AMERICAN JOINT COMMITTEE ON CANCER

# AJCC CANCER STAGING HANDBOOK

Seventh Edition

American Joint Committee on Cancer
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# Larynx

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

## *At-A-Glance*

**SUMMARY OF CHANGES**

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



**ANATOMIC STAGE/PROGNOSTIC GROUPS**

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

**ICD-O-3 TOPOGRAPHY CODES**

| | |
|---|---|
| C10.1 | Anterior (lingual) surface of epiglottis |
| C32.0 | Glottis |
| C32.1 | Supraglottis (laryngeal surface) |
| C32.2 | Subglottis |
| C32.8* | Overlapping lesion of larynx |
| C32.9* | Larynx, NOS |

* Stage by location of tumor bulk or epicenter

**ICD-O-3 HISTOLOGY CODE RANGES**

8000–8576, 8940–8950, 8980–8981

## ANATOMY

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

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# Mucosal Melanoma of the Head and Neck

## *At-A-Glance*

**SUMMARY OF CHANGES**

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

**ANATOMIC STAGE/PROGNOSTIC GROUPS**

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

**ICD-O-3 TOPOGRAPHY CODES**

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

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

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

The following topography codes are excluded:

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

**ICD-O-3 HISTOLOGY CODE RANGES**

8720–8790

## ANATOMIC STAGE/PROGNOSTIC GROUPS (*CONTINUED*)

*Adenocarcinoma*

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

C16.2 Body of stomach, proximal 5 cm only*

**Note*: If gastric tumor extends to or above esophagogastric junction.

### ICD-O-3 HISTOLOGY CODE RANGES

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

## INTRODUCTION

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

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

Although at first glance these multiple trade-offs seem to create a less orderly arrangement of cancer classifications within and among stage

**ANATOMIC STAGE/PROGNOSTIC GROUPS (*CONTINUED*)**

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

| | |
|---|---|
| C16.6 | Greater curvature of stomach, NOS |
| C16.8 | Overlapping lesion of stomach |
| C16.9 | Stomach, NOS |

**ICD-O-3 HISTOLOGY CODE RANGES**

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

## INTRODUCTION

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

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

## ANATOMY

**Primary Site.** The stomach is the first division of the abdominal portion of the alimentary tract, beginning at the esophagogastric junction and extending to the pylorus. The proximal stomach is located immediately below the diaphragm and is termed the cardia. The remaining portions are the

# 12

# Small Intestine

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

## *At-A-Glance*

### SUMMARY OF CHANGES

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

### ANATOMIC STAGE/PROGNOSTIC GROUPS

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

### ICD-O-3 TOPOGRAPHY CODES

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

### ICD-O-3 HISTOLOGY CODE RANGES

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

## INTRODUCTION

Although the small intestine accounts for one of the largest surface areas in the human body, it is one of the least common cancer sites in the digestive system, accounting for less than 2% of all malignant tumors of the gastrointestinal tract. A variety of tumors occur in the small intestine, with approximately 25–50% of the primary malignant tumors being adenocarcinomas, depending upon the population surveyed. At the beginning of the twenty-first century, approximately 5,600 new cases of cancer involving the small intestine are seen annually in the USA. The 1,100 deaths predicted

## ANATOMIC STAGE/PROGNOSTIC GROUPS

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

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

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

### ICD-O-3 TOPOGRAPHY CODES

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

### ICD-O-3 HISTOLOGY CODE RANGES

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

## INTRODUCTION

The TNM classification for carcinomas of the colon and rectum provides more detail than other staging systems. Compatible with the Dukes' system, the TNM adds greater precision in the identification of prognostic subgroups. TNM staging is based on the depth of tumor invasion into or beyond the wall of the colorectum (T), invasion of or adherence to adjacent organs or structures (T), the number of regional lymph nodes involved (N), and the presence or absence of distant metastasis (M). The TNM classification applies to both clinical and pathologic staging. Most cancers of the colon and many cancers of the rectum are staged after pathologic examination of a resected specimen. However, patients with

specimens of ascending colon, descending colon, or upper rectum is only partially peritonealized, and the demarcation between the peritonealized surface and the nonperitonealized surface (corresponding to the CRM) of such specimens is not always easily appreciated on pathologic examination. Therefore, the surgeon is encouraged to mark the peritoneal reflection and/or the area of deepest tumor penetration adjacent to a nonperitonealized surface with a clip or suture so that the pathologist may accurately identify and evaluate the CRM.

For mid and distal rectal cancers (subperitoneal location), the entire surface of the resection specimen corresponds to a CRM (anterior, posterior, medial, lateral). For proximal rectal or retroperitoneal colon cancers (ascending, descending, possibly cecum), surgically dissected margins will include those that lie in a retroperitoneal or subperitoneal location as described above (Figure 14.3). For segments of the colon that are entirely covered by a visceral peritoneum (transverse, sigmoid, possibly cecum), the only specimen margin that is surgically dissected is the mesenteric margin, unless the cancer is adherent to or invading an adjacent organ or structure. Therefore, for cancers of the cecum, transverse or sigmoid colon that extends to the cut edge of the mesentery, assignment of a positive CRM is appropriate.

For rectal cancer, the quality of the surgical technique is likely a key factor in the success of surgical outcomes relative to local recurrence and possibly long-term survival. Numerous nonrandomized studies have demonstrated that total mesorectal excision (TME) with adequate surgical clearance around the penetrating edge of the tumor decreases the rate of local relapse. The TME technique entails precise sharp dissection within the areolar plane of loose connective tissue outside (lateral to) the visceral mesorectal fascia in order to remove the rectum. With this approach, all mesorectal soft tissues encasing the rectum, which includes the mesentery

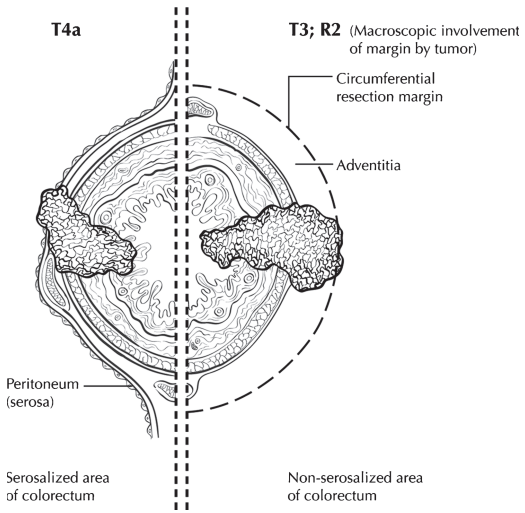
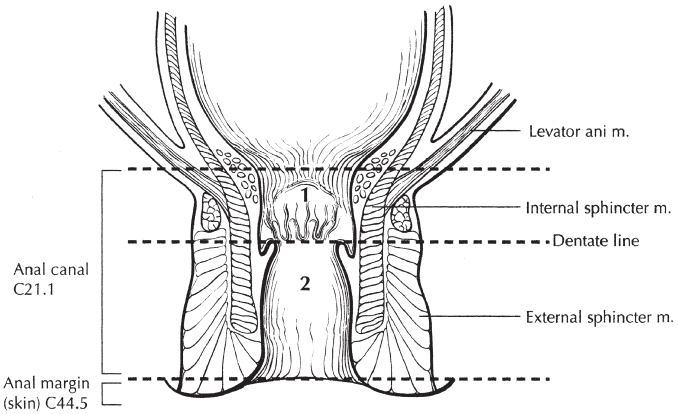



**FIGURE 14.3.** Circumferential resection margin.




1. Transitional epithelium
2. Squamous epithelium devoid of hair and glands (not skin)

**FIGURE 15.1.** Anatomic subsites of the anal canal.

Determination of the anatomic site of origin of carcinomas that overlap the anorectal junction may be problematic. For staging purposes, such tumors should be classified as rectal cancers if their epicenter is located more than 2 cm proximal to the dentate line or proximal to the anorectal ring on digital examination and as anal canal cancers if their epicenter is 2 cm or less from the dentate line. For rectal cancers that extend beyond the dentate line, as for anal canal cancers, the superficial inguinal lymph nodes are among the regional nodal groups at risk of metastatic spread and included in cN/pN analysis (see later).

**Regional Lymph Nodes.** Lymphatic drainage and nodal involvement of anal cancers depend on the location of the primary tumor. Tumors above the dentate line spread primarily to the anorectal, perirectal, and paravertebral nodes, whereas tumors below the dentate line spread primarily to the superficial inguinal nodes.

The regional lymph nodes are as follows (Figure 15.2):

- Perirectal
  - Anorectal
  - Perirectal
  - Lateral sacral
- Internal iliac (hypogastric)
- Inguinal
  - Superficial

All other nodal groups represent sites of distant metastasis.

**Metastatic Sites.** Cancers of the anus may metastasize to any organs, but the liver and lungs are the distal organs that are most frequently involved. Involvement of the abdominal cavity is not unusual.

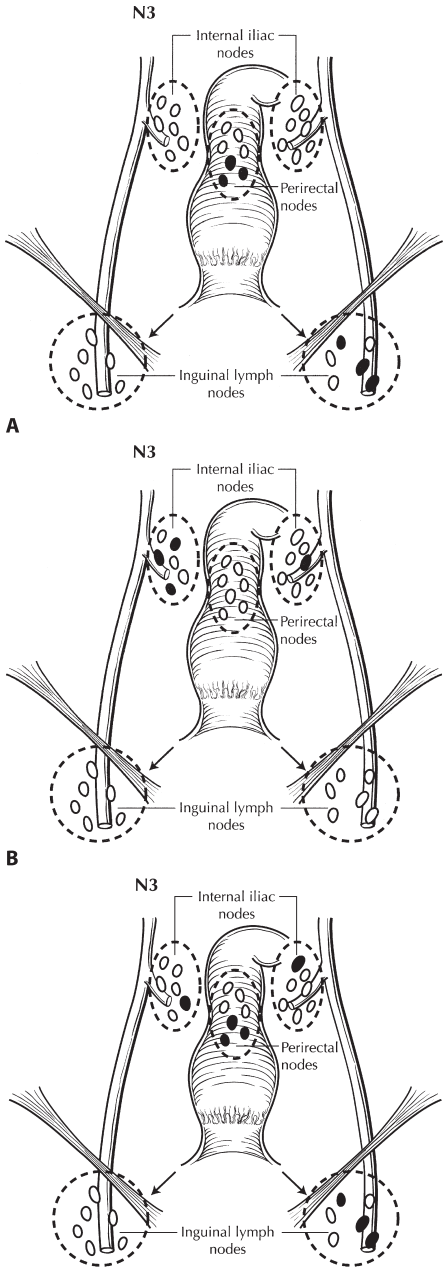



**FIGURE 15.10.** (**A**) N3 is defined as metastasis in perirectal and inguinal lymph nodes (as illustrated) and/or bilateral internal iliac and/or inguinal lymph nodes. (**B**) N3: metastases in bilateral internal iliac lymph nodes. (**C**) N3: metastases in bilateral internal iliac *and* inguinal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

# 16

# Gastrointestinal Stromal Tumor

## *At-A-Glance*



### SUMMARY OF CHANGES

- This staging system is new for the seventh edition

### ANATOMIC STAGE/PROGNOSTIC GROUPS

*Gastric GIST**

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

*Small Intestinal GIST***

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

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

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

### ICD-O-3 TOPOGRAPHY CODES

| | |
|---|---|
| C15.0–C15.9 | Esophagus |
| C16.0–C16.9 | Stomach |
| C17.0–C17.2, C17.8–C17.9 | Small intestine |
| C18.0–C18.9 | Colon |
| C19.9 | Recto-sigmoid junction |
| C20.9 | Rectum |
| C48.0–C48.8 | Retroperitoneum and Peritoneum |

### ICD-O-3 HISTOLOGY CODE RANGES

8935, 8936

**TABLE 16.2.** Disease progression in small intestinal GIST

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

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



## DEFINITIONS OF TNM (FOR GISTS AT ALL SITES)

***Primary Tumor (T)***

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

***Regional Lymph Nodes (N)***

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

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

***Distant Metastasis (M)***

| | |
|---|---|
| M0 | No distant metastasis |
| M1 | Distant metastasis |

## HISTOPATHOLOGIC GRADE

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

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

**ICD-O-3 TOPOGRAPHY CODES**

C22.0 Liver
C22.1 Intrahepatic bile duct

**ICD-O-3 HISTOLOGY CODE RANGES**

8170–8175

## INTRODUCTION

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

## ANATOMY

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

# 19

# Intrahepatic Bile Ducts

## *At-A-Glance*

### SUMMARY OF CHANGES

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



### ANATOMIC STAGE/PROGNOSTIC GROUPS

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

### ICD-O-3 TOPOGRAPHY CODES

| | |
|---|---|
| C22.0 | Liver |
| C22.1 | Intrahepatic bile duct |

### ICD-O-3 HISTOLOGY CODE RANGES

8160, 8161, 8180

## INTRODUCTION

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

Tumors of intrahepatic bile duct origin represent 15–20% of all primary liver malignancies. The tumors of the bile ducts can be anatomically subdivided into three categories including intrahepatic, perihilar, and

the liver edge is more densely adherent to the liver (cystic plate) and much of this is often left behind at the time of cholecystectomy. For this reason, partial hepatic resection incorporating portions of segments IVb and V is undertaken for some cases. Primary carcinomas of the cystic duct are included in this staging classification schema.

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

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

## RULES FOR CLASSIFICATION

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



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

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

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

The extent of resection (R0, complete resection with grossly and microscopically negative margins of resection; R1, grossly negative but

# 23

# Ampulla of Vater

## *At-A-Glance*

**SUMMARY OF CHANGES**

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

**ANATOMIC STAGE/PROGNOSTIC GROUPS**

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

**ICD-O-3 TOPOGRAPHY CODES**

C24.1 Ampulla of Vater

**ICD-O-3 HISTOLOGY CODE RANGES**

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

## INTRODUCTION

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



## ANATOMY

**Primary Site.** The ampulla is a small dilated duct less than 1.5-cm long, formed in most individuals by the union of the terminal segments of the pancreatic and common bile ducts. In 42% of individuals, however,

| ANATOMIC STAGE/PROGNOSTIC GROUPS | | | |
|---|---|---|---|
| Stage 0 | Tis | N0 | M0 |
| Stage IA | T1 | N0 | M0 |
| Stage IB | T2 | N0 | M0 |
| Stage IIA | T3 | N0 | M0 |
| Stage IIB | T1 | N1 | M0 |
| | T2 | N1 | M0 |
| | T3 | N1 | M0 |
| Stage III | T4 | Any N | M0 |
| Stage IV | Any T | Any N | M1 |

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

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

## HISTOLOGIC GRADE (G)

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

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

## HISTOPATHOLOGIC TYPE

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

- Severe ductal dysplasia/carcinoma in situ (PanIn III; pancreatic intraepithelial neoplasia)
- Ductal adenocarcinoma
- Mucinous noncystic carcinoma
- Signet ring cell carcinoma
- Adenosquamous carcinoma

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

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

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

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

**ANATOMIC STAGE/PROGNOSTIC GROUPS**

| **Occult carcinoma** | **TX** | **N0** | **M0** |
|---|---|---|---|
| Stage 0 | Tis | N0 | M0 |
| Stage IA | T1a | N0 | M0 |
| | T1b | N0 | M0 |
| Stage IB | T2a | N0 | M0 |
| Stage IIA | T2b | N0 | M0 |
| | T1a | N1 | M0 |
| | T1b | N1 | M0 |
| | T2a | N1 | M0 |
| Stage IIB | T2b | N1 | M0 |
| | T3 | N0 | M0 |
| Stage IIIA | T1a | N2 | M0 |
| | T1b | N2 | M0 |
| | T2a | N2 | M0 |
| | T2b | N2 | M0 |
| | T3 | N1 | M0 |

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

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

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

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

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

**Restaging of Recurrent Tumors.** The same staging should be used when a patient requires restaging of sarcoma recurrence. Such reports should specify whether patients have primary lesions or lesions that were previously treated and have subsequently recurred. The identification and reporting of etiologic factors such as radiation exposure and inherited or genetic syndromes are encouraged.

## DEFINITIONS OF TNM

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

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

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

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

## ANATOMIC STAGE/PROGNOSTIC GROUPS

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

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

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

Finally, the new N staging definitions are congruent with Head and Neck staging and reflect recent data that suggests that prognosis is inversely correlated with increasing nodal disease.

## DEFINITIONS OF TNM

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



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

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

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

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

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

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

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

| ***Distant Metastasis (M)*** | |
|---|---|
| M0 | No distant metastases |
| M1 | Distant metastases |

## ANATOMIC STAGE/PROGNOSTIC GROUPS

Patients with primary cSCC or other cutaneous carcinomas with no evidence (clinical, radiologic, or pathologic) of regional or distant metastases are divided into two stages: Stage I for tumors measuring ≤2 cm in size and Stage II for those that are greater than 2 cm in size. In instances where there is clinical concern for extension of tumor into bone and radiologic evaluation has been performed (and is negative), these data may be included to support the Stage I vs. II designation. Tumors that are ≤2 cm in size can be upstaged to Stage II if they contain two or more high-risk features. Stage III patients are those with (1) clinical, histologic, or radiologic evidence of one solitary node measuring ≤3 cm in size or (2) Tumor extension into bone: maxilla, mandible, orbit, or temporal bone. Stage IV patients are those with (1) tumor with direct or perineural invasion of skull base or axial skeleton, (2) ≥2 lymph nodes or (3) single or multiple lymph nodes measuring >3 cm in size or (4) distant metastasis.

**ANATOMIC STAGE/PROGNOSTIC GROUPS (*CONTINUED*)**

| | | | |
|---|---|---|---|
| Stage IIIA | Any T | N1a | M0 |
| Stage IIIB | Any T | cN1/N1b/N2 | M0 |
| Stage IV | Any T | Any N | M1 |

**ICD-O-3 HISTOLOGY CODE RANGES**
8247

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

## INTRODUCTION

Merkel cell carcinoma (MCC) is a relatively rare, potentially aggressive primary cutaneous neuroendocrine carcinoma, originally described by Tang and Toker in 1972 as trabecular carcinoma.[1] The mortality rate is twice that observed in melanoma (33% vs. 15%). Although the molecular pathogenesis remains largely unknown, ultraviolet radiation and immune suppression are likely significant predisposing factors. The identification of a novel polyomavirus termed *Merkel cell polyomavirus* in the majority of MCC tumors suggests a viral component in many cases.[2] Merkel cell carcinoma occurs most commonly on sun-exposed skin in fair-skinned individuals older than 50 years with a slight male predominance.[3,4] An increased incidence is also observed in patients with HIV infection, leukemias, and organ transplantation.[4–6] Merkel cell carcinoma is increasing in frequency, rising from 0.15 cases per 100,000 in 1986 to 0.44 cases per 100,000 in 2001. Much of this increase in reported frequency is likely due to increased recognition and improved techniques for diagnosis.[7] Currently in the United States, approximately 1,500 cases of MCC are diagnosed annually.[8] As the US population ages and improved transplantation regimens prolong the lives of organ transplant recipients, the incidence of MCC will likely continue to rise.

Merkel cell carcinoma has a nonspecific clinical presentation, though rapid growth of a firm, red to violaceous, nontender papule or nodule is often noted.[4] Diagnosis is made via biopsy, almost invariably with the aid of immunohistochemistry, classically demonstrating a peri-nuclear dot pattern of cytokeratin-20 staining. The majority of patients present with clinically localized disease. However, the disease can rapidly spread to regional and distant sites. The regional draining nodal basin is the most common site for recurrence.[9] The natural history of the disease is variable but heavily dependent on the stage at time of diagnosis.

Five different staging systems for Merkel cell carcinoma have been described in the literature and all are currently in use.[10–14] Depending on the system used, Stage III MCC could represent local, nodal, or metastatic disease. This situation impedes effective patient–physician communication, data comparison, and outcomes analysis. Therefore, development of a standardized, data-driven staging system is important for improving clinical care and research in this disease. Moreover, a separate staging system for MCC is appropriate given its unique behavior compared with other malignancies that will remain in the "Cutaneous Squamous Cell Carcinoma and other Cutaneous Carcinomas" staging chapter (see Chap. 29). This new staging system is based on an analysis of over 4,700 patients using the National Cancer Database as well as extensive review of the literature.

both clinical evidence of nodal metastases *and* pathologic examination confirming nodal metastases are defined by convention as having "macroscopic" or "clinically apparent" nodal metastases. Nodes clinically positive by exam and negative by pathology would be classified as pN0. Clinically positive nodes in the draining nodal basin that are assumed to be involved with Merkel cell carcinoma but are without pathologic confirmation (no pathology performed) should be classified as N1b and the pathologic classification would be NX. Then in determining the stage grouping, it would be Stage IIIB defaulting to the higher N category.

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



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

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

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

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

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

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

| *Distant Metastasis (M)* | |
|---|---|
| M0 | No distant metastasis |
| M1 | Metastasis beyond regional lymph nodes |
| M1a | Metastasis to skin, subcutaneous tissues or distant lymph nodes |
| M1b | Metastasis to lung |
| M1c | Metastasis to all other visceral sites |

## ANATOMIC STAGE/PROGNOSTIC GROUPS

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

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

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

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

| | |
|---|---|
| Required for staging | None |
| Clinically significant | Measured thickness (depth)<br>Tumor base transection status<br>Profound immune suppression<br>Tumor infiltrating lymphocytes in the primary tumor (TIL)<br>Growth pattern of primary tumor<br>Size of tumor nests in regional lymph nodes |

***Pathologic (pN)****

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

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

| | |
|---|---|
| pN0(i−) | No regional lymph node metastases histologically, negative IHC |
| pN0(i+) | Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC) |
| pN0(mol−) | No regional lymph node metastases histologically, negative molecular findings (RT-PCR) |
| pN0(mol+) | Positive molecular findings (RT-PCR),** but no regional lymph node metastases detected by histology or IHC |
| pN1 | Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected*** |
| pN1mi | Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm) |
| pN1a | Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2.0 mm |
| pN1b | Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected*** |
| pN1c | Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected |
| pN2 | Metastases in 4–9 axillary lymph nodes; or in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases |
| pN2a | Metastases in 4–9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm) |
| pN2b | Metastases in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases |
| pN3 | Metastases in ten or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected**** ipsilateral internal mammary lymph nodes in the *presence* of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***; or in ipsilateral supraclavicular lymph nodes |

| *Pathologic (pN)* (Continued)* | |
|---|---|
| pN3a | Metastases in ten or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes |
| pN3b | Metastases in clinically detected**** ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected*** |
| pN3c | Metastases in ipsilateral supraclavicular lymph nodes |

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

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

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

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

***Posttreatment ypN***

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

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

***Posttreatment yp M classification.*** The M category for patients treated with neoadjuvant therapy is the category assigned in the clinical stage, prior to initiation of neoadjuvant therapy. Identification of distant metastases after

# 33

# Vulva

*(Mucosal malignant melanoma is not included)*

## *At-A-Glance*

**SUMMARY OF CHANGES**

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

**ANATOMIC STAGE/PROGNOSTIC GROUPS**

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

**ICD-O-3 TOPOGRAPHY CODES**

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

**ICD-O-3 HISTOLOGY CODE RANGES**

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



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

## ANATOMY

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

**Regional Lymph Nodes.** The femoral and inguinal nodes are the sites of regional spread. For pN, histologic examination of regional lymphadenectomy specimens will ordinarily include six or more lymph nodes. For TNM staging, cases with fewer than six resected nodes should be classified using the TNM pathologic classification according to the status of those nodes

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

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

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

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

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

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

## PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)
## (Recommended for Collection for Carcinomas and Sarcomas)

| | |
|---|---|
| Required for staging | None |
| Clinically significant | FIGO Stage<br>Peritoneal cytology results<br>Pelvic nodal dissection with number of nodes positive/examined<br>Para-aortic nodal dissection with number of nodes positive/examined<br>Percentage of nonendometrioid cell type in mixed histology tumors<br>Omentectomy performed |

## 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 nonsquamous or nonmorular solid growth pattern |
| G2 | 6–50% of a nonsquamous or nonmorular solid growth pattern |
| G3 | More than 50% of a nonsquamous or nonmorular solid growth pattern |

### Notes on Pathologic Grading

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



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

### Leiomyosarcoma and Endometrial Stromal Sarcoma

| ***Primary Tumor (T)*** | | |
|---|---|---|
| *TNM Categories* | *FIGO Stages* | *Definition* |
| TX | | Primary tumor cannot be assessed |
| T0 | | No evidence of primary tumor |
| T1 | I | Tumor limited to the uterus |

# 37

# Ovary and Primary Peritoneal Carcinoma

## *At-A-Glance*

**SUMMARY OF CHANGES**

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

**ANATOMIC STAGE/PROGNOSTIC GROUPS**

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

**ICD-O-3 TOPOGRAPHY CODES**

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

**ICD-O-3 HISTOLOGY CODE RANGES**

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



## ANATOMY

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

In some cases, an adenocarcinoma is primary in the peritoneum. The ovaries are not involved or are only involved with minimal surface implants. The clinical presentation, surgical therapy, chemotherapy, and

## 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 nonanatomic 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 39.1). Each stage is anatomically defined, but substage A (low risk) and B (high risk) are assigned on the basis of a nonanatomic 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 6 or less, and high risk is a score of 7 or greater.

## PROGNOSTIC FEATURES

**Outcomes Results.** Gestational trophoblastic tumors may require only uterine evacuation for treatment, but even when chemotherapy is required, cure rates approach 100%. Prognostic factors are listed in the

The multiple variables in addition to anatomic stage that have been proposed as prognostic in penile carcinoma have been recently evaluated using an outcomes prediction nomogram tool to define lymph node involvement by Ficarra et al. Their group has proposed the prediction tool shown in Table 40.1 and which was designed and validated in 175 patients from 11 centers in Italy. This tool may serve as a clinically useful adjunct to standard anatomic staging enabling physicians to counsel patients regarding the selection of therapeutic interventions based on risk of clinical recurrence. This model will need to be validated in larger groups of patients prior to widespread implementation.

### Clinical Staging

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

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

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

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

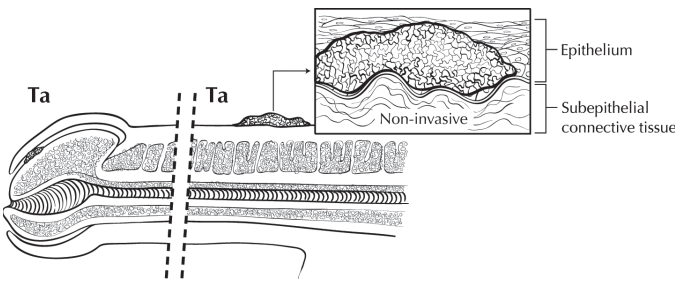



**FIGURE 40.1.** Ta: Noninvasive verrucous carcinoma.

# 41

# Prostate

*(Sarcomas and transitional cell carcinomas are not included)*



## *At-A-Glance*

**SUMMARY OF CHANGES**

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

**ANATOMIC STAGE/PROGNOSTIC GROUPS***

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

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

**ICD-O-3 TOPOGRAPHY CODES**

C61.9 Prostate gland

**ICD-O-3 HISTOLOGY CODE RANGES**

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

***pT3.*** The sixth edition of the AJCC TNM staging system subdivides pT3 disease into two categories pT3a and pT3b as determined by the presence of extracapsular invasion in any location and presence of seminal vesical invasion with or without extracapsular invasion. The 1992 version of the AJCC TNM system (fifth edition) subdivided patients with extracapsular extension into either unilateral or bilateral and separated seminal vesical involvement. Several retrospective outcome data analyses have challenged the utility of eliminating this subdivision in the subsequent sixth edition. A thorough review of these analyses has revealed conflicting evidence regarding the correlation of subdividing unilateral and bilateral extracapsular extension and biochemical recurrence rates following surgery. Again, definitive data do not exist to allow correlation of particular pT3 stage subgroupings with survival in localized prostate cancer, and a reversion to the previous subdividing classification was not made. Data continue to be accumulated in the NCDB and other institutional databases to help determine the pT3 staging system.

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

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

## PROGNOSTIC FEATURES

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

predictors of serum prostate-specific antigen, Gleason score, and tumor stage all have a clear, recognized, and significant impact on prognosis.

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



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

## OUTCOMES BY STAGE, GRADE, AND PSA

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

## DEFINITIONS OF TNM

***Primary Tumor (T)***

*Clinical*

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

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

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

***Pathologic (pT)****

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

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

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

# 42

# Testis

## *At-A-Glance*



### SUMMARY OF CHANGES

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

### ANATOMIC STAGE/PROGNOSTIC GROUPS

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

### ICD-O-3 TOPOGRAPHY CODES

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

### ICD-O-3 HISTOLOGY CODE RANGES

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

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



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

## RULES FOR CLASSIFICATION

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

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

***Regional Lymph Nodes (N) (continued)***

| | |
|---|---|
| N2 | Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, any one mass greater than 2 cm but not more than 5 cm in greatest dimension |
| N3 | Metastasis with a lymph node mass more than 5 cm in greatest dimension |

*Pathologic (pN)*

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

***Distant Metastasis (M)***

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

**ANATOMIC STAGE/PROGNOSTIC GROUPS**

| Group | T | N | M | S (Serum Tumor Markers) |
|---|---|---|---|---|
| Stage 0 | pTis | N0 | M0 | S0 |
| Stage I | pT1–4 | N0 | M0 | SX |
| Stage IA | pT1 | N0 | M0 | S0 |
| Stage IB | pT2 | N0 | M0 | S0 |
| | pT3 | N0 | M0 | S0 |
| | pT4 | N0 | M0 | S0 |
| Stage IS | Any pT/Tx | N0 | M0 | S1–3 |
| Stage II | Any pT/Tx | N1–3 | M0 | SX |
| Stage IIA | Any pT/Tx | N1 | M0 | S0 |
| | Any pT/Tx | N1 | M0 | S1 |
| Stage IIB | Any pT/Tx | N2 | M0 | S0 |
| | Any pT/Tx | N2 | M0 | S1 |
| Stage IIC | Any pT/Tx | N3 | M0 | S0 |
| | Any pT/Tx | N3 | M0 | S1 |

| | | | | |
|---|---|---|---|---|
| Stage III | Any pT/Tx | Any N | M1 | SX |
| Stage IIIA | Any pT/Tx | Any N | M1a | S0 |
| | Any pT/Tx | Any N | M1a | S1 |
| Stage IIIB | Any pT/Tx | N1–3 | M0 | S2 |
| | Any pT/Tx | Any N | M1a | S2 |
| Stage IIIC | Any pT/Tx | N1–3 | M0 | S3 |
| | Any pT/Tx | Any N | M1a | S3 |
| | Any pT/Tx | Any N | M1b | Any S |



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

Required for staging — Serum tumor markers (S)

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

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

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

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

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

Clinically significant — Size of largest metastases in lymph nodes
Radical orchiectomy performed

## HISTOPATHOLOGIC TYPE

Following the guidelines of the *World Health Organization Histological Classification of Tumours,* germ cell tumors may be either seminomatous or nonseminomatous. 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. The presence of an elevated AFP level in a patient with pure seminoma found at orchiectomy should be classified as having nonseminomatous germ cell tumor. Nonseminomatous germ cell tumors may be pure (embryonal carcinoma, yolk sac tumor,

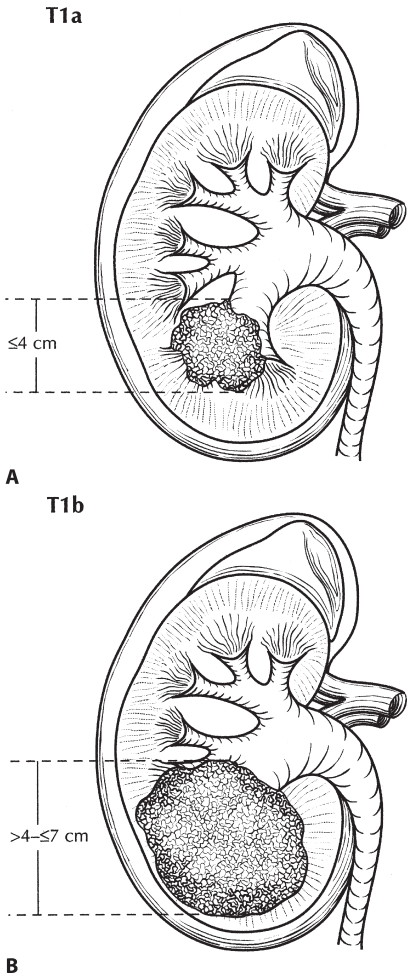



**FIGURE 43.4.** (**A**) T1a: Tumor 4 cm or less in greatest dimension, limited to the kidney. (**B**) T1b: Tumor more than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney.

| ANATOMIC STAGE/PROGNOSTIC GROUPS | | | |
|---|---|---|---|
| Stage I | T1 | N0 | M0 |
| Stage II | T2 | N0 | M0 |
| Stage III | T1 or T2 | N1 | M0 |
| | T3 | N0 or N1 | M0 |
| StageIV | T4 | any N | M0 |
| | Any T | Any N | M1 |

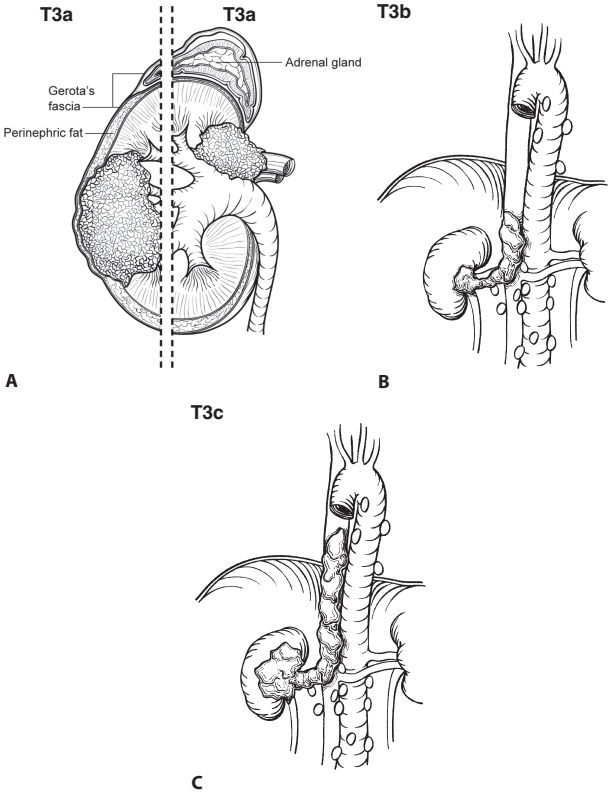



**FIGURE 43.6.** (**A**) (*Left*) T3a: Invasion into perirenal and/or renal sinus fat but not beyond Gerota's fascia. (*Right*) T3a: In addition to perirenal and/or renal sinus fat, tumor grossly invades into the renal vein. (**B**) T3b: Tumor grossly extends into the renal vein or its segmental (muscle-containing)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

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

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

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

| *Distant Metastasis (M)* | |
|---|---|
| M0 | No distant metastasis |
| M1 | Distant metastasis |
| M1a | Largest diameter of the largest metastasis 3 cm or less |
| M1b | Largest diameter of the largest metastasis 3.1–8.0 cm |
| M1c | Largest diameter of the largest metastasis 8.1 cm or more |

**ANATOMIC STAGE/PROGNOSTIC GROUPS**

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

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

| | |
|---|---|
| Required for staging | Height |
| | Largest tumor diameter |
| Clinically significant | Measured thickness (height) |
| | Chromosomal alterations |
| | Gene expression profile |
| | Positron emission tomography/computed tomography |
| | Mitotic count per 40 high power fields (HPF) |
| | Mean diameter of the ten largest nucleoli (MLN) |
| | Presence of extravascular matrix patterns |
| | Microvascular density (MVD) |

# 53 Carcinoma of the Lacrimal Gland

## *At-A-Glance*

### SUMMARY OF CHANGES

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

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

### ANATOMIC STAGE/PROGNOSTIC GROUPS

No stage grouping is presently recommended

### ICD-O-3 TOPOGRAPHY CODES

C69.5 Lacrimal gland (excluding lacrimal sac)

### ICD-O-3 HISTOLOGY CODE RANGES

8000–8576, 8940–8950, 8980–8981

## INTRODUCTION

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

## ANATOMY

**Primary Site.** In the normal, fully developed orbit, the lacrimal gland is clinically impalpable and is situated in the lacrimal fossa posterior to the superotemporal orbital rim. The gland is not truly encapsulated and

Preoperative chemotherapy
Postoperative chemotherapy

## HISTOLOGIC GRADE (G)

In most cases, the histology defines the grade of malignancy in lacrimal gland carcinomas as in salivary gland carcinomas.

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

## HISTOPATHOLOGIC TYPE

The major malignant primary epithelial tumors include the following:

***Low Grade***

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

***High Grade***

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

Other Rare and Unclassifiable Carcinomas

# 54

# Sarcoma of the Orbit



## *At-A-Glance*

**SUMMARY OF CHANGES**

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

**ANATOMIC STAGE/PROGNOSTIC GROUPS**

No stage grouping is presently recommended

**ICD-O-3 TOPOGRAPHY CODES**

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

**ICD-O-3 HISTOLOGY CODE RANGES**

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

## INTRODUCTION

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

## ANATOMY

The orbit is a cone-shaped bony structure with a volume of 30 ml in which the 7-ml globe is positioned centrally and anteriorly. All the support systems of the globe, including the optic nerve and its meninges, lacrimal gland and lymphoid tissue, extraocular muscles, fibroadipose tissue, peripheral nerves, ganglionic tissue, and blood vessels are designed to be confined within approximately 25 ml of space surrounding the eyeball. Many types of tissues are crowded in this limited space and give origin to a variety of primary carcinomatous, sarcomatous, lymphoid and melanocytic tumors. Secondary neoplasia (from adjacent structures such as paranasal sinuses, conjunctiva, globe, etc.) as well as metastatic tumors from distant organs are encountered in the orbit. Also, and because of their immediate proximity, the orbital primary tumors often present invasions into CNS, nasal cavity,

**TABLE 56.3.** WHO grades of CNS tumors (continued)

| | I | II | III | IV |
|---|---|---|---|---|
| **Pineal tumors** | | | | |
| Pineocytoma | • | | | |
| Pineal parenchymal tumor of intermediate differentiation | | • | • | |
| Pineoblastoma | | | | • |
| Papillary tumor of the pineal region | | • | • | |
| **Embryonal tumors** | | | | |
| Medulloblastoma | | | | • |
| CNS primitive neuroectodermal tumor (PNET) | | | | • |
| Atypical teratoid/rhabdoid tumor | | | | • |
| **Tumors of the cranial and paraspinal nerves** | | | | |
| Schwannoma | • | | | |
| Neurofibroma | • | | | |
| Perineurioma | • | • | • | |
| Malignant peripheral nerve sheath tumor (MPNST) | | • | • | • |
| **Meningeal tumors** | | | | |
| Meningioma | • | | | |
| Atypical meningioma | | • | | |
| Anaplastic/malignant meningioma | | | • | |
| Hemangiopericytoma | | • | | |
| Anaplastic hemangiopericytoma | | | • | |
| Hemangioblastoma | • | | | |
| **Tumors of the sellar region** | | | | |
| Craniopharyngioma | • | | | |
| Granular cell tumor of the neurohypophysis | • | | | |
| Pituicytoma | • | | | |
| **Spindle cell oncocytoma of the adenohypophysis** | • | | | |

From World Health Organization (http://www.who.int/en/), with permission.



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 and ideally is accompanied by MRI-based quantitative assessment. Any staging system to be developed for CNS tumors should take into account, in a systematic and clearly documented fashion, the extent of removal and residual tumor.

**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.

malignant cell is derived from a post thymic T cell that typically bears a CD4+ helper/memory antigen profile. The disease is characterized by erythematous patches (usually in sun-protected areas) that progress to plaques or tumors. Initial evaluation should include delineation of skin involvement with photographs; skin biopsy (histopathology, immunophenotyping, and T-cell receptor (TCR) gene analysis); CBC with differential, Sézary cell count (peripheral blood); chemistry panel with LDH; and in select instances peripheral blood flow cytometric analysis of T-cell subsets (CD4/CD8 ratio); TCR gene analysis on peripheral blood; lymph node biopsy and bone marrow biopsies (histopathology, immunophenotyping and TCR gene analysis); CT/PET scans; and serologic tests (HTLV-1 and HIV). Skin directed and systemic therapies are determined by the patient's stage and symptoms. Prognosis is stage dependent.

*Sézary Syndrome*. Sézary syndrome is the aggressive leukemic, and erythrodermic form of CTCL, which is characterized by circulating atypical, malignant T lymphocytes with cerebriform nuclei (Sézary cells), and lymphadenopathy. The Sézary cells also have a mature memory T-cell phenotype (CD3+, CD4+) with loss of CD7 and CD26.

## DEFINITIONS OF TNM

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

| | |
|---|---|
| *Skin* | |
| T1 | Limited patches,* papules, and/or plaques** covering less than 10% of the skin surface. May further stratify into T1a (patch only) vs. T1b (plaque ± patch) |
| T2 | Patches, papules or plaques covering 10% or more of the skin surface. May further stratify into T2a (patch only) vs. T2b (plaque ± patch) |
| T3 | One or more tumors*** (≥1-cm diameter) |
| T4 | Confluence of erythema covering 80% or more of body surface area |

| | |
|---|---|
| *Node* | |
| N0 | No clinically abnormal peripheral lymph nodes****; biopsy not required |
| N1 | Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN0-2 |
| N1a | Clone negative***** |
| N1b | Clone positive***** |
| N2 | Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN3 |
| N2a | Clone negative***** |
| N2b | Clone positive***** |
| N3 | Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3–4 or NCI LN4; clone positive or negative |
| Nx | Clinically abnormal peripheral lymph nodes; no histologic confirmation |

| | |
|---|---|
| *Visceral* | |
| M0 | No visceral organ involvement |
| M1 | Visceral involvement (must have pathology confirmation^ and organ involved should be specified) |

| | |
|---|---|
| *Peripheral Blood Involvement* | |
| B0 | Absence of significant blood involvement: 5% or less of peripheral blood lymphocytes are atypical (Sézary) cells^^ |
| B0a | Clone negative***** |
| B0b | Clone positive***** |
| B1 | Low blood tumor burden: more than 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B2 |
| B1a | Clone negative***** |
| B1b | Clone positive***** |
| B2 | High blood tumor burden: 1000/μL Sézary cells^^ or more with positive clone***** |



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

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

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

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

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

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

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

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