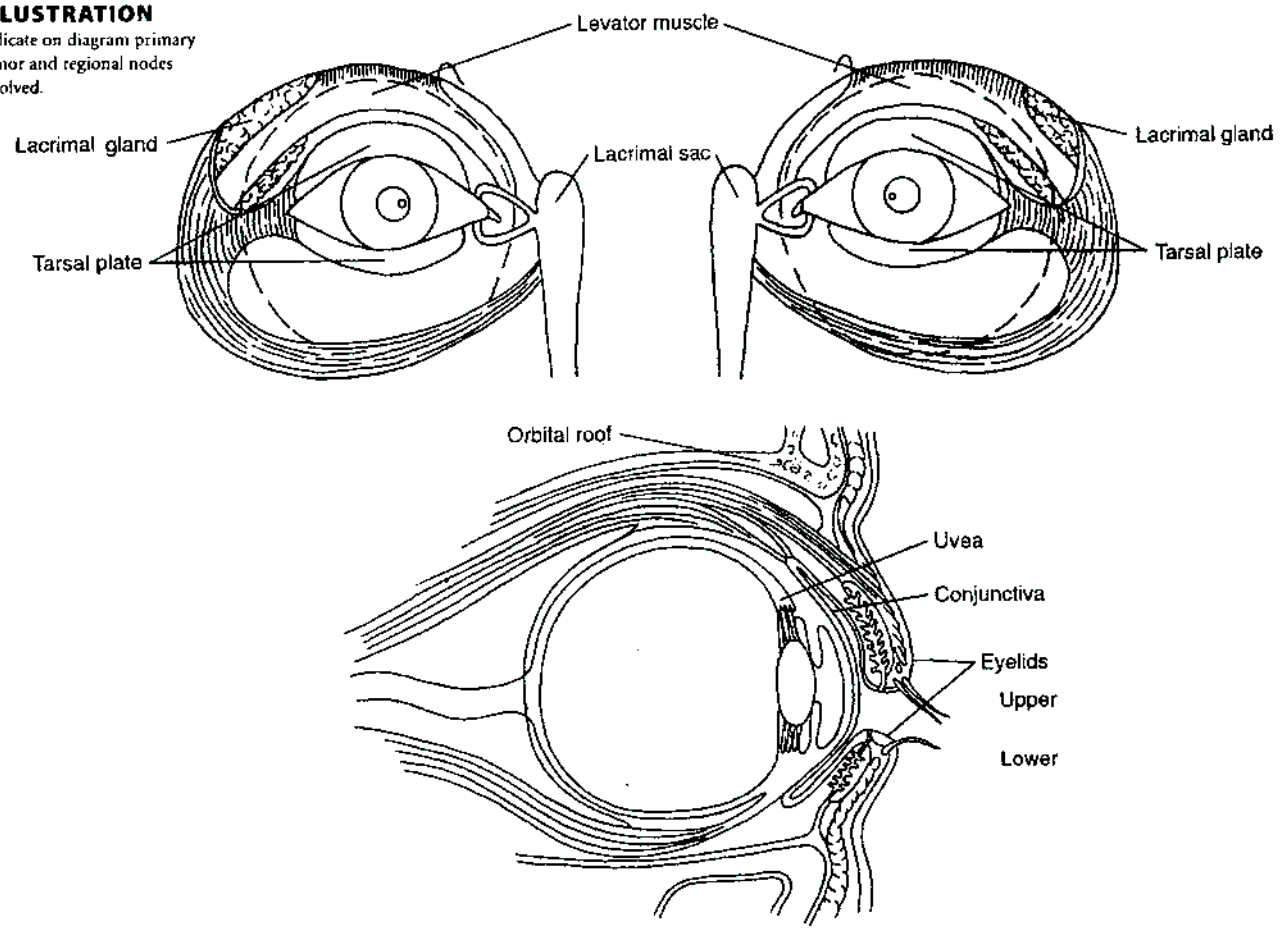
LX Lymphatic vessel invasion cannot be assessed
L0 No lymphatic vessel invasion
L1 Lymphatic vessel invasion

Venous Invasion (V)

VX Venous invasion cannot be assessed
V0 No venous invasion
V1 Microscopic venous invasion
V2 Macroscopic venous invasion

ILLUSTRATION

Indicate on diagram primary tumor and regional nodes involved.



Physician's Signature _____ Date _____

43

Malignant Melanoma of the Uvea

C69.3 Choroid

C69.4 Ciliary body and iris

SUMMARY OF CHANGES

Iris

- T1 lesions have been divided into T1a, T1b, and T1c.
- T1a is defined as tumor limited to the iris not more than 3 clock hours in size.
- T1b is defined as tumor limited to the iris more than 3 clock hours in size.
- T1c is defined as tumor limited to the iris with melanomalytic glaucoma.
- The definition of T2 lesions has been modified, and T2 has been divided by the addition T2a.
- T2 is defined as tumor confluent with or extending into the ciliary body and/or choroid.
- T2a is defined as tumor confluent with or extending into the ciliary body and/or choroid with melanomalytic glaucoma.
- The definition of T3 lesions has been modified, and T3 has been divided by the addition T3a.
- T3 is defined as tumor confluent with or extending into the ciliary body and/or choroid with extra scleral extension.
- T3a is defined as tumor confluent with or extending into the ciliary body with extrascleral extension and melanomalytic glaucoma.

Ciliary Body and Choroid

- The definition of T1 lesions has been modified, and T1 has been divided into T1a, T1b, and T1c.
- T1 is defined as tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness).
- T1a is defined as tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness) without extraocular extension.
- T1b is defined as tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness) with microscopic extraocular extension.
- T1c is defined as tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness) with macroscopic extraocular extension.
- The definition of T2 lesions has been modified, and T2 has been divided into T2a, T2b, and T2c.

continued

SUMMARY OF CHANGES (CONTINUED)

- T2 is defined as tumor 10 mm to 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height.
- T2a is defined as tumor 10 mm to 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height without extraocular extension.
- T2b is defined as tumor 10 mm to 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height with microscopic extraocular extension.
- T2c is defined as tumor 10 mm to 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height with macroscopic extraocular extension.

ANATOMY

Primary Site. The uvea (uveal tract) is the middle layer of the eye, situated between the cornea and sclera externally and the retina and its analogous tissues internally. The uveal tract is divided into three regions—iris, ciliary body, and choroid—and it is a highly vascular structure. The choroid primarily comprises blood vessels with little intervening stroma. Uveal melanomas are believed to arise from uveal melanocytes and are therefore of neural crest origin. Because there are no lymphatic channels within the eye, uveal melanomas are thought to metastasize exclusively hematogenously to visceral organs. In the rare event that uveal melanoma metastasizes to lymph nodes, it is typically after extraocular spread and invasion of conjunctival, adnexal, and/or orbital lymphatics.

Uveal melanomas arise most commonly in the choroid, less in the ciliary body, and least in the iris. Choroidal melanomas extend commonly through Bruch's membrane into the retina and vitreous, less commonly through the sclera into the orbit, and rarely into the optic nerve.

Intraocular location of a uveal melanoma can also affect a patient's prognosis for metastasis. Tumors confined to the iris carry the most favorable prognosis, followed by those in the choroids; ciliary involvement carries the least favorable prognosis. Tumor size (primarily largest tumor diameter) continues to be the dominant predictor for metastasis. It is currently impossible to distinguish clinically between a large nevus and a small uveal melanoma. Clinical findings of orange pigment, subretinal fluid, and thickness greater than 2 mm are more commonly associated with uveal melanomas than with nevi.

Pigmented iris tumors that demonstrate intrinsic vascularity, size greater than 3 clock hours and thickness greater than 1 mm, sector cataract, pigment dispersion (melanocytes and melanin granules or melanocytic tumor cells), secondary glaucoma, and extrascleral extension are more likely to be malignant melanomas than benign melanocytic proliferations. In general, small uveal melanocytic lesions are observed for growth prior to being clinically defined as uveal melanomas.

Regional Lymph Nodes. This category applies only to extrascleral extension and conjunctival invasion. Regional lymphadenectomy will ordinarily include six or more regional lymph nodes. The regional lymph nodes are:

Preauricular
Submandibular
Cervical

Metastatic Sites. Uveal melanomas may metastasize hematogenously to various visceral organs. The liver is the most common site, and often the only site, of clinically detectable metastasis. Less common sites include the lung, pleura, subcutaneous tissues, bone, and brain.

RULES FOR CLASSIFICATION

Clinical Staging. The assessment of the tumor is based on clinical examination, including slit-lamp examination and direct and indirect ophthalmoscopy. Additional methods, such as ultrasonography, computerized stereometry, fluorescein angiography, and isotope examination, may enhance the accuracy of appraisal.

Pathologic Staging. Resection of the primary site by iridectomy, iridocyclectomy, eye wall resection, or enucleation is needed for complete pathologic staging. Assessment of the extent of the tumor, measured in clock hours of involvement, basal dimension, and height and margins of resection, is necessary. Resection or needle biopsy of enlarged regional lymph nodes or orbital masses is desirable.

DEFINITION OF TNM

These definitions apply to both clinical* and pathologic staging.

Primary Tumor

All Uveal Melanomas

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor

Iris

T1 Tumor limited to the iris
T1a Tumor limited to the iris not more than 3 clock hours in size
T1b Tumor limited to the iris more than 3 clock hours in size
T1c Tumor limited to the iris with melanomalytic glaucoma
T2 Tumor confluent with or extending into the ciliary body and/or choroid
T2a Tumor confluent with or extending into the ciliary body and/or choroid with melanomalytic glaucoma
T3 Tumor confluent with or extending into the ciliary body and/or choroid with scleral extension
T3a Tumor confluent with or extending into the ciliary body with scleral extension and melanomalytic glaucoma
T4 Tumor with extraocular extension

Ciliary Body and Choroid

T1* Tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness)
T1a Tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness) without microscopic extraocular extension
T1b Tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness) with microscopic extraocular extension
T1c Tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness) with macroscopic extraocular extension
T2* Tumor greater than 10 mm but not more than 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height (thickness)
T2a Tumor 10 mm to 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height (thickness) without microscopic extraocular extension
T2b Tumor 10 mm to 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height (thickness) with microscopic extraocular extension
T2c Tumor 10 mm to 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height (thickness) with macroscopic extraocular extension
T3* Tumor more than 16 mm in greatest diameter and/or greater than 10 mm in maximum height (thickness) without extraocular extension
T4 Tumor more than 16 mm in greatest diameter and/or greater than 10 mm in maximum height (thickness) with extraocular extension

**Note:* When basal dimension and apical height do not fit this classification, the largest tumor diameter should be used for classification. In clinical practice, the tumor base may be estimated in optic disc diameters (dd) (average: 1 dd = 1.5 mm). The height may be estimated in diopters (average: 3 diopters = 1 mm). Techniques such as ultrasonography, visualization, and photography are frequently used to provide more accurate measurements.

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)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

STAGE GROUPING

Stage I	T1	N0	M0
	T1a	N0	M0
	T1b	N0	M0
	T1c	N0	M0
Stage II	T2	N0	M0
	T2a	N0	M0
	T2b	N0	M0
	T2c	N0	M0
Stage III	T3	N0	M0
	T4	N0	M0
Stage IV	Any T	N1	M0
	Any T	Any N	M1

HISTOPATHOLOGIC TYPE

The histopathologic types are

Spindle cell melanoma
Mixed cell melanoma
Epithelioid cell melanoma

HISTOLOGIC GRADE (G)

GX Grade cannot be assessed
G1 Spindle cell melanoma
G2 Mixed cell melanoma
G3 Epithelioid cell melanoma

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HISTOLOGIES—MALIGNANT MELANOMA OF THE UVEA

8720/2	Melanoma *in situ*
8720/3	Malignant melanoma, NOS
8723/3	Malignant melanoma, regressing
8730/3	Amelanotic melanoma
8740/3	Malignant melanoma in junctional nevus
8741/2	Precancerous melanosis, NOS
8741/3	Malignant melanoma in precancerous melanosis
8742/2	Lentigo maligna
8742/3	Lentigo maligna melanoma
8743/3	Superficial spreading melanoma
8744/3	Acral lentiginous melanoma, malignant
8745/3	Desmoplastic melanoma, malignant
8761/3	Malignant melanoma in giant pigmented nevus
8770/3	Mixed epithelioid and spindle cell melanoma
8771/3	Epithelioid cell melanoma
8772/3	Spindle cell melanoma

MALIGNANT MELANOMA OF THE UVEA

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____ Laterality: ☐ Bilateral ☐ Left ☐ Right

DEFINITIONS

Clinical	Pathologic	Primary Tumor (T)	
		All Uveal Melanomas	
☐	☐	TX	Primary tumor cannot be assessed
☐	☐	T0	No evidence of primary tumor
		Iris	
☐	☐	T1	Tumor limited to the iris
☐	☐	T1a	Tumor limited to the iris (not more than 3 clock hours in size)
☐	☐	T1b	Tumor limited to the iris (more than 3 clock hours in size)
☐	☐	T1c	Tumor limited to iris with melanomalytic glaucoma
☐	☐	T2	Tumor confluent with or extending into the ciliary body and/or choroid
☐	☐	T2a	Tumor confluent with or extending into the ciliary body and/or choroid with melanomalytic glaucoma
☐	☐	T3	Tumor confluent with or extending into the ciliary body and/or choroid with scleral extension
☐	☐	T3a	Tumor confluent with or extending into the ciliary body with scleral extension and melanomalytic glaucoma
☐	☐	T4	Tumor with extraocular extension
		Ciliary Body and Choroid	
☐	☐	T1	Tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness)[1]
☐	☐	T1a	Tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness) without microscopic extraocular extension
☐	☐	T1b	Tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness) with microscopic extraocular extension
☐	☐	T1c	Tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness) with macroscopic extraocular extension
☐	☐	T2	Tumor greater than 10 mm but not more than 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height (thickness)[1]
☐	☐	T2a	Tumor 10 mm to 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height (thickness) without microscopic extraocular extension
☐	☐	T2b	Tumor 10 mm to 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height (thickness) with microscopic extraocular extension
☐	☐	T2c	Tumor 10 mm to 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height (thickness) with macroscopic extraocular extension
☐	☐	T3	Tumor more than 16 mm in greatest diameter and/or greater than 10 mm in maximum height (thickness) without extraocular extension[1]
☐	☐	T4	Tumor more than 16 mm in greatest diameter and/or greater than 10 mm in maximum height (thickness) with extraocular extension

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)

☐ MX Distant metastasis cannot be assessed
☐ M0 No distant metastasis
☐ M1 Distant metastasis

Biopsy of metastatic site performed ..... ☐Y ..... ☐N

Source of pathologic metastatic specimen _____

Notes

1. When basal dimension and apical height do not fit this classification, the largest tumor diameter should be used for classification. In clinical practice, the tumor base may be estimated in optic disc diameters (dd) (average: 1 dd=1.5 mm). The height may be estimated in diopters (average: 3 diopters=1 mm). Techniques such as ultrasonography, visualization, and photography are frequently used to provide more accurate measurements.

(continued on reverse side)

Clinical	Pathologic	Stage Grouping			
☐	☐	I	T1	N0	M0
			T1a	N0	M0
			T1b	N0	M0
			T1c	N0	M0
☐	☐	II	T2	N0	M0
			T2a	N0	M0
			T2b	N0	M0
			T2c	N0	M0
☐	☐	III	T3	N0	M0
			T4	N0	M0
☐	☐	IV	Any T	N1	M0
			Any T	Any N	M1

Notes

Additional Descriptors

Lymphatic Vessel Invasion (L)

LX Lymphatic vessel invasion cannot be assessed
L0 No lymphatic vessel invasion
L1 Lymphatic vessel invasion

Histologic Grade (G)

☐ GX Grade cannot be assessed
☐ G1 Spindle cell melanoma
☐ G2 Mixed cell melanoma
☐ G3 Epithelioid cell melanoma

Residual Tumor (R)

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

Venous Invasion (V)

☐ VX Venous invasion cannot be assessed
☐ V0 No venous invasion
☐ V1 Microscopic venous invasion
☐ V2 Macroscopic venous invasion

Visual Acuity _____ (Snellen or equivalent)

Additional Descriptors

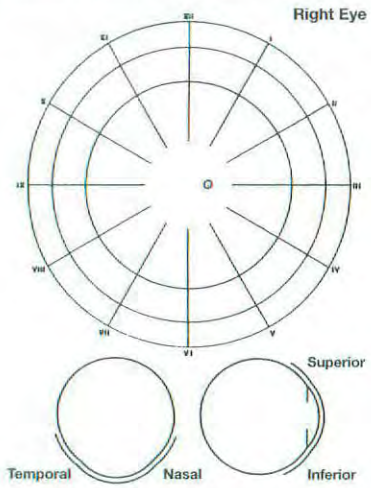
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

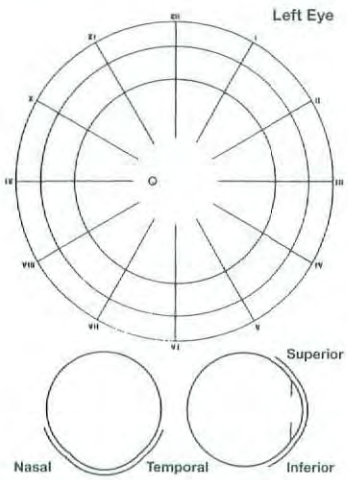
☐ **m suffix** indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.
☐ **y prefix** indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a "y" prefix. 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.

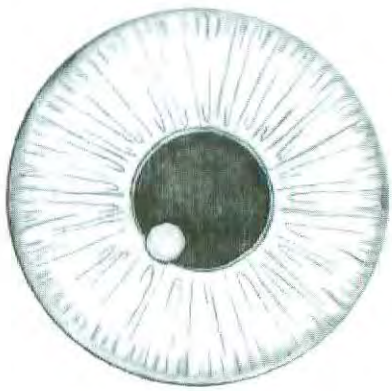
Prognostic Indicators (if applicable)

ILLUSTRATION

Indicate on diagrams and describe exact location and characteristics of tumor.







Physician's Signature _____ Date _____

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Retinoblastoma

C69.2 Retina

SUMMARY OF CHANGES

- T1 was redefined, and the lesions have been divided into T1a and T1b.
- T2 was redefined, and the lesions have been divided into T2a, T2b, and T2c.
- T3 was redefined, and T3a, T3b, and T3c have been removed.
- T4a and T4b have been removed.
- N2 (distant lymph node involvement) has been added to regional lymph nodes (N).
- pT1, pT2, and pT3 have been redefined.
- pT2 lesions have been divided into pT2a, pT2b, and pT2c.
- pM1 has been divided into pM1a and pM1b.
- No stage grouping applies to retinoblastoma.

ANATOMY

Primary Site. The retina is composed of neurons and glial cells. The precursors of the neuronal elements give rise to retinoblastoma, whereas the glial cells give rise to astrocytomas, which are benign and extremely rare in the retina. The retina is limited internally by a membrane that separates it from the vitreous cavity. Externally, it is limited by the retinal pigment epithelium and Bruch's membrane, which separate it from the choroid and act as natural barriers to extension of retinal tumors into the choroid. The continuation of the retina with the optic nerve allows direct extension of retinoblastomas into the optic nerve and then to the subarachnoid space. Because the retina has no lymphatics, spread of retinal tumors is either by direct extension into adjacent structures or by distant metastasis through hematogenous routes.

Regional Lymph Nodes. Because there are no intraocular lymphatics, this category of staging applies only to anterior extrascleral extension. The regional lymph nodes are preauricular (parotid), submandibular, and cervical.

Local Extension. Local extension anteriorly can result in soft tissue involvement of the face or a mass protruding from between the lids. Posterior extension results in retinoblastoma extending into the orbit, paranasal sinuses, and/or brain.

Metastatic Sites. Retinoblastoma can metastasize through hematogenous routes to various sites, most notably the bone marrow, skull, long bones, and brain.

RULES FOR CLASSIFICATION

Clinical Staging. All suspected cases of retinoblastoma should have a neural imaging scan. If it is possible to obtain only one imaging study, computerized tomography (CT) is recommended because detection of calcium in the eye on CT confirms the clinical suspicion of retinoblastoma. The request should include cuts through the pineal region of the brain. Magnetic resonance imaging is particularly useful if extension into either the extraocular space or the optic nerve is suspected or if there is a concern about the possible presence of a primitive neuroectodermal tumor (PNET) in the pineal region (trilateral retinoblastoma).

A staging examination under anesthesia should include ocular ultrasound and retinal drawings of each eye, with each identifiable tumor measured and numbered. Digital images

of the retina may be very helpful. In bilateral cases, each eye must be classified separately. This classification does not apply to complete spontaneous regression of the tumor. Tumor size or the distance from the tumor to the disc or fovea is recorded in millimeters. These millimeter distances are measured by ultrasound, estimated by comparison with a normalized optic disc (1.5 mm), or deduced from the fact that the field of a 28-diopter condensing lens has a retinal diameter of 13 mm.

Pathologic Staging. If one eye is enucleated, pathologic staging of that eye provides information supplemental to the clinical staging. First, the pathology should provide histologic verification of the disease. All clinical and pathologic data from the resected specimen are to be used.

DEFINITION OF TNM

Clinical Classification (cTNM). The classification that follows was extensively revised from the last publication. In T1 eyes, the tumor is confined to the retina, the tissue of origin. The classification below reflects a decade's experience with the response to chemotherapy followed by focal consolidation. The likelihood of salvaging good vision and the eye goes down progressively from T1 through T2. There is a corresponding increase in the morbidity and intensity of therapy from T1 through T2.

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Tumor confined to the retina (no vitreous seeding or significant retinal detachment). No retinal detachment or subretinal fluid >5 mm from the base of the tumor
T1a Any eye in which the largest tumor is less than or equal to 3 mm in height **and** no tumor is located closer than 1 DD (1.5 mm) to the optic nerve or fovea
T1b All other eyes in which the tumor(s) are confined to the retina regardless of location or size (up to half the volume of the eye). No vitreous seeding. **No** retinal detachment or subretinal fluid >5 mm from the base of the tumor
T2 Tumor with contiguous spread to adjacent tissues or spaces (vitreous or subretinal space)
T2a *Minimal tumor spread to vitreous and/or subretinal space.* Fine local or diffuse vitreous seeding and/or serous retinal detachment up to total detachment may be present, but **no** clumps, lumps, snowballs, or avascular masses **are allowed** in the vitreous or subretinal space. Calcium flecks in the vitreous or subretinal space are allowed. The tumor may fill up to 2/3 the volume of the eye.
T2b *Massive tumor spread to the vitreous and/or subretinal space.* Vitreous seeding and/or subretinal implantation may consist of lumps, clumps, snowballs, or avascular tumor masses. Retinal detachment may be total. Tumor may fill up to 2/3 the volume of the eye.
T2c Unsalvageable intraocular disease. Tumor fills more than 2/3 the eye **or** there is no possibility of visual rehabilitation **or** one or more of the following are present:
- Tumor-associated glaucoma, either neovascular or angle closure
- Anterior segment extension of tumor
- Ciliary body extension of tumor
- Hyphema (significant)
- Massive vitreous hemorrhage
- Tumor in contact with lens
- Orbital cellulitis-like clinical presentation (massive tumor necrosis)

T3 Invasion of the optic nerve and/or optic coats
T4 Extraocular tumor

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node involvement
N1 Regional lymph node involvement (preauricular, submandibular, or cervical)
N2 Distant lymph node involvement

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Metastasis to central nervous system and/or bone, bone marrow, or other sites

Pathologic Classification (pTNM). There is one major difference in the pathologic classification from the last edition. No differentiating pathologic separation is proposed for those eyes in which the tumor may vary in size but is confined to the retina, vitreous, or subretinal space.

Primary Tumor (pT)

pTX Primary tumor cannot be assessed
pT0 No evidence of primary tumor
pT1 Tumor confined to the retina, vitreous, or subretinal space. No optic nerve or choroidal invasion
pT2 Minimal invasion of the optic nerve and/or optic coats
pT2a Tumor invades optic nerve up to, but not through, the level of the lamina cribrosa
pT2b Tumor invades choroid focally
pT2c Tumor invades optic nerve up to, but not through, the level of the lamina cribrosa **and** invades the choroid focally
pT3 Significant invasion of the optic nerve and/or optic coats
pT3a Tumor invades optic nerve through the level of the lamina cribrosa but not to the line of resection
pT3b Tumor massively invades the choroid
pT3c Tumor invades the optic nerve through the level of the lamina cribrosa but not to the line of resection **and** massively invades the choroid

pT4 Extraocular tumor extension that includes:
Invasion of optic nerve to the line of resection
Invasion of orbit through the sclera
Extension both anteriorly or posteriorly into the orbit
Extension into the brain
Extension into the subarachnoidal space of the optic nerve
Extension to the apex of the orbit
Extension to, but not through, the chiasm
Extension into the brain beyond the chiasm

Regional Lymph Nodes (pN)

pNX Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastasis
pN1 Regional lymph node metastasis

Distant Metastasis (pM)

pMX Distant metastasis cannot be assessed
pM0 No distant metastasis
pM1 Distant metastasis
pM1a Bone marrow
pM1b Other sites

STAGE GROUPING

No stage grouping applies.

HISTOPATHOLOGIC TYPE

This classification applies only to retinoblastoma.

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HISTOLOGIES—RETINOBLASTOMA

9510/3 Retinoblastoma, NOS
9511/3 Retinoblastoma, differentiated
9512/3 Retinoblastoma, undifferentiated
9513/3 Retinoblastoma, diffuse

RETINOBLASTOMA

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____ Laterality: ☐ Bilateral ☐ Left ☐ Right

DEFINITIONS

Pathologic	Primary Tumor (T)	
☐	pTX	Primary tumor cannot be assessed
☐	pT0	No evidence of primary tumor
☐	pT1	Tumor confined to the retina, vitreous, or subretinal space. No optic nerve or choroidal invasion
☐	pT2	Minimal invasion of the optic nerve and/or optic coats
☐	pT2a	Tumor invades optic nerve up to, but not through, the level of the lamina cribrosa
☐	pT2b	Tumor invades choroid focally
☐	pT2c	Tumor invades optic nerve up to, but not through, the level of the lamina cribrosa **and** invades the choroid focally
☐	pT3	Significant invasion of the optic nerve and/or optic coats
☐	pT3a	Tumor invades optic nerve through the level of the lamina cribosa but not to the line of resection
☐	pT3b	Tumor massively invades the choroid
☐	pT3c	Tumor invades the optic nerve through the level of the lamina cribosa but not to the line of resection **and** massively invades the choroid
☐	pT4	Extraocular extension which includes: • *Tumor invades optic nerve to the line of resection* • *Tumor invades the orbit through the sclera* • *Tumor extends both anteriorly or posteriorly into the orbit* • *Extension into the brain* • *Extension into the subarachnoidal space of the optic nerve* • *Extension to the apex of the orbit* • *Extension to, but not through, the chiasm, or* • *Extension into the brain beyond the chiasm*

Clinical	Primary Tumor (T)	
☐	TX	Primary tumor cannot be assessed
☐	T0	No evidence of primary tumor
☐	T1	Tumor confined to the retina (no vitreous seeding or significant retinal detachment)
☐	T1a	Any eye in which the largest tumor is less than or equal to 3 mm in height **and** no tumor is located closer than 1 DD (1.5 mm) to the optic nerve or fovea
☐	T1b	All other eyes in which the tumor(s) are confined to the retina regardless of location or size (up to half the volume of the eye). **No** vitreous seeding. **No** retinal detachment or subretinal fluid >5 mm from the base of the tumor
☐	T2	Tumor with contiguous spread to adjacent tissues or spaces (vitreous or subretinal space)
☐	T2a	*Minimal tumor spread to vitreous and/or subretinal space.* Fine local or diffuse vitreous seeding and/or serous retinal detachment up to total detachment may be present, but **no** clumps, lumps, snowballs, or avascular masses **are allowed** in the vitreous or subretinal space. Calcium flecks in the vitreous or subretinal space are allowed. The tumor may fill up to 2/3 the volume of the eye.
☐	T2b	*Massive tumor spread to the vitreous and/ or subretinal space.* Vitreous seeding and/or subretinal implantation may consist of lumps, clumps, snowballs, or avascular tumor masses. Retinal detachment may be total. Tumor may fill up to 2/3 the volume of the eye.
☐	T2c	Unsalvageable intraocular disease. Tumor fills more than 2/3 the eye or there is no possibility of visual rehabilitation **or** one or more of the following are present: • *Tumor-associated glaucoma, either neovascular or angle closure;* • *Anterior segment extension of tumor;* • *Ciliary body extension of tumor;* • *Hyphema (significant);* • *Massive vitreous hemorrhage;* • *Tumor in contact with lens;* • *Orbital cellulitis-like clinical presentation (massive tumor necrosis)*
☐	T3	Invasion of the optic nerve and/or optic coats
☐	T4	Extraocular Tumor

(continued on reverse side)

Pathologic

Regional Lymph Nodes (N)

- ☐ pNX Regional lymph nodes cannot be assessed
- ☐ pN0 No regional lymph node metastasis
- ☐ pN1 Regional lymph node metastasis

Distant Metastasis (M)

- ☐ pMX Distant metastasis cannot be assessed
- ☐ pM0 No distant metastasis
- ☐ pM1 Distant metastasis
- ☐ pM1a Bone marrow
- ☐ pM1b Other sites

Biopsy of metastatic site performed ☐Y ☐N

Source of pathologic metastatic specimen

Clinical

Regional Lymph Nodes (N)

- ☐ NX Regional lymph nodes cannot be assessed
- ☐ N0 No regional lymph node involvement
- ☐ N1 Regional lymph node involvement (preauricular, submandibular, or cervical)
- ☐ N2 Distant lymph node involvement

Distant Metastasis (M)

- ☐ MX Distant metastasis cannot be assessed
- ☐ M0 No distant metastasis
- ☐ M1 Metastases to central nervous system, and/or bone, bone marrow, or other sites

Stage Grouping

No applicable stage grouping for pathological or clinical.

Residual Tumor (R)

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

Additional Descriptors

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.

Prognostic Indicators (if applicable)

Notes

Additional Descriptors

Lymphatic Vessel Invasion (L)

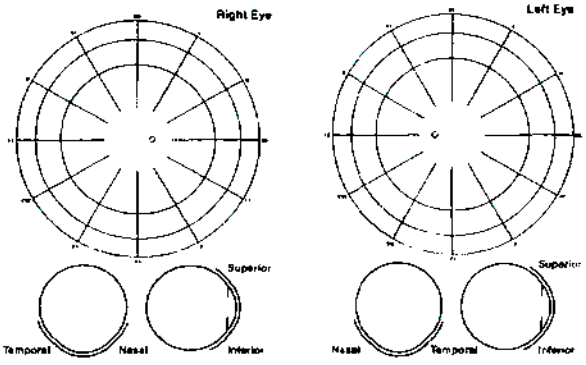
- LX Lymphatic vessel invasion cannot be assessed
- L0 No lymphatic vessel invasion
- L1 Lymphatic vessel invasion

Venous Invasion (V)

- VX Venous invasion cannot be assessed
- V0 No venous invasion
- V1 Microscopic venous invasion
- V2 Macroscopic venous invasion

ILLUSTRATION

Indicate on diagrams and describe exact location and characteristics of tumor.



Physician's Signature _____ Date _____

45

Carcinoma of the Lacrimal Gland

C69.5 Lacrimal gland

SUMMARY OF CHANGES

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

INTRODUCTION

The retrospective study of 265 epithelial tumors of the lacrimal gland conducted by the Armed Forces Institute of Pathology has improved our understanding of the histologic classification and clinical behavior of epithelial tumors of the lacrimal gland. Our current understanding of lacrimal gland carcinoma is based on a solid foundation. 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 is a modification of the World Health Organization (WHO) classification of salivary gland tumors.

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. The lacrimal gland is divided into the deep orbital and the superficial palpebral lobes by the levator aponeurosis.

Regional Lymph Nodes. The regional lymph nodes include:

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. A complete physical examination and imaging of the orbit should be performed. Computed tomography and/or magnetic resonance imaging can provide critical diagnostic and staging data.

Pathologic Staging. Complete resection of the mass is indicated. The specimen should be thoroughly sampled for evaluation of surgical margins, type of tumor, and the grade of malignancy. Perineural spread, most characteristic of adenoid cystic carcinoma, frequently results in an underestimation of the true extent of disease.

DEFINITION OF TNM

This classification applies to both clinical and pathologic staging of lacrimal gland carcinomas.

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2.5 cm or less in greatest dimension, limited to the lacrimal gland
T2	Tumor more than 2.5 cm but not more than 5 cm in greatest dimension, limited to the lacrimal gland
T3	Tumor invades the periosteum
T3a	Tumor not more than 5 cm invades the periosteum of the lacrimal gland fossa
T3b	Tumor more than 5 cm in greatest dimension with periosteal invasion
T4	Tumor invades the orbital soft tissues, optic nerve, or globe with or without bone invasion; tumor extends beyond the orbit to adjacent structures, including brain

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)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

STAGE GROUPING

No stage grouping is presently recommended.

HISTOPATHOLOGIC TYPE

The major malignant primary epithelial tumors include the following:

Malignant mixed tumor (carcinoma arising in pleomorphic adenoma), which includes adenocarcinoma and adenoid cystic carcinoma arising in a pleomorphic adenoma (benign mixed tumor).
Adenoid cystic carcinoma, arising *de novo*
Adenocarcinoma, arising *de novo*
Mucoepidermoid carcinoma
Squamous cell carcinoma

HISTOLOGIC GRADE (G)

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated: includes adenoid cystic carcinoma without basaloid (solid) pattern
G3 Poorly differentiated: includes adenoid cystic carcinoma with basaloid (solid) pattern
G4 Undifferentiated

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HISTOLOGIES—CARCINOMA OF THE LACRIMAL GLAND

8010/3 Carcinoma, NOS
8020/3 Carcinoma, undifferentiated, NOS
8021/3 Carcinoma, anaplastic, NOS
8070/3 Squamous cell carcinoma, NOS
8071/3 Squamous cell carcinoma, keratinizing, NOS
8072/3 Squamous cell carcinoma, large cell, nonkeratinizing, NOS
8073/3 Squamous cell carcinoma, small cell, nonkeratinizing
8074/3 Squamous cell carcinoma, spindle cell
8075/3 Squamous cell carcinoma, adenoid
8140/3 Adenocarcinoma, NOS
8200/3 Adenoid cystic carcinoma
8430/3 Mucoepidermoid carcinoma
8562/3 Epithelial-myoepithelial carcinoma
8940/3 Mixed tumor, malignant, NOS
8941/3 Carcinoma in pleomorphic adenoma

CARCINOMA OF THE LACRIMAL GLAND

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____ Laterality: ☐ Bilateral ☐ Left ☐ Right

DEFINITIONS

Clinical	*Pathologic*	**Primary Tumor (T)**	
☐	☐	TX	Primary tumor cannot be assessed
☐	☐	T0	No evidence of primary tumor
☐	☐	T1	Tumor 2.5 cm or less in greatest dimension, limited to the lacrimal gland
☐	☐	T2	Tumor more than 2.5 cm but not more than 5 cm in greatest dimension, limited to the lacrimal gland
☐	☐	T3	Tumor invades the periosteum
☐	☐	T3a	Tumor not more than 5 cm invades the periosteum of the lacrimal gland fossa
☐	☐	T3b	Tumor more than 5 cm in greatest dimension with periosteal invasion
☐	☐	T4	Tumor invades the orbital soft tissues, optic nerve, or globe with or without bone invasion; tumor extends beyond the orbit to adjacent structures, including brain

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)

☐	☐	MX	Distant metastasis cannot be assessed
☐	☐	M0	No distant metastasis
☐	☐	M1	Distant metastasis Biopsy of metastatic site performed ..... ☐Y ..... ☐N Source of pathologic metastatic specimen _____

Stage Grouping

No stage grouping is presently recommended.

Histologic Grade (G)

☐	GX	Grade cannot be assessed
☐	G1	Well differentiated
☐	G2	Moderately differentiated: includes adenoid cystic carcinoma without baseloid (solid) pattern
☐	G3	Poorly differentiated: includes adenoid cystic carcinoma with baseloid (solid) pattern
☐	G4	Undifferentiated

Residual Tumor (R)

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

(continued on reverse side)

Additional Descriptors

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.

Prognostic Indicators (if applicable)

Notes

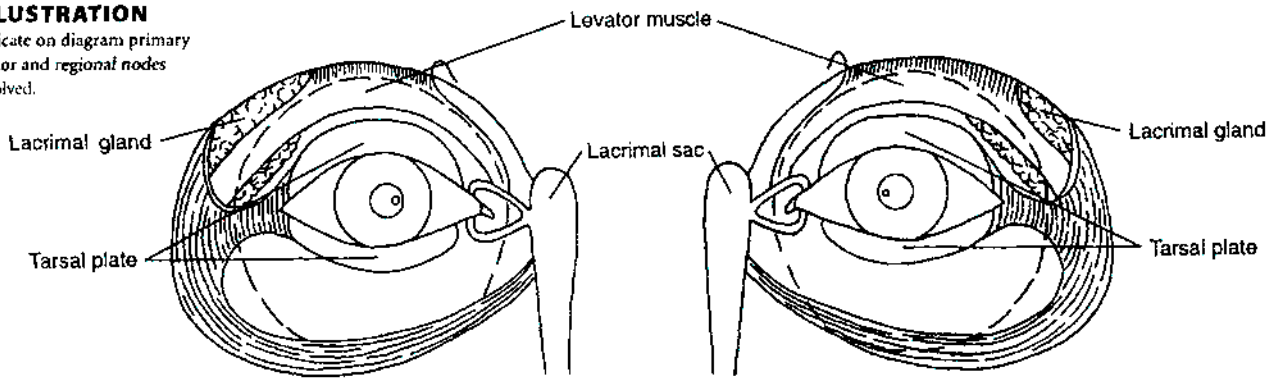
Additional Descriptors

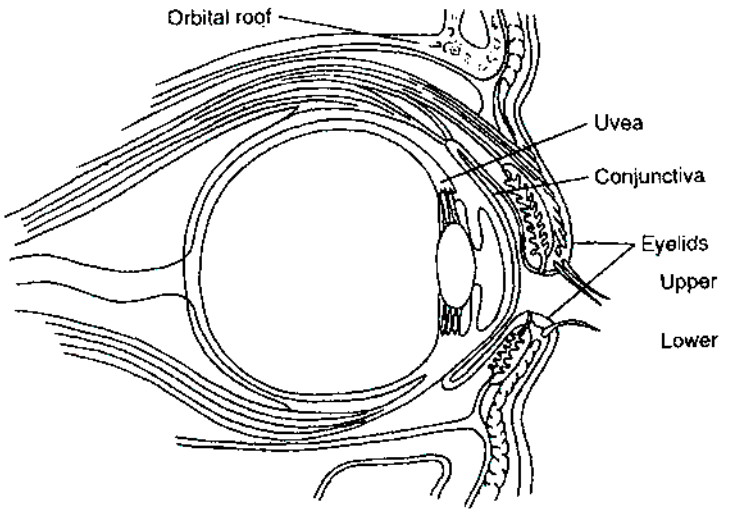
Lymphatic Vessel Invasion (L)
- LX Lymphatic vessel invasion cannot be assessed
- L0 No lymphatic vessel invasion
- L1 Lymphatic vessel invasion

Venous Invasion (V)
- VX Venous invasion cannot be assessed
- V0 No venous invasion
- V1 Microscopic venous invasion
- V2 Macroscopic venous invasion

ILLUSTRATION

Indicate on diagram primary tumor and *regional nodes* involved.





Physician's Signature _____ Date_____

46

Sarcoma of the Orbit

C69.6 Orbit, NOS

C69.8 Overlappning lesion of eye and adnexa

SUMMARY OF CHANGES

- A listing of site-specific categories is now included in T4.

INTRODUCTION

The 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

Primary Site. The orbital sarcomas originate from 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).

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

Local Invasion. The malignancy of the orbit may directly extend into adjacent structures. Therefore, local tumor invasion (T4) would include extension to involve the eyelid, globe, temporal fossa, nasal cavity and paranasal sinuses, and central nervous system.

Metastatic Sites. Metastatic spread occurs by the bloodstream and lymphatics.

RULES FOR CLASSIFICATION

Clinical Staging. Clinical classification should be based on the symptoms and signs related to loss of vision and visual field, degree of global displacement and loss of extraocular motility, and degree of compressive optic neuropathy. Diagnostic tests should include ultrasonography, computed tomography, magnetic resonance imaging, and other imaging procedures when indicated.

Pathologic Staging. The nature of the histopathology specimen (fine-needle aspiration biopsy, excisional biopsy, lumpectomy, or total excision) should be noted. Pathologic classification is based on the specific histopathology of the tumor, its differentiation (grade), and the extent of removal (evaluation of its excisional margins). In total excision specimens, evaluation of the surgical margins should be mandatory.

DEFINITION OF TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 15 mm or less in greatest dimension
T2	Tumor more than 15 mm in greatest dimension without invasion of globe or bony wall
T3	Tumor of any size with invasion of orbital tissues and/or bony walls
T4	Tumor invasion of globe or periorbital structure, such as eyelids, temporal fossa, nasal cavity and paranasal sinuses, and/or central nervous system

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)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastatsis

STAGE GROUPING

No stage grouping is presently recommended.

HISTOPATHOLOGIC TYPE

Malignancies of the orbit primarily include a broad spectrum of malignant soft tissue tumors.

HISTOLOGIC GRADE (G)

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

BIBLIOGRAPHY

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HISTOLOGIES—SARCOMA OF THE ORBIT

8800/3 Sarcoma, NOS
8801/3 Spindle cell sarcoma
8802/3 Giant cell sarcoma
8803/3 Small cell sarcoma
8804/3 Epithelioid sarcoma
8805/3 Undifferentiated sarcoma
8806/3 Desmoplastic small round cell tumor
8810/3 Fibrosarcoma, NOS
8811/3 Fibromyxosarcoma
8812/3 Periosteal fibrosarcoma
8813/3 Fascial fibrosarcoma
8814/3 Infantile fibrosarcoma
8815/3 Solitary fibrous tumor, malignant
8830/3 Malignant fibrous histiocytoma
8840/3 Myxosarcoma
8850/3 Liposarcoma, NOS
8851/3 Liposarcoma, well differentiated
8852/3 Myxoid liposarcoma
8853/3 Round cell liposarcoma
8854/3 Pleomorphic liposarcoma
8855/3 Mixed liposarcoma
8857/3 Fibroblastic liposarcoma
8858/3 Dedifferentiated liposarcoma
8890/3 Leiomyosarcoma, NOS
8891/3 Epithelioid leiomyosarcoma
8896/3 Myxoid leiomyosarcoma
8900/3 Rhabdomyosarcoma, NOS
8901/3 Pleomorphic rhabdomyosarcoma, adult type
8902/3 Mixed type rhabdomyosarcoma
8910/3 Embryonal rhabdomyosarcoma, NOS
8912/3 Spindle cell rhabdomyosarcoma
8920/3 Alveolar rhabdomyosarcoma
8963/3 Malignant rhabdoid tumor
9040/3 Synovial sarcoma, NOS
9044/3 Clear cell sarcoma, NOS
9050/3 Mesothelioma, malignant
9120/3 Hemangiosarcoma
9130/3 Hemangioendothelioma, malignant
9133/3 Epithelioid hemangioendothelioma
9140/3 Kaposi's sarcoma
9150/3 Hemangiopericytoma, malignant
9180/3 Osteosarcoma, NOS
9181/3 Chondroblastic osteosarcoma
9182/3 Fibroblastic osteosarcoma
9184/3 Osteosarcoma in Paget disease of bone
9220/3 Chondrosarcoma, NOS
9231/3 Myxoid chondrosarcoma
9240/3 Mesenchymal chondrosarcoma
9243/3 Dedifferentiated chondrosarcoma
9250/3 Giant cell tumor of bone, malignant
9260/3 Ewing sarcoma
9370/3 Chordoma, NOS
9490/3 Ganglioneuroblastoma
9500/3 Neuroblastoma, NOS
9501/3 Medulloepithelioma, NOS
9502/3 Teratoid medulloepithelioma
9503/3 Neuroepithelioma, NOS

SARCOMA OF THE ORBIT

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____ Laterality: ☐ Bilateral ☐ Left ☐ Right

DEFINITIONS

Clinical	*Pathologic*	**Primary Tumor (T)**	
☐	☐	TX	Primary tumor cannot be assessed
☐	☐	T0	No evidence of primary tumor
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☐	☐	T4	Tumor invasion of globe or periorbital structure, such as eyelids, temporal fossa, nasal cavity and paranasal sinuses, and/or central nervous system

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)

☐	☐	MX	Distant metastasis cannot be assessed
☐	☐	M0	No distant metastasis
☐	☐	M1	Distant metastasis

Biopsy of metastatic site performed ..... ☐Y ..... ☐N

Source of pathologic metastatic specimen _____

Stage Grouping

No stage grouping is presently recommended.

Histologic Grade (G)

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

Residual Tumor (R)

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

(continued on reverse side)

Additional Descriptors

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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- ☐ **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.

Prognostic Indicators (if applicable)

Notes

Additional Descriptors

Lymphatic Vessel Invasion (L)

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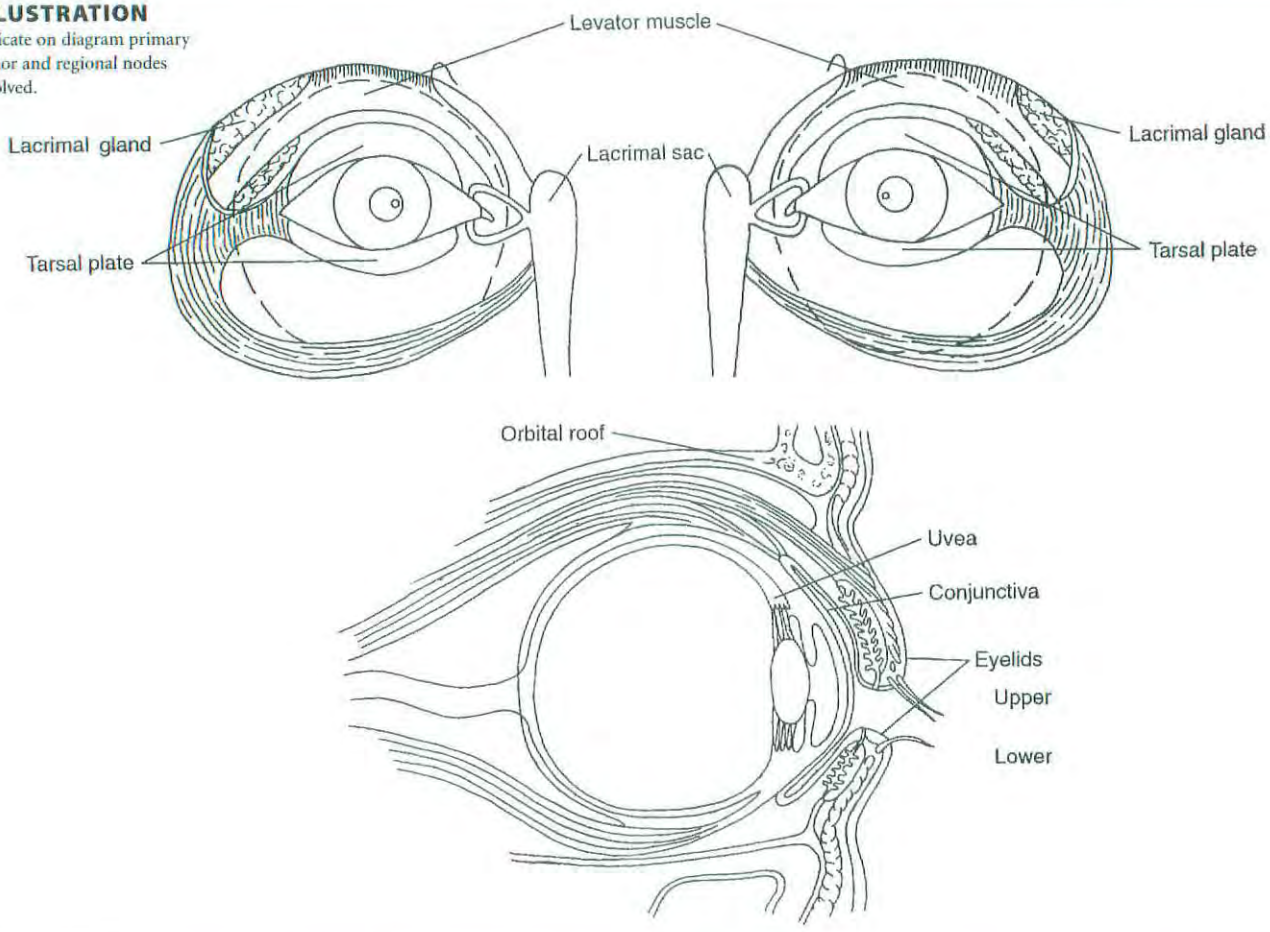
L1 Lymphatic vessel invasion

Venous Invasion (V)

VX Venous invasion cannot be assessed
V0 No venous invasion
V1 Microscopic venous invasion
V2 Macroscopic venous invasion

ILLUSTRATION

Indicate on diagram primary tumor and regional nodes involved.



Physician's Signature _____ Date _____

PART XI
Central Nervous System

47

Brain and Spinal Cord

Code	*Location*	*Diagnosis*
C70.0	Cerebral meninges	Meningioma
C71.0	Cerebrum	Astrocytoma
C71.1	Frontal lobe	Anaplastic astrocytoma
C71.2	Temporal lobe	Glioblastoma
C71.3	Parietal lobe	Oligodendroglioma
C71.4	Occipital lobe	Ganglioglioma
C71.5	Ventricle NOS	Ependymoma
C71.6	Cerebellum NOS	Central neurocytoma
C71.7	Brain stem	Pilocytic astrocytoma
C71.8	Overlapping lesion of brain	Medulloblastoma
C71.9	Brain NOS	Brain stem glioma
C72.0	Spinal cord	Any, if location is not specified
C72.1	Cauda equina	Any, involving more than one site
C72.2	Olfactory nerve	Astrocytoma, ependymoma
C72.3	Optic nerve	Ependymoma
C72.4	Acoustic/vestibular nerve	Esthesioneuroblastoma
C72.5	Cranial nerve, NOS	Optic glioma
C72.8	Overlapping lesion of brain and central nervous system	Vestibular schwannoma Schwannoma
C72.9	Nervous system, NOS	PNET, CNS lymphoma
C75.1	Pituitary gland	
C75.2	Craniopharyngeal duct	
C75.3	Pineal gland	

SUMMARY OF CHANGES

- Central Nervous System Tumors continue to have no TNM designation.

INTRODUCTION

Attempts at developing a TNM-based classification and staging system for tumors of the central nervous system (CNS) have largely been unsuccessful. Previous editions of this manual had proposed a system that was used with poor compliance and proved not to be particularly useful as a predictor of outcome in clinical trials for the management of patients with primary CNS tumors. The reasons for this are several and have to do with the fact that tumor size is significantly less relevant than tumor histology and the location of the tumor, so that the T classification is less pertinent than the biologic nature of the tumor tissue itself. Because the brain and spinal cord have no lymphatics, the N classification does not apply at all, as there are no lymph nodes that can be identified in either classification or staging. An M classification is not pertinent to the majority of neoplasms that affect the central nervous system, because most patients with tumors of the central nervous system do not live long enough to develop metastatic disease (except for some pediatric tumors that tend to "seed" through the cerebrospinal fluid spaces).

Many important studies have been done regarding the most common tumors affecting the brain and spinal cord, and a variety of prognostic factors have been identified. Unfortunately, these factors do not easily fall into the usual categories that have traditionally been part of the American Joint Committee on Cancer (AJCC) TNM system.

For those reasons, it was the recommendation of the CNS Tumor Task Force that a formal classification and staging system not be attempted at this time. This chapter, however, will attempt to highlight what is known about prognostic factors in tumors of the central nervous system. (Table 47.1).

TABLE 47.1. Prognostic factors in CNS tumors

Histology
Pathologic grade and accuracy of diagnosis
Presence and extent of necrosis
Presence of gemistocytes
Proliferative fraction
Presence of oligodendroglial component
Presence or absence of cells in mitosis
Age of patient
Functional neurologic status
Karnofsky Performance Score
Symptom presentation and duration before diagnosis
Presentation with seizure, long duration are favorable prognostic factors
Location of tumor
Unifocal or multifocal
Primary or recurrent tumor
Extent of resection
Biopsy, subtotal, radical removal
Metastatic spread
CNS or extraneural
Patterns of enhancement on imaging studies

PROGNOSTIC FACTORS IN CNS TUMORS

Tumor Histology. The histology of tumors that affect the brain and spinal cord is by far the most important variable with regard to prognosis, and in many cases it determines the treatment modalities that are employed. The latest World Health Organization (WHO) classification system has combined tumor nomenclature with an associated grading system, so the actual histologic diagnosis directly correlates with the histologic grade of the tumor. This should clarify some of the inconsistencies that existed in the past when a number of different grading systems, each slightly different from the others, were used. The most common histologies for brain and spinal cord tumors are given in Table 47.2, along with the tumor grade for each different diagnostic category. *Note:* The histologic grade code used for staging purposes is *not* the same code that is assigned as the differentiation code in the sixth digit of the ICD-O morphology code.

Age of the Patient. Most retrospective outcome studies of brain tumor therapy show that the age of the patient at the time of diagnosis is one of the most powerful predictors of outcome. This fact holds true for the gliomas, which are the most common primary brain tumors, and for most other tumors that affect the adult population, including most metastatic tumors to the brain. There are, however, some childhood tumors that have a very poor prognosis, are inherently high grade, and rapidly progress to a fatal outcome. Some metastatic tumors, such as melanoma, occur in younger patients and also violate this general statement with regard to the specific effect of age on prognosis.

Extent of Tumor Resection. In patients who are treated surgically for tumors of the central nervous system, the extent of resection is often directly correlated with the outcome. This is a less powerful predictor than tumor histology or age, but most retrospective studies confirm that extent of removal is positively correlated with survival. For this reason, documentation of whether a surgical tumor removal is "gross total," "subtotal," or "biopsy only," is useful in determining future therapy and prognosis. Any staging system to be developed for CNS tumors should take into account, in a systematic and clearly documented fashion, extent of removal or tumor residual.

Tumor Location. Because of the differential *importance* of various areas of the brain, the location of a given tumor affecting the brain can have a major impact on the functional outcome, survival, and nature of therapy. The location codes available for tumors affecting the central nervous system in the ICD-O and ICD-10 manuals are generally satisfactory, and they offer the advantage of consistency to the records of patients with CNS tumors.

Functional Neurologic Status. Another important prognostic factor in most retrospective studies of CNS tumors is the functional neurologic status of the patient at the time of diagnosis. This traditionally has been estimated using the Karnofsky Performance Scale, which is reproducible, is well known by most investigators, and is in common use for stratification of patients entering clinical trials for the treatment of brain tumors. The outcome and prognosis of patients correlate fairly well with functional neurologic status, and once again, any staging system should include a validated and reliable measure of this parameter. Other measures of outcome, both cognitive and functional, are increasingly used in studies of CNS tumors.

Metastatic Spread. Tumors affecting the central nervous system rarely develop extraneural metastases, probably because of inherent biologic characteristics of these tumors, and also because the brain does not have a well-developed lymphatic drainage system. In addition, many patients with tumors of the central nervous system have a short life expectancy, which further limits the likelihood of metastatic spread. Certain tumors do spread through cerebrospinal fluid (CSF) pathways, and such spread has a major impact on survival. Dissemination through the CSF pathway is a hallmark of certain childhood tumors, many of which carry a poor prognosis; this phenomenon, however, is rarely seen in adult patients with the more common CNS tumors. Primary lymphomas of the central nervous system may spread along the craniospinal axis and sometimes exhibit intraocular dissemination. Although metastatic spread is of importance in certain instances, its overall impact in staging is relatively minor. The M category, however, should be part of any classification and staging system that is developed in the future for CNS tumors, and it should differentiate between extra-

TABLE 47.2. Histologies for brain and spinal cord tumors: WHO classification of tumors of the nervous system

Tumors of Neuroepithelial Tissue	
Astrocytic tumors	
Diffuse astrocytoma	9400/3[1]
Fibrillary astrocytoma	9420/3
Protoplasmic astrocytoma	9410/3
Gemistocytic astrocytoma	9411/3
Anaplastic astrocytoma	9401/3
Glioblastoma	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Pilocytic astrocytoma	9421/3
Pleomorphic xanthoastrocytoma	9424/3
Subependymal giant cell astrocytoma	9384/1
Oligodendroglial tumors	
Oligodendroglioma	9450/3
Anaplastic oligodendroglioma	9451/3
Mixed gliomas	
Oligoastrocytoma	9382/3
Anaplastic oligoastrocytoma	9382/3
Ependymal tumors	
Ependymoma	9391/3
Cellular	9391/3
Papillary	9393/3
Clear cell	9391/3
Tanycytic	9391/3
Anaplastic ependymoma	9392/3
Myxopapillary ependymoma	9394/1
Subependymoma	9383/1
Choroid plexus tumors	
Choroid plexus papilloma	9390/0
Choroid plexus carcinoma	9390/3
Glial tumors of uncertain origin	
Astroblastoma	9430/3
Gliomatosis cerebri	9381/3
Chordoid glioma of the third ventricle	9444/1
Neuronal and mixed neuronal-glial tumors	
Gangliocytoma	9492/0
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	9493/0
Desmoplastic infantile astrocytoma/ganglioglioma	9412/1
Dysembryoplastic neuroepithelial tumor	9413/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Central neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma of the filum terminale	8680/1
Neuroblastic tumors	
Olfactory neuroblastoma (aesthesioneuroblastoma)	9522/3
Olfactory neuroepithelioma	9523/3
Neuroblastomas of the adrenal gland and sympathetic nervous system	9500/3
Pineal parenchymal tumors	
Pineocytoma	9361/1
Pineoblastoma	9362/3
Pineal parenchymal tumor of intermediate differentiation	9362/3
Embryonal tumors	
Medulloepithelioma	9501/3
Ependymoblastoma	9392/3
Medulloblastoma	9470/3
Desmoplastic medulloblastoma	9471/3
Large cell medulloblastoma	9474/3
Medullomyoblastoma	9472/3
Melanotic medulloblastoma	9470/3
Supratentorial primitive neuroectodermal tumor (PNET)	9473/3
Neuroblastoma	9500/3
Ganglioneuroblastoma	9490/3
Atypical teratoid/rhabdoid tumor	9508/3
Tumors of Peripheral Nerves	
Schwannoma	
(neurilemmoma, neurinoma)	9560/0
Cellular	9560/0
Plexiform	9560/0
Melanotic	9560/0
Neurofibroma	9540/0
Plexiform	9550/0
Perineurioma	9471/0
Intraneural perineurioma	9571/0
Soft tissue perineurioma	9571/0
Malignant peripheral nerve sheath tumor (MPNST)	9540/3
Epithelioid	9540/3
MPNST with divergent mesenchymal and / or epithelial differentiation	9540/3
Melanotic	9540/3
Melanotic psammomatous	9540/3
Tumors of the Meninges	
Tumors of meningothelial cells	
Meningioma	9530/0
Meningothelial	9531/0
Fibrous (fibroblastic)	9532/0
Transitional (mixed)	9537/0
Psammomatous	9533/0
Angiomatous	9534/0
Microcystic	9530/0
Secretory	9530/0
Lymphoplasmacyte-rich	9530/0
Metaplastic	9530/0
Clear cell	9538/1
Chordoid	9538/1
Atypical	9539/1
Papillary	9538/3
Rhabdoid	9538/3
Anaplastic meningioma	9530/3
Mesenchymal, non-meningothelial tumors	
Lipoma	8850/0
Angiolipoma	8861/0
Hibernoma	8880/0
Liposarcoma (intracranial)	8850/3
Solitary fibrous tumor	8815/0
Fibrosarcoma	8810/3
Malignant fibrous histiocytoma	8830/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyoma	8900/0
Rhabdomyosarcoma	8900/3
Chondroma	9220/0
Chondrosarcoma	9220/3
Osteoma	9180/0
Osteosarcoma	9180/3
Osteochondroma	9210/0
Hemangioma	9120/0
Epithelioid hemangioendothelioma	9133/1
Hemangiopericytoma	9150/1
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Primary melanocytic lesions	
Diffuse melanocytosis	8728/0
Meningeal melanocytoma	8728/1
Malignant melanoma	8720/3
Meningeal melanomatosis	8728/3
Tumors of uncertain histogenesis	
Hemangioblastoma	9161/1
Lymphomas & Haemopoietic Neoplasms	
Malignant lymphomas (not otherwise specified)	9590/3
Plasmacytoma	9731/3
Granulocytic sarcoma	9930/3
Germ Cell Tumors	
Germinoma	9064/3
Embryonal carcinoma	9070/3
Yolk sac tumor	9071/3
Choriocarcinoma	9100/3
Teratoma	9080/1
Mature	9080/0
Immature	9080/3
Teratoma with malignant transformation	9084/3
Mixed germ cell tumor	9085/3
Tumors of the Sellar Region	
Craniopharyngioma	9350/1
Adamantinomatous	9351/1
Papillary	9352/1
Granular cell tumor	9582/0
Metastatic Tumors	

[1]Morphology code of the International Classification of Diseases for Oncology (ICD-O) and the Systematized Nomenclature of Medicine (SNOMED). Behavior is Coded /0 for benign tumors, /1 for low or uncertain malignant potential or borderline malignancy, /2 for *in situ* lesions, and /3 for malignant tumors.

Source: P. Kleihues and W. Cavenee (Eds.), World Health Organization Classification of Tumours: Pathology and Genetics. Tumours of the Nervous System (Lyon: International Agency for Research on Cancer, 2000).

TABLE 47.3. Prognostic biogenetic markers (under investigation)

Proliferation index—Ki-67(MIB-1), PCNA, bcl-2 expression, cyclin-D1 expression
DNA studies—flow cytometry, DNA index, BrdULI, comparative genomic hybridization
Activation of cellular oncogenes—ras, N-myc, C-myc, pescadillo
Inactivation of tumor suppressor genes—p53, p16(CDKN2A), Rb, PTEN, DMBT1, MDM2, NF2
Allelic loss / loss of heterozygosity (LOH)— chromosomes 10, 22q, 19q, 17p
Cytokine dysregulation—CDK4, EGFR, VEGF, PKC
Chromosomal aberrations—chromosomes 1, 9, 10, 11, 17, 19, and 22
Other molecular observations—telomerase activity and hTERT expression, DNA methyltransferase, double minutes, AgNOR instability

neural metastasis and metastasis within the CNS and CSF pathways.

BRAIN TUMOR SURVIVAL DATA

Data are available from the SEER program for current survival statistics for "brain tumors," a category that includes malignant primary brain tumors (gliomas). For this relatively ill-defined group of patients, there are 17,200 new cases estimated for 2001. Five-year survivals are 30% in adults and 64% in children.

Excellent observational data for malignant gliomas (glioblastomas and malignant [grade 3] gliomas) are available from the Glioma Outcome Project, evaluating 788 patients accrued from 1997 through 2000. The 50% survival for glioblastoma multiforme (GBM) is 10.6 months, and the 96-week survival is 10%. For grade 3 gliomas, 70% have survived 96 weeks. Approximately 11% of the patients were enrolled in clinical trials.

PROGNOSTIC BIOGENETIC MARKERS (UNDER INVESTIGATION)

The field of molecular neuropathology has provided us with a number of potential biogenetic markers that may be useful in staging CNS tumors and in making recommendations for therapy. The discovery of the pivotal role of oncogenes and of the loss of tumor suppressor genes in the tumorigenesis of CNS tumors has led to a flurry of activity that may prove quite fruitful in providing valid biologic markers in these difficult tumors. Table 47.3 provides a glimpse of some of the current markers and techniques under investigation. It is hoped that ways will be found to apply these methods of scientific analysis of tumor growth potential to predict survival more effectively than is possible today.

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PART XII
Lymphoid Neoplasms

12

48

Lymphoid Neoplasms

SUMMARY OF CHANGES

- The Hodgkin lymphoma and non-Hodgkin lymphoma chapters have been combined into one chapter titled " Lymphoid Neoplasms."

INTRODUCTION

Lymphoid malignancies are a diverse and sometimes confusing group of disorders. These malignancies share derivation from B-cells, T-cells, and NK-cells, but they have a wide range of presentations, clinical course, and response to therapy. The incidence of lymphoid malignancies is significant and increasing. Non-Hodgkin lymphomas occur in approximately 55,000 new individuals each year and have been increasing rapidly in incidence over the past several decades. Hodgkin lymphoma occurs in approximately 8,000 new individuals each year in the United States and seems stable in incidence. Approximately 13,000 new cases of multiple myeloma and up to 15,000 new cases of lymphoid leukemias occur annually in the United States.

PATHOLOGY

Lymphoid neoplasms include Hodgkin disease (Hodgkin lymphoma) and B-cell, T-cell, and NK-cell (natural killer cell) neoplasms (collectively known as non-Hodgkin lymphomas [NHL] and lymphoid leukemias). Traditionally, classifications have distinguished between "lymphomas"—neoplasms that typically present with an obvious tumor or mass of lymph nodes or extranodal sites—and "leukemias"—neoplasms that typically involve the bone marrow and peripheral blood, without tumor masses. However, we now know that many B- and T/NK-cell neoplasms may have both tissue masses *and* circulating cells, either in the same patient or from one patient to another. Thus it is artificial to call them different diseases, when in fact they are just different stages or phases of the same disease. For this reason, we now refer to these diseases as lymphoid neoplasms rather than as lymphomas or leukemias, reserving the latter terms for the specific clinical presentation. In the current classification of lymphoid neoplasms, diseases that typically produce tumor masses are called lymphomas, those that typically have only circulating cells are called leukemias, and those that often have both solid and circulating phases are designated lymphoma/leukemia. Finally, plasma cell neoplasms, including multiple myeloma and plasmacytoma, have typically not been considered "lymphomas," but plasma cells are part of the B-cell lineage, and thus these tumors are B-cell neoplasms, which are now included in the classification of lymphoid neoplasms.

Lymphoid neoplasms are malignancies of lymphoid cells. Lymphoid cells include lymphoblasts, lymphocytes, follicle center cells (centrocytes and centroblasts), immunoblasts, and plasma cells. These cells are responsible for immune responses to infections. Immune responses involve recognition by lymphocytes of foreign molecules, followed by proliferation and differentiation to generate either specific cytotoxic cells (T or NK—natural killer—cells) or antibodies (B-cells and plasma cells). Lymphoid cells are normally found in greatest numbers in lymph nodes and in other lymphoid tissues such as Waldeyer's ring (which includes the palatine and lingual tonsils and adenoids), the thymus, Peyer's patches of the small intestine, the spleen, and the bone marrow. Lymphocytes also circulate in the peripheral blood and are found in small numbers in almost every organ of the body, where they either wait to encounter antigens or carry out specific immune reactions. Lymphoid neoplasms may occur in any site to which lymphocytes normally travel. Because lymphocytes normally do travel—in contrast to epithelial cells, for example—it is often impossible to determine the "primary site" of a lymphoid neoplasm or to use a staging scheme that was developed for epithelial cancers, such as the TNM scheme.

For the purposes of coding and staging, lymph nodes, Waldeyer's ring, and spleen are considered *nodal* or *lymphatic* sites. *Extranodal* or *extralymphatic* sites include the bone marrow, the gastrointestinal tract, skin, bone, central nervous system, lung, gonads, ocular adnexae (conjunctiva, lachrymal glands, and orbital soft tissue), liver, kidneys and uterus. Hodgkin lymphoma rarely presents in an extranodal site, but about 25% of non-Hodgkin lymphomas are extranodal at presentation. The frequency of extranodal presentation varies dramatically among different lymphomas, however, with some (mycosis fungoides and MALT lymphomas) being virtually always extranodal and some (follicular lymphoma, B-cell small lymphocytic lymphoma) seldom being extranodal, except for bone marrow involvement.

CLASSIFICATION OF LYMPHOID NEOPLASMS

Many different classification schemes have been proposed for lymphoid neoplasms, and this had led to much confusion on the part of both pathologists and oncologists. Until recently in the United States, a classification called the Working Formulation was used. This scheme had the advantage of being simple, with only 10 categories, and not requiring any special studies such as immunophenotyping or genetic studies. In addition, it provided simple clinical groupings for determining the approach to treatment (low, intermediate, and high clinical grades). Since it was introduced in 1982, advances in understanding of the immune system and of the lymphoid neoplasms have led to the recognition of many new categories of lymphoid neoplasms and the development of better methods for diagnosis and classification—as well as for treatment—and the Working Formulation has become obsolete. In 1994 the International Lymphoma Study Group (ILSG) introduced a new classification, called the Revised European–American Classification of Lymphoid Neoplasms (REAL), which incorporated both morphology, new information such as immunophenotype and genetic features, and clinical features, to define over 25 different categories of lymphoid neoplasms, including Hodgkin lymphoma. More recently, the World Health Organization (WHO) decided to update its Classification of Diseases of the Hematopoietic and Lymphoid Systems and has adopted the REAL classification for lymphoid neoplasms (the WHO classification also includes myeloid and histiocytic neoplasms). The REAL/WHO classification is now the standard for clinical trials in lymphoma (Table 48.1).

The REAL/WHO classification is a list of distinct disease entities, which are defined by a combination of morphology, immunophenotype, and genetic features and which have distinct clinical features. The relative importance of each of these features varies among diseases, and there is no one "gold standard." Morphology remains the first and most basic approach and is sufficient for both diagnosis and classification in many typical cases of lymphoma. Immunophenotyping and—particularly—molecular genetic studies are not needed in all cases, but they are very important in some diseases, are useful in difficult cases, and improve interobserver reproducibility. As mentioned above, the classification includes all lymphoid neoplasms: Hodgkin lymphoma, non-Hodgkin lymphomas, lymphoid leukemias, and plasma cell neoplasms. Both lymphomas and lymphoid leukemias are included, because both solid and circulating phases are present in many lymphoid neoplasms, and drawing a distinction between them is artificial. Thus, B-cell chronic lymphocytic leukemia and B-cell small lymphocytic lymphoma are simply different manifestations of the same neoplasm, as are lymphoblastic lymphomas and acute lymphoblastic leukemias. In addition, Hodgkin lymphoma and plasma cell myeloma are now recognized as lymphoid neoplasms of B-lineage and therefore belong in a compilation of lymphoid neoplasms.

TABLE 48.1. WHO classification of lymphoid neoplasms

B-cell Neoplasms
Precursor B-cell neoplasm
• Precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia)
Mature (peripheral) B-cell neoplasms
• B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
• B-cell prolymphocytic leukemia
• Lymphoplasmacytic lymphoma
• Splenic marginal zone B-cell lymphoma (with or without villous lymphocytes)
• Hairy cell leukemia
• Plasma cell myeloma/plasmacytoma
• Extranodal marginal zone B-cell lymphoma of MALT type
• Nodal marginal zone B-cell lymphoma (with or without monocytoid B cells)
• Follicular lymphoma
• Mantle cell lymphoma
• Diffuse large B-cell lymphoma
• Burkitt lymphoma/Burkitt cell leukemia
T-cell and NK-cell Neoplasms
Precursor T-cell neoplasm
• Precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia)
Mature (peripheral) T/NK-cell neoplasms
• T-cell prolymphocytic leukemia
• T-cell granular lymphocytic leukemia
• Aggressive NK-cell leukemia
• Adult T-cell lymphoma/leukemia (HTLV1+)
• Extranodal NK/T-cell lymphoma, nasal type
• Enteropathy-type T-cell lymphoma
• Hepatosplenic γδ T-cell lymphoma
• Subcutaneous panniculitis-like T-cell lymphoma
• Mycosis fungoides/Sezary syndrome
• Anaplastic large cell lymphoma, T/null cell, primary cutaneous type
• Peripheral T-cell lymphoma, not otherwise characterized
• Angioimmunoblastic T-cell lymphoma
• Anaplastic large cell lymphoma, T/null cell, primary systemic type

Major Categories of Hodgkin Lymphoma

Nodular lymphocyte predominance Hodgkin lymphoma (NLPHL)
Classic Hodgkin lymphoma (CHL)
  Nodular sclerosis Hodgkin lymphoma (NSHL)
  Mixed cellularity Hodgkin lymphoma (MCHL)
  Lymphocyte rich classic Hodgkin lymphoma (LRCHL)
  Lymphocyte depletion Hodgkin lymphoma (LDHL)

T-cell Neoplasms. T-cell neoplasms, other than precursor T-lymphoblastic lymphoma/leukemia and mycosis fungoides, are uncommon in the United States and Europe, accounting for 10%–15% of all non-Hodgkin lymphomas (Table 48.1).

NON-HODGKIN LYMPHOMAS

All newly diagnosed patients with non-Hodgkin lymphomas should have formal documentation of the anatomic disease extent prior to the initial therapeutic intervention; that is, clinical stage must be assigned and recorded. Patients with recurrent disease should not have clinical stage assigned again at the time of relapse, although recording of the anatomic disease extent at the time of recurrence is recommended. The retreatment classification (see the section "General Rules of the TNM System") using "r-stage" may be used for this purpose. However, the clinical stage at diagnosis should not be confused with the "r-stage."

The current anatomic staging classification for non-Hodgkin lymphoma, known as the Ann Arbor classification, was originally developed for Hodgkin lymphoma, and its use was subsequently extended to non-Hodgkin lymphoma. The pattern of disease in Hodgkin lymphoma varies considerably from that encountered in non-Hodgkin lymphoma. Consequently, significant difficulties arose when the Ann Arbor classification was applied to non-Hodgkin lymphoma. However, the Ann Arbor classification has been used in Hodgkin lymphoma and non-Hodgkin lymphoma for over 30 years. It has been accepted as the best means of describing the anatomic disease extent and has been found useful as a universal system for a variety of lymphomas. The AJCC and UICC have adopted the Ann Arbor classification as the official system for classifying the anatomic extent of disease in Hodgkin lymphoma and non-Hodgkin lymphoma.

STAGING

Stage I: Involvement of a single lymph node region (I); or localized involvement of a single extralymphatic organ or site in the absence of any lymph node involvement (IE) (rare in Hodgkin lymphoma).

Stage II: Involvement of two or more lymph node regions on the same side of the diaphragm (II); or localized involvement of a single extralymphatic organ or site in association with regional lymph node involvement with or without involvement of other lymph node regions on the same side of the diaphragm (IIE). The number of regions involved may be indicated by a subscript, as in, for example, II_3.

Stage III: Involvement of lymph node regions on both sides of the diaphragm (III), which also may be accompanied by extralymphatic extension in association with adjacent lymph node involvement (IIIE) or by involvement of the spleen (IIIS) or both (IIIE,S).

Stage IV: Diffuse or disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s). Any involvement of the liver or bone marrow, or nodular involvement of the lung(s). The location of Stage IV disease is identified further by specifying the site according to the notations listed on page 400.

Although anatomic disease extent is one prognostic factor in non-Hodgkin lymphoma, the prognostic factors that form the International Prognostic Index for non-Hodgkin lymphoma (Table 48.4) should be used for treatment decisions along with histologic subtype of lymphoma. Additional factors that have been reported to affect the outcome in preliminary studies include tumor bulk, beta-2 microglobulin, and S-phase fraction.

ANATOMY

The Ann Arbor staging system is further described in the section on Hodgkin lymphoma. It is proposed that for non-Hodgkin lymphoma, the E designation should indicate the presentation of lymphoma in extranodal sites and the lack of an E designation should indicate lymphomas presenting in lymph nodes.

Clinical Staging. Clinical staging includes the careful recording of medical history and physical examination; imaging of chest, abdomen, and pelvis; blood chemistry determination; complete blood count; and bone marrow biopsy (Table 48.2).

TABLE 48.2. Recommendation for the diagnostic evaluation of patients with lymphoma

A. Mandatory procedures
   1. Biopsy, with interpretation by a qualified pathologist
   2. History, with special attention to the presence and duration of fever, night sweats, and unexplained loss of 10% or more of body weight in the previous 6 months
   3. Physical examination
   4. Laboratory tests
      a. Complete blood cell count and platelet count
      b. Erythrocyte sedimentation rate
      c. Liver function tests
   5. Radiographic examinations
      a. Chest X-ray
      b. CT of chest, abdomen, and pelvis
      c. Gallium scan
   6. Bone marrow biopsy

B. Ancillary procedures
   1. Laparotomy and splenectomy if decisions regarding management are likely to be influenced
   2. Liver biopsy (needle), if there is a strong clinical indication of hepatic involvement
   3. Radioisotopic bone scans, in selected patients with bone pain
   4. CT of head and neck in extranodal or nodal presentation to define disease extent
   5. Gastroscopy and/or GI series in patients with GI presentations
   6. MRI spine in patients with suspected spinal involvement
   7. CSF cytology in patients with Stage IV disease and bone marrow involvement, testis involvement, or parameningeal involvement

The basic staging investigation in non-Hodgkin lymphoma includes physical examination, complete blood count, LDH, liver function tests, chest X-ray, CT scan of abdomen and pelvis, and bone marrow biopsy. CT scans of the neck, thorax, abdomen, and pelvis are commonly obtained. In patients presenting with extranodal lymphoma, imaging of the presenting area with either CT or MRI is required to define local disease extent. In patients at high risk for occult CNS involvement, CSF cytology is performed. Gallium scan is commonly used to determine extent of disease and gallium avidity. Biopsies of any suspicious lesions may also be conducted as part of the initial clinical staging, especially if this would alter stage assignment. Bone marrow biopsy is a standard clinical staging investigation. However, liver biopsy is not required as part of clinical staging, unless abnormal liver function occurs in the presence of otherwise limited stage disease.

Pathologic Staging. The use of the term *pathologic staging* is reserved for patients who undergo staging laparotomy with an explicit intent to assess the presence of abdominal disease or to define histologic microscopic disease extent in the abdomen. Staging laparotomy and pathologic staging have been essentially abandoned as useful procedures.

Definition of Lymph Node Regions. The staging classification for non-Hodgkin lymphoma uses the term *lymph node region*. The lymph node regions were defined at the Rye symposium in 1965 and have been used in the Ann Arbor classification. They are not based on any physiological principles but, rather, have been agreed upon by convention. The currently accepted classification of core nodal regions is as follows: right cervical (including cervical, supraclavicular, occipital, and preauricular lymph nodes) nodes and left cervical nodes, right axillary, left axillary, right infraclavicular, and left infraclavicular lymph nodes, mediastinal lymph nodes, hilar lymph nodes, para-aortic lymph nodes, mesenteric lymph nodes, right pelvic lymph nodes, left pelvic lymph nodes, right inguinofemoral lymph nodes and left inguinofemoral lymph nodes. In addition to these core regions, non-Hodgkin lymphoma may involve epitochlear lymph nodes, popliteal lymph nodes, internal mammary lymph nodes, occipital lymph nodes, submental lymph nodes, preauricular lymph nodes, and many other small nodal areas.

Definition of Extranodal Involvement. Lymphomas presenting in extranodal sites should be staged using the E suffix. For example, lymphoma presenting in the thyroid gland with cervical lymph node involvement should be staged as IIE, lymphoma presenting only in cervical lymph nodes as Stage I. Frequently, extensive lymph node involvement is associated with extranodal extension of disease that may also directly invade other organs. Such extension may be described with an E suffix but should not be recorded as Stage IV. For example, mediastinal lymph nodes with lung extension should be classified as Stage IIE disease. Primary lung lymphoma with hilar and mediastinal lymph node involvement should be classified as Stage IIE.

By convention, any involvement of bone marrow, liver, pleura, or CSF calls for classification as Stage IV disease.

Mycosis fungoides is a primary cutaneous T-cell lymphoma with its own staging system. A TNM classification for mycosis fungoides has been in clinical use and should be maintained (Table 48.3).

ANATOMIC STAGING CRITERIA

Clinical Staging. *Lymph node involvement* is demonstrated by (a) clinical enlargement of node when alternative pathology may reasonably be ruled out (suspicious nodes should always be biopsied if treatment decisions are based on their involvement) and (b) enlargement on plain radiograph, CT, or lymphangiography. Nodes larger than 1.5 cm are considered abnormal.

Spleen involvement is demonstrated by unequivocal palpable splenomegaly alone, by equivocal palpable splenomegaly with radiologic confirmation (ultrasound or CT), or by either enlargement or multiple focal defects that are neither cystic nor vascular (radiologic enlargement alone is inadequate).

Liver involvement is demonstrated by multiple focal defects that are neither cystic nor vascular. Clinical enlargement alone, with or without abnormalities of liver function tests, is not adequate. Liver biopsy may be used to confirm the presence of liver involvement in a patient with abnormal liver function tests or when imaging assessment is equivocal.

Lung involvement is demonstrated by radiologic evidence of parenchymal involvement in the absence of other likely causes, especially infection. Lung biopsy may be performed to clarify equivocal cases.

Bone involvement is demonstrated using appropriate imaging studies.

CNS involvement is demonstrated by (a) a spinal intradural deposit or spinal cord or meningeal involvement, which may be diagnosed on the basis of the clinical history and findings supported by plain radiology, CSF examination, myelography, CT, and/or MRI (spinal extradural deposits should be carefully assessed, because they may be the result of soft tissue disease that represents extension from bone metastasis or disseminated disease) and (b) intracranial involvement, which will rarely be diagnosed clinically at presentation. It should be considered on the basis of a space-occupying lesion in the face of disease in additional extranodal sites.

Bone marrow involvement is assessed by an aspiration and bone marrow biopsy.

International Prognostic Index (IPI). The International Non-Hodgkin Lymphoma Prognostic Factors Project used pretreatment prognostic factors in a sample of several thousand patients with aggressive lymphomas treated with doxorubicin-based combination chemotherapy to develop a

TABLE 48.3. TNM(B) classification for mycosis fungoides

T1 Limited patch/plaque	(<10% of skin surface involved)
T2 Generalized patch/plaque	(≥10% of skin surface involved)
T3 Cutaneous tumors	(one or more)
T4 Generalized erythroderma	(with or without patches, plaques, or tumors)
N0 Lymph nodes clinically uninvolved	
N1 Lymph nodes clinically enlarged, histologically uninvolved	
N2 Lymph nodes clinically unenlarged, histologically involved	
N3 Lymph nodes enlarged and histologically involved	
M0 No visceral disease	
M1 Visceral disease present	
B0 No circulating atypical cells (<1000 Sezary cells [CD4+CD7−]/ml)	
B1 Circulating atypical cells (≥1000 Sezary cells [CD4+CD7−]/ml)	

Stage Classification of Mycosis Fungoides

IA	T1	N0	M0
IB	T2	N0	M0
IIA	T1–2	N1	M0
IIB	T3	N0–1	M0
IIIA	T4	N0	M0
IIIB	T4	N1	M0
IVA	T1–4	N2–3	M0
IVB	T1–4	N0–3	M1

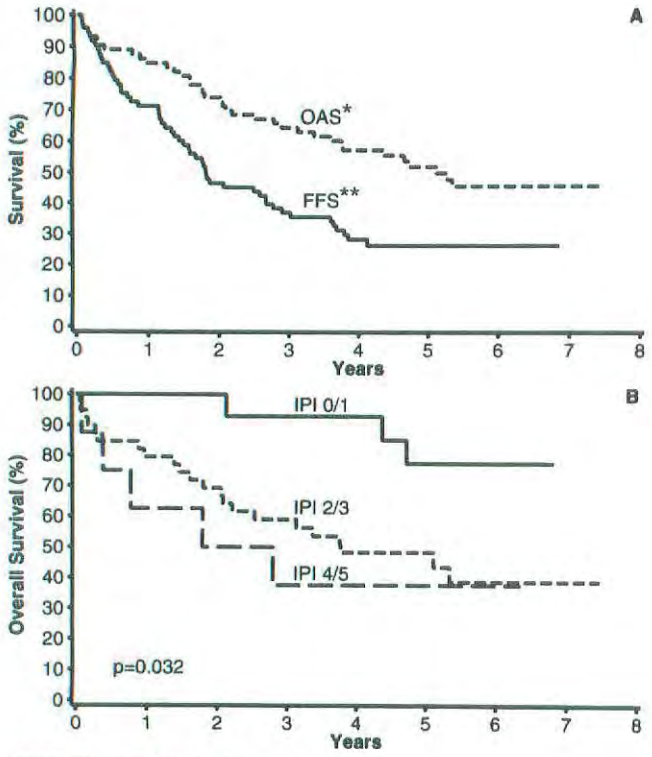
predictive model of outcome for aggressive non-Hodgkin lymphoma. On the basis of factors identified in multivariate analysis of the above data set, the International Prognostic Index (Table 48.4) was proposed. Five pretreatment characteristics were found to be independent statistically significant factors: age in years (60 vs. >60); tumor stage I or II (localized) versus III or IV (advanced); number of extranodal sites of involvement (1 vs. >1); patient's performance status (0 or 1 vs. >2); and serum LDH level (normal vs. abnormal). With the use of these five pretreatment risk factors, patients could be assigned to one of the four risk groups on the basis of the number of presenting risk factors: low (0 or 1), low intermediate (2), high intermediate (3), and high (4 or 5). When patients were analyzed by risk factors, they were found to have very different outcomes with regard to complete response (CR), relapse-free survival (RFS), and overall survival (OS) (Fig. 48.1–48.7). The outcomes indicated that the low-risk patients had an 87% CR rate and an OS rate of 73% at 5 years in contrast to a 44% CR rate and 26% 5-year survival in patients in the high-risk group. A similar pattern of decreasing survival with a number of adverse factors was observed when younger patients only were considered. The IPI was useful in indolent lymphomas, and the validity of the IPI has been confirmed in a population of patients with T-cell lymphomas.

TABLE 48.4. Risk Factors in the International Prognostic Index

Age ≥60 years
Ann Arbor Stage III or IV
Elevated LDH
Reduced performance status (such as ECOG ≥2)
≥ Extranodal sites of disease

HODGKIN LYMPHOMA

A TNM classification system for Hodgkin lymphoma is not practical. Because Hodgkin lymphoma arises in lymph nodes and usually spreads in a contiguous fashion to the other lymph nodes and ultimately to visceral sites or bone marrow, the concepts of T and N classifications cannot be applied. On the other hand, the Ann Arbor classification system has served oncology well, with only minor modifications, since its introduction in 1971. Two major innovations of the Ann Arbor system were the concept of localized extralymphatic disease (the E designation) and the incorporation of pathologic, as well as clinical, staging into the final stage designation. The E designation remains an important concept, although a precise definition has been elusive. Surgical (laparotomy) staging is now only rarely performed in Hodgkin lymphoma, so the important distinction of clinical versus pathologic staging no longer exists. On the other hand, there is now wide acceptance that the concept of "bulky" disease, especially as it applies to the extent of disease in the mediastinum, is important in staging, because it affects prognosis and treatment selection.



*OAS: Overall Survival
**FFS: Failure Free Survival

Fig 48.1. B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma (B-cell CLL/SLL)

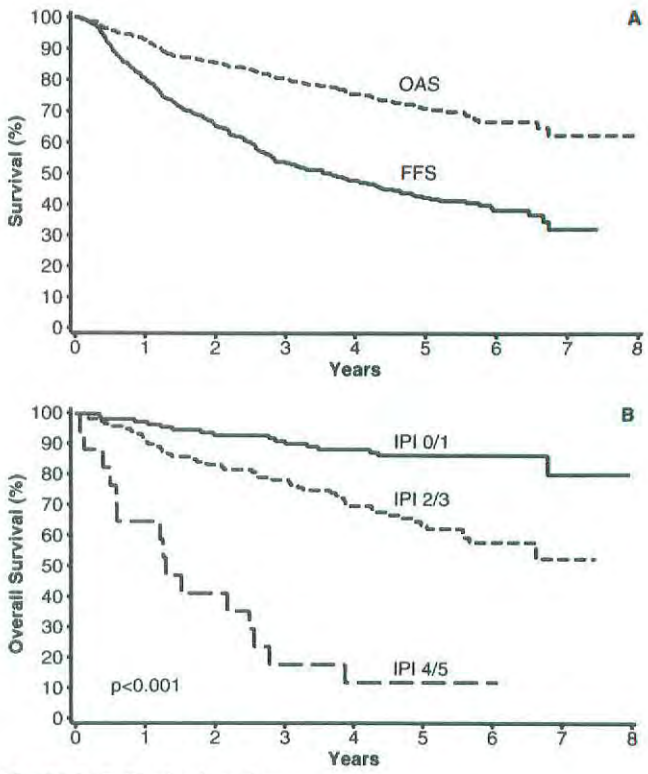


Fig 48.3. Follicular lymphoma

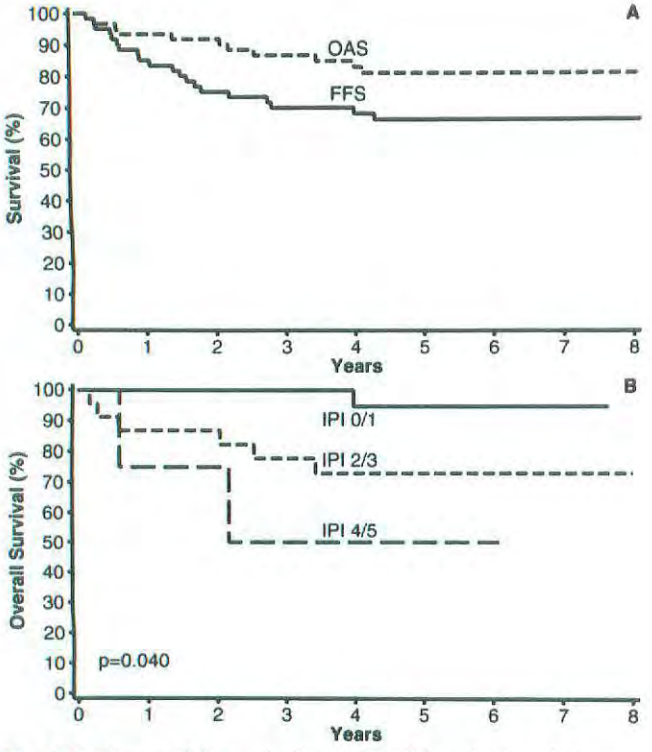


Fig 48.2. Extranodal marginal-zone B-cell lymphoma of mucosa-associated lymphoid tissues (MALT) type (MALT lymphoma)

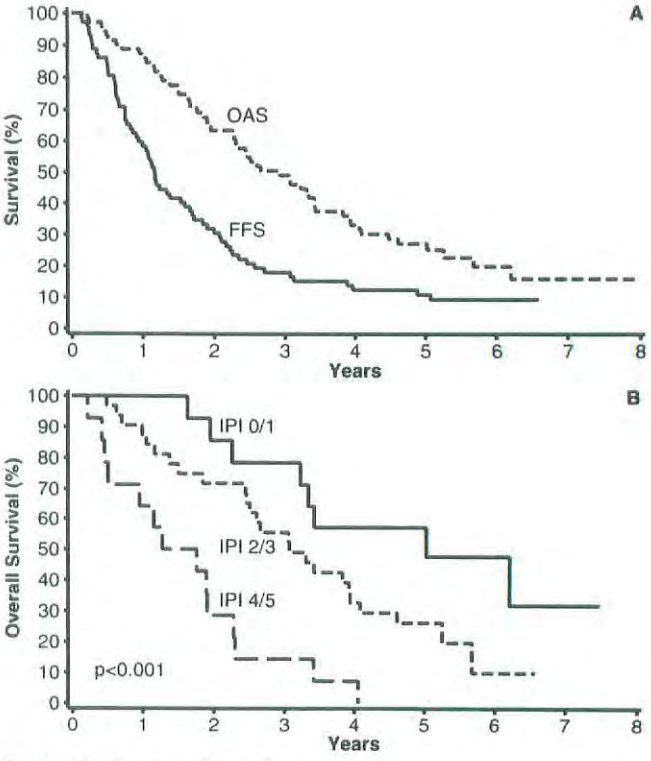


Fig 48.4. Mantle cell lymphoma

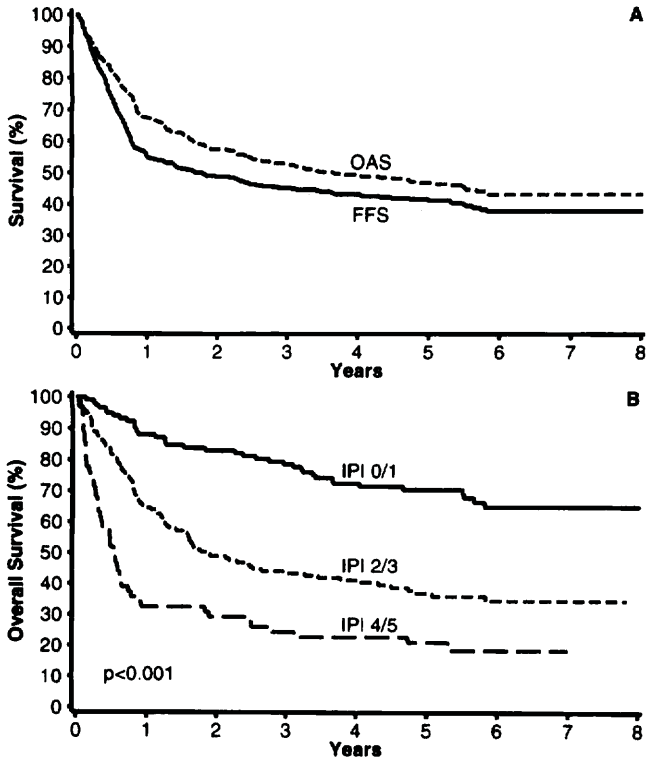


Fig 48.5. Diffuse large B-cell lymphoma

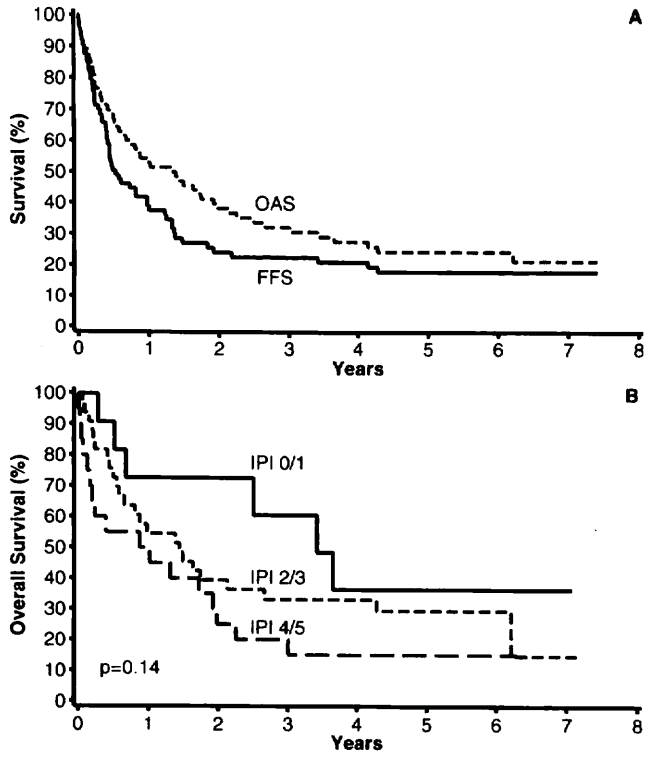


Fig 48.6. Peripheral T-cell lymphoma, not otherwise specified

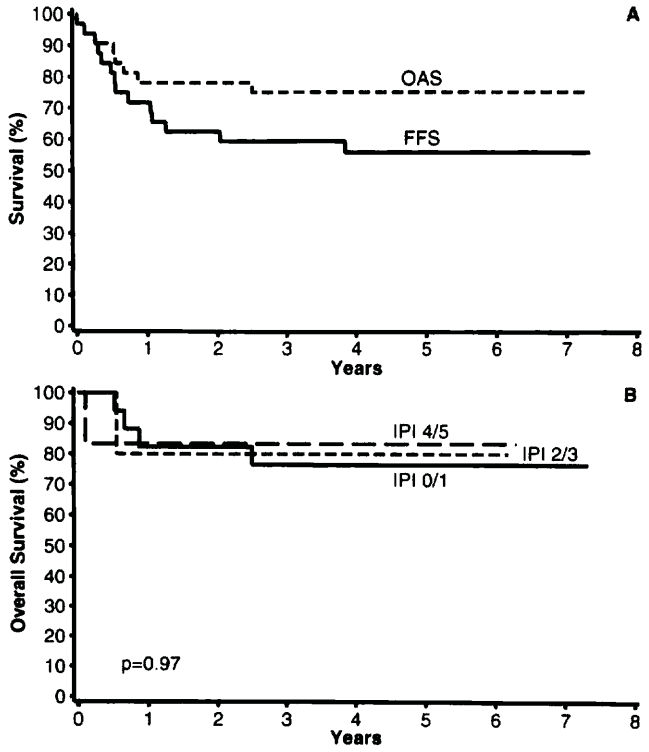


Fig 48.7. Anaplastic large T-cell lymphoma, primary systemic type

STAGING

Staging is based on the result of multiple clinical evaluations, including history, physical examination, blood analysis, imaging studies, the initial biopsy report, and other biopsies as indicated.

The E Lesion. The Ann Arbor system defined E as extralymphatic. Disease in sites such as Waldeyer's ring, the thymus, and the spleen, although extranodal, is not extralymphatic and therefore is not considered to be an E lesion. However, the distinction between certain presentations of extralymphatic disease versus Stage IV disease is not explicit in the Ann Arbor system. For the purpose of this revised AJCC staging system, an E lesion is defined as disease that involves extralymphatic site(s) adjacent to site(s) of lymphatic involvement but in which direct extension is not necessarily demonstrable.

Examples of E lesions include extension into pulmonary parenchyma from adjacent pulmonary hilar or mediastinal lymph nodes; extension into the anterior chest wall *and* into the pericardium from a large mediastinal mass (two areas of extralymphatic involvement); involvement of the iliac bone in the presence of adjacent iliac lymph node involvement; involvement of a lumbar vertebral body in conjunction with para-aortic lymph node involvement; involvement of the pleura as an extension from adjacent internal mammary nodes; and involvement of the thyroid with adjacent cervical lymph node involvement. A pleural or pericardial effusion with negative (or unknown) cytology is not an E lesion.

Lymph Node Involvement. For the purpose of staging, lymph node involvement includes disease affecting lymph nodes in any of the major lymph node regions. This may be based on physical examination, imaging studies, or biopsy.

A modification of the Ann Arbor system is to include the "infraclavicular" region as a part of the axilla, because anatomic landmarks separating these two regions are difficult to define. Other lymphatic structures include the spleen, appendix, Peyer's patches, Waldeyer's ring (the lymphatic tissue of the tonsils, oropharynx, and nasopharynx), and thymus.

Spleen Involvement. Involvement of the spleen is accepted if there is evidence of one or more nodule(s) in the spleen, of any size, on imaging evaluation or if there is histologic involvement documented by biopsy or splenectomy. Splenic enlargement alone (indicated by physical examination or imaging study) is insufficient to support a diagnosis of splenic involvement. Splenic involvement is designated by the letter S.

Hepatic Involvement. Involvement of the liver is accepted if there is evidence of one or more nodule(s) in the liver, of any size, on imaging evaluation or if there is histologic involvement documented by biopsy. Hepatic enlargement alone (indicated by physical examination or imaging study) is insufficient to support a diagnosis of liver involvement. Hepatic involvement is designated by the letter H. Liver involvement is always considered as diffuse extralymphatic disease (Stage IV).

Bone Marrow Involvement. Suspected bone marrow involvement must be documented by biopsy from a clinically/radiographically uninvolved area of bone. Bone marrow involvement is designated by the letter M. Bone marrow involvement is always considered as diffuse extralymphatic disease (Stage IV).

Lung Involvement. Lung involvement (one or more lobes) that represents extension from adjacent mediastinal or hilar lymph nodes is considered extralymphatic extension (E lesion). Pulmonary nodular disease (any number of nodules) is considered as diffuse extralymphatic disease (Stage IV). Lung involvement is designated by the letter L.

Detailed Site Information. Details of specific sites involved are designated by letter subscripts. When the involved sites have been documented by biopsy, a plus (+) sign is added following the letter subscript. If a biopsy has been performed but the tissue/organ is uninvolved, a minus (−) sign is added following the letter subscript. If the tissue/organ is involved clinically but a biopsy has not been performed, neither a plus nor a minus sign is added.

Spleen	S
Pulmonary (lung)	L
Bone marrow	M
Hepatic	H
Pericardium	Pcard
Pleura	P
Waldeyer's (tonsil, naso-oropharynx)	W
Osseous (bone)	O
Gastrointestinal	GI
Skin	D
Soft tissue	Softis
Thyroid	Thy

Stages. Stage I: Involvement of a single lymph node region (I); or localized involvement of a single extralymphatic organ or site in the absence of any lymph node involvement (IE) (rare in Hodgkin lymphoma).

Stage II: Involvement of two or more lymph node regions on the same side of the diaphragm (II); or localized involvement of a single extralymphatic organ or site in association with regional lymph node involvement with or without involvement of other lymph node regions on the same side of the diaphragm (IIE). The number of regions involved may be indicated by a subscript, as in, for example, II_3.

Stage III: Involvement of lymph node regions on both sides of the diaphragm (III), which also may be accompanied by extralymphatic extension in association with adjacent lymph node involvement (IIIE) or by involvement of the spleen (IIIS) or both (IIIE,S).

Stage IV: Diffuse or disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s); or any involvement of the liver or bone marrow, or nodular involvement of the lung(s). The location of Stage IV disease is identified further by specifying the site according to the notations listed above.

Bulky Mediastinal Disease. The extent of mediastinal disease is defined by a ratio between the maximum single width of the mediastinal mass on a standing PA chest radiograph and the maximum intrathoracic diameter on the same radiograph. A ratio greater than or equal to 1/3 defines a large (bulky) mediastinal mass. The presence of a large mediastinal mass is designated by the subscript letter X. The presence of bulky disease in locations other than the mediastinum is not identified.

A and B Classification (Symptoms). Each stage should be classified as either A or B according to the absence or presence of defined constitutional symptoms. These are

1. *Fevers.* Unexplained fever with temperature above 38°C.
2. *Night sweats.* Drenching sweats that require change of bedclothes.
3. *Weight loss.* Unexplained weight loss of more than 10% of the usual body weight in the 6 months prior to diagnosis.

Note: Pruritus alone does not qualify for B classification, nor does alcohol intolerance, fatigue, or a short, febrile illness associated with suspected infections.

Examples. Involvement of the mediastinum and bilateral supraclavicular regions only. The mediastinal mass ratio is 0.25. Weight loss is 15 pounds (usual weight 125 pounds). Bone marrow is involved on biopsy. Stage II_3B_M

Involvement of the mediastinum and bilateral supraclavicular regions. The mediastinal mass ratio is 0.4. There is clinical extension of disease into the anterior chest wall and onto the pericardium. There are no constitutional symptoms. Stage $II_{3XE}A_{Pcard,\ softis}$

Involvement of the right tonsil and right cervical/supraclavicular nodes only. There are no constitutional symptoms. Stage II_2A

Involvement of the right cervical/supraclavicular nodes, Para-aortic nodes and spleen. Unexplained fevers to 39°C. A bone marrow biopsy demonstrates involvement. Stage IV_3B_{M+}

Involvement of the right supraclavicular, mediastinal (ratio = 0.30), and right hilar lymph nodes with extension into the pulmonary parenchyma of the right lung. No constitutional symptoms are present. A bone marrow biopsy indicates no involvement. Stage $II_{3E}A_{L,M-}$

Involvement of the right supraclavicular, mediastinal (ratio = 0.30), and right hilar lymph nodes with a pulmonary nodule in the right middle lobe. No constitutional symptoms are present. A bone marrow biopsy indicates no involvement. Stage $IV_3A_{L,M-}$

Involvement of bilateral supraclavicular and mediastinal lymph nodes and spleen. No constitutional symptoms are present (ratio = 0.42). A bone marrow biopsy indicates no involvement. Stage $III_{3X}A_{S,M-}$

MULTIPLE MYELOMA

Multiple myeloma is a neoplastic disorder characterized by the proliferation of a single clone of plasma cells derived from B-cells. This clone of plasma cells grows in the bone marrow and frequently invades the adjacent bone, producing skeletal destruction that results in bone pain and fractures. Other common clinical findings include anemia, hypercalcemia, and renal insufficiency. Recurrent bacterial infections and bleeding can occur, but the hyperviscosity syndrome is rare. The clone of plasma cells produces monoclonal (M-protein) of IgG or IgM and rarely IgD or IgE or free monoclonal light chains (kappa or lambda) (Bence Jones protein). The diagnosis depends on identification of monoclonal plasma cells in the bone marrow, M-protein in the serum or urine, osteolytic lesions, and a consistent clinical picture with multiple myeloma.

RULES FOR CLASSIFICATION

Diagnosis. Minimal criteria for the diagnosis of multiple myeloma includes a bone marrow containing more than 10% plasma cells or a plasmacytoma plus at least one of the following: (1) an M-protein in the serum (usually > 3 g/dL), (2) an M-protein in the urine, or (3) lytic bone lesions. In addition, the patient must have the usual clinical features of multiple myeloma. Metastatic carcinoma, lymphoma, leukemia, and connective tissue disorders must be excluded in the differential diagnosis. In addition, monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) must be excluded. MGUS is characterized by the absence of symptoms, M-protein < 3 g/dL, fewer than 10% plasma cells in the bone marrow, and no lytic lesions, anemia, hypercalcemia, or renal insufficiency. Smoldering multiple myeloma is characterized by an M-protein > 3 g/dL and > 10% plasma cells in the bone marrow. These patients have no lytic lesions, anemia, or hypercalcemia. The plasma cell labeling index is helpful in differentiating MGUS and SMM from multiple myeloma. An elevated plasma cell labeling index (PCLI) is a strong indication of active multiple myeloma. However, 40% of patients with symptomatic multiple myeloma have a normal PCLI. Monoclonal plasma cells of the same isotype can be detected in the peripheral blood of 80% of patients with active multiple myeloma. Circulating plasma cells either are

absent or are present in only small numbers in MGUS and SMM.

Staging. The Durie-Salmon staging system has been utilized for the past 25 years. Stage I requires hemoglobin > 10.0 g/dL, serum calcium ≤ 12 mg/dL, normal bone X-rays or a solitary bone lesion, IgG < 5 g/dL, IgA < 3 g/dL, and urine M-protein < 4 g/24 h. Stage III includes one or more of the following: hemoglobin < 8.5 g/dL, serum calcium > 12 mg/dL, advanced lytic bone lesions, IgG > 7 g/dL, IgA > 5 g/dL, or urine M-protein > 12 g/24 h. Stage II patients fit neither Stage I nor Stage III. Patients are further subclassed as (A) serum creatinine $<$ 2.0 mg/dL and (B) serum creatinine $\geq$ 2.0 mg/dL. The median survival is approximately 5 years for those with Stage IA disease and is 15 months for those with Stage IIIB disease. This system primarily measures tumor cell burden and has major limitations. Other staging systems have been proposed, but utilization of independent prognostic factors is more useful.

PROGNOSTIC FACTORS

The plasma cell labeling index (PCLI) and beta-2 microglobulin values are the most important prognostic factors. The PCLI is a measurement of the proliferative activity of the plasma cells in myeloma. The monoclonal antibody (BU-1) that reacts with 5-bromo-2-deoxyuridine identifies the cells that synthesize DNA. This antibody does not require denaturation, so fluorescence-conjugated immunoglobulin antisera (kappa and lambda) identify monoclonal plasma cells and plasmacytoid lymphocytes. The high PCLI predicts poor overall and progression-free survival. In multivariate analysis, the PCLI has consistently demonstrated independent prognostic value. Most investigators use a cutoff PCLI value of 1%.

Beta-2 microglobulin correlates with the myeloma tumor burden. A high value predicts poor survival following both conventional chemotherapy and autologous stem cell transplantation. Cytogenetic abnormalities are of major prognostic significance in multiple myeloma. Abnormalities that involve chromosome 11 or 13 and translocations are the most unfavorable prognostic features. Conventional cytogenetics detects abnormalities in only 40% of patients, whereas fluorescence *in situ* hybridization (FISH) demonstrates abnormalities in approximately 80% of patients. CRP (C-reactive protein) is an acute phase reactant and has been used as a surrogate for measurement for Il-6 levels. Il-6 is a potent growth factor for plasma cells. Soluble interleukin-6 receptor (SIl-6R) is an independent predictor of a poor outcome in multiple myeloma. Lactate dehydrogenase (LDH), when elevated, is an important prognostic factor indicating progressive disease. However, fewer than 10% of patients with multiple myeloma have an elevated LDH level.

Plasmablastic Morphology. The presence of 2% or more plasmablasts in the bone marrow is an unfavorable prognostic factor. In addition, the presence of $> 3 \times 10^6$ circulating plasma cells in the peripheral blood is associated with a poor prognosis. Bone marrow angiogenesis is increased in multiple myeloma and represents a prognostic factor. The degree of angiogenesis can be determined by using immunohistochemical staining for factor VIII–related antigen to identify microvessels. The overall survival is significantly longer in patients with low-grade angiogenesis compared to those with high-grade angiogenesis. The expression of K-ras gene is associated with a shorter median survival than is observed in patients with N-ras mutations. Other findings that affect survival are age, hemoglobin value, degree of renal insufficiency, plasma cell content of the bone marrow, and level of CD19+ or CD4+ cells in the peripheral blood.

PEDIATRIC LYMPHOID MALIGNANCY

Diagnosis. Children with NHL usually have Burkitt lymphoma, lymphoblastic lymphoma, or diffuse large B-cell lymphoma. The diagnosis of NHL is most readily established by examination of tissue obtained by open biopsy of the involved area. Histologic, immunophenotypic, cytogenetic, and molecular studies are all helpful in confirming the diagnosis. In cases where the patient is too unstable for general anesthesia, as in the case of a child with a large anterior mediastinal mass, a fine-needle aspiration of the mass may be sufficient to establish the diagnosis. Bone marrow and cerebrospinal fluid examination should be performed early in the workup of a child with suspected NHL, because they may be diagnostic and may preclude the need for more invasive procedures.

Workup. The workup of a child with newly diagnosed NHL should include a history and physical examination, a complete blood count, and a chemistry panel. Diagnostic imaging studies should include CT scans of chest, abdomen, and pelvis and a bone scan. A gallium scan may be helpful in evaluating residual masses. MRI of the base of the skull should be considered in children with cranial nerve palsies. Examination of the cerebrospinal fluid and bone marrow (bilateral iliac crest bone marrow aspiration and biopsy) should be performed in all patients.

Upon completion of the foregoing workup, the child is usually assigned a disease stage according to the St. Jude system described by Murphy (Table 48.5), which was designed to accommodate the noncontiguous nature of disease spread, predominant extranodal involvement, and involvement of the central nervous system and bone marrow that characterize the pediatric NHLs. Stages I and II are considered to represent limited stage disease, whereas Stages III and IV are considered advanced stages.

TABLE 48.5. St. Jude Staging System

Stage I
A single tumor (extranodal) or single anatomic area (nodal), with the exclusion of mediastinum or abdomen
Stage II
A single tumor (extranodal) with regional node involvement
Two or more nodal areas on the same side of the diaphragm
Two single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm
A primary gastrointestinal tract tumor, usually in the ileocecal area, with or without involvement of associated mesenteric nodes only*
Stage III
Two single tumors (extranodal) on opposite sides of the diaphragm
Two or more nodal areas above and below the diaphragm
All primary intrathoracic tumors (mediastinal, pleural, thymic)
All extensive primary intra-abdominal disease*
All paraspinal or epidural tumors, regardless of other tumor site(s)
Stage IV
Any of the above with initial CNS and/or bone marrow involvement**

*A distinction is made between apparently localized GI tract lymphoma and more extensive intra-abdominal disease because of their quite different patterns of survival after appropriate therapy. Stage II disease typically is limited to segment of the gut plus or minus the associated mesenteric nodes only, and the primary tumor can be completely removed grossly by segmental excision. Stage III disease typically exhibits spread to para-aortic and retroperitoneal areas by implants and plaques in mesentery or peritoneum, or by direct infiltration of structures adjacent to the primary tumor. Ascites may be present, and complete resection of all gross tumor is not possible.

**If the marrow involvement is present initially, the number of abnormal cells must be 25% or less in an otherwise normal marrow aspirate with a normal peripheral blood picture.

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HISTOLOGIES—LYMPHOID NEOPLASMS

9590/3	Malignant lymphoma, NOS
9591/3	Malignant lymphoma, non-Hodgkin, NOS
9596/3	Composite Hodgkin and non-Hodgkin lymphoma
9650/3	Hodgkin lymphoma, NOS
9651/3	Hodgkin lymphoma, lymphocyte-rich
9652/3	Hodgkin lymphoma, mixed cellularity, NOS
9653/3	Hodgkin lymphoma, lymphocyte depletion, NOS
9654/3	Hodgkin lymphoma, lymphocyte depletion, diffuse fibrosis
9655/3	Hodgkin lymphoma, lymphocyte depletion, reticular
9659/3	Hodgkin lymphoma, nodular lymphocyte predominance
9661/3	Hodgkin granuloma
9662/3	Hodgkin sarcoma
9663/3	Hodgkin lymphoma, nodular sclerosis, NOS
9664/3	Hodgkin lymphoma, nodular sclerosis, cellular phase
9665/3	Hodgkin lymphoma, nodular sclerosis, grade 1
9667/3	Hodgkin lymphoma, nodular sclerosis, grade 2
9670/3	Malignant lymphoma, small B lymphocytic, NOS
9671/3	Malignant lymphoma, lymphoplasmacytic
9673/3	Mantle cell lymphoma
9675/3	Malignant lymphoma, mixed small and large cell, diffuse
9678/3	Primary effusion lymphoma
9679/3	Mediastinal large B-cell lymphoma
9680/3	Malignant lymphoma, large B-cell, diffuse, NOS
9684/3	Malignant lymphoma, large B-cell, diffuse, immunoblastic, NOS
9687/3	Burkitt lymphoma, NOS
9689/3	Splenic marginal zone B-cell lymphoma
9690/3	Follicular lymphoma, NOS
9691/3	Follicular lymphoma, grade 2
9695/3	Follicular lymphoma, grade 1
9698/3	Follicular lymphoma, grade 3
9699/3	Marginal zone B-cell lymphoma, NOS
9700/3	Mycosis fungoides
9701/3	Sezary syndrome
9702/3	Mature T-cell lymphoma, NOS
9705/3	Angioimmunoblastic T-cell lymphoma
9708/3	Subcutaneous panniculitis-like T-cell lymphoma
9709/3	Cutaneous T-cell lymphoma, NOS
9714/3	Anaplastic large cell lymphoma, T-cell and Null cell type
9716/3	Hepatosplenic γδ (gamma-delta) cell lymphoma
9717/3	Intestinal T-cell lymphoma
9718/3	Primary cutaneous CD30+ T-cell lymphoproliferative disorder
9719/3	NK/T-cell lymphoma, nasal and nasal-type
9727/3	Precursor cell lymphoblastic lymphoma, NOS
9728/3	Precursor cell lymphoblastic lymphoma, NOS
9728/3	Precursor B-cell lymphoblastic lymphoma
9729/3	Precursor T-cell lymphoblastic lymphoma

LYMPHOID NEOPLASMS

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____ Laterality: ☐ Bilateral ☐ Left ☐ Right

Site

☐ Nodal
☐ Extranodal

Multiple Nodal Chains ..... ☐Y..... ☐N

Laterality (if applicable)

☐ Bilateral
☐ Left
☐ Right

Histopathologic Type

☐ Working Formulation
☐ REAL Classification
☐ T-Cell and Putative NK-Cell Neoplasms

Ann Arbor Stage

☐ *Stage I:* Involvement of a single lymph node region (I), or localized involvement of a single extralymphatic organ or site in the absence of any lymph node involvement (IE) (rare in Hodgkin lymphoma).

☐ *Stage II:* Involvement of two or more lymph node regions on the same side of the diaphragm (II), or localized involvement of a single extralymphatic organ or site in association with regional lymph node involvement with or without involvement of other lymph node regions on the same side of the diaphragm (IIE). The number of regions involved may be indicated by a subscript, for example, II_3.

☐ *Stage III:* Involvement of lymph node regions on both sides of the diaphragm (III), which also may be accompanied by extralymphatic extension in association with adjacent lymph node involvement (IIIE) or by involvement of the spleen (III_S) or both ($III_{E,S}$).

☐ *Stage IV:* Diffuse or disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s). Any involvement of the liver or bone marrow, or nodular involvement of the lung(s). The location of Stage IV disease is identified further by designating the specific site.

(continued on reverse side)

Prognostic Factors

Ann Arbor Stage	***Adverse Risk***	***Score***
Ann Arbor Stage	III or IV	1 point ☐
LDH	Greater than maximum normal value	1 point ☐
Age	60 or older	1 point ☐
Extranodal Disease	More than 1 site of extranodal disease	1 point ☐
Performance Status	Depressed performance status, ECOG 2 or greater	1 point ☐
		_____ Total

IPI Score

☐ 0–1 point	Low
☐ 2 points	Low Intermediate
☐ 3 points	High Intermediate
☐ 4–5 points	High

Physician's Signature _____ Date _____

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AJCC Cancer Staging Manual

The *AJCC Cancer Staging Manual* and *Handbook*, prepared by the American Joint Committee on Cancer, are used by physicians and health care professionals throughout the world to facilitate the uniform description of neoplastic diseases. Proper classification and staging allow the physician to determine treatment more appropriately, evaluate results of management more reliably, and compare worldwide statistics reported from various institutions on a local, regional, and national basis more confidently. The fully revised and updated Sixth Edition of the *AJCC Cancer Staging Manual* brings together all currently available information on staging of cancer at various anatomic sites and incorporates newly acquired knowledge on the etiology and pathology of cancer. As more is learned, cancer staging must adapt to accommodate new information and this revised edition provides an evidence-based staging system based upon the established tenets of TNM classification. All of the TNM staging information included in the Sixth Edition is uniform between the AJCC and the UICC (International Union Against Cancer).

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