Eighth Edition Staging of Thoracic Malignancies

Implications for the Reporting Pathologist

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• ***Context.***—**The Staging and Prognostic Factors Committee of the International Association for the Study of Lung Cancer, in conjunction with the International Mesothelioma Interest Group, the International Thymic Malignancy Interest Group, and the Worldwide Esophageal Cancer Collaboration, developed proposals for the 8th edition of their respective tumor, node, metastasis (TNM) staging classification systems.**

Objective.—**To review these changes and discuss issues for the reporting pathologist.**

Data Sources.—**Proposals were based on international databases of lung (N = 94 708), with an external validation using the US National Cancer Database; mesothelioma (N = 3519); thymic epithelial tumors (10 808); and epithelial cancers of the esophagus and esophagogastric junction (N = 22 654).**

Conclusions.—**These proposals have been mostly accepted by the Union for International Cancer Control and the American Joint Committee on Cancer and incorporated into their respective staging manuals (2017). The Union for International Cancer Control recommended implementation beginning in January 2017; however, the American Joint Committee on Cancer has deferred deployment of the eighth TNM until January 1, 2018, to ensure appropriate infrastructure for data collection. This manuscript summarizes the updated staging of thoracic malignancies, specifically highlighting changes from the 7th edition that are relevant to pathologic staging. Histopathologists should become familiar with, and start to incorporate, the 8th edition staging in their daily reporting of thoracic cancers henceforth.**

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Work on the 8th edition staging manuals began immediately following the publication of the 7th edition,[1–11] and the Staging and Prognostic Factors Committee of the International Association for the Study of Lung Cancer (IASLC), using an international database of 94 708 patients with lung cancer, subsequently produced staging proposals for the 8th edition.[12–19] Within a similar time period, the International Mesothelioma Interest Group, the International Thymic Malignancy Interest Group (ITMIG), and the Worldwide Esophageal Cancer Collaboration, in conjunction with the IASLC, developed proposals, assembled databases, and recommended tumor, node, metastasis (TNM) system categories for mesothelioma (N = 3519),[20–23] thymic epithelial tumors (N = 10 808),[24–27] and esophageal/esophagogastric junction (EGJ) cancers.[28–34]

The purpose of this article is to present 8th edition staging of thoracic malignancies, specifically highlighting changes from the 7th edition that are relevant to pathologic staging, and to make the pathology community aware of the challenges that may present in daily reporting.

SUMMARY OF THE 8TH EDITION FOR STAGING OF THORACIC CANCERS

A note of caution must be given concerning terminology. There are differences between the Union for International

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Table 1. Differences Between Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) Staging Terminology

	UICC[35,45]	AJCC[36]
Prefix (c, yc, p, yp, r, and a)	Classification	Classification
T, N, and M	Component	Category
Tx T0 Tis T1–4, Nx N0–3, M0–1	Category	Category
TNM subscripts (T1a, N1a, M1a, etc)	Subdivision	Subcategory
Non-TNM factor	Other prognostic factor	Category
Definitions	Descriptors	Criteria
Stage group (TNM only)	Stage group	Prognostic stage group (anatomic stage group only when both TNM and non-TNM factor)
Stage group (TNM and non-TNM factors)	Prognostic group	Prognostic stage group

Abbreviations: a, first determined at autopsy; c, clinical; M, metastasis; N, node; p, pathologic; r, recurrent tumor; T, tumor; x, cannot be assessed; y, neoadjuvant chemotherapy.

Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) terminologies. Most notably, anatomic TNM and nonanatomic cancer characteristics are termed *classification* by the UICC and *category* by the AJCC. The term classification as used by the AJCC denotes when in the course of a cancer the staging is done. Because this impacts the esophagus primarily, this manuscript will use UICC terminology for lung, mesothelioma, and thymic staging, and AJCC terminology for esophagus and EGJ staging. This strategy both avoids confusion with terminology and is educational by illustrating differences between the two 8th edition staging manuals (Table 1).[35,36]

STAGING OF LUNG CANCER

T: Primary Tumor

Size of Tumor.—Proposed T classifications (UICC) are presented in Table 2, with changes from the 7th edition in Table 3. From 1 to 5 cm, each centimeter increase in cancer diameter is associated with worsening survival. Only the invasive component of tumors should be used for the T size measurement in nonmucinous lung adenocarcinomas.[37] Cancers greater than 5 cm but less than or equal to 7 cm are now staged as T3, and those greater than 7 cm as T4. The T2 classification is now used for tumors involving the main bronchus and tumors associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving either part of the lung or the whole lung. Involvement of the diaphragm has a T4 prognosis. Invasion of the mediastinal pleura was seldom used and has been discontinued.[14]

Involvement of the Pleura.—When the visceral pleura is infiltrated by cancer, defined as cancer cells infiltrating beyond the outer elastic layer (PL1) or cancer infiltrating beyond the outer elastic layer and onto the visceral pleura surface (PL2) (Figure 1, A through C), a pT1 cancer by size (3 cm or less) continues to be upstaged to pT2a. Elastic stains are of value in identifying pleural invasion in this setting.[38] Involvement of the visceral pleura in pT2a (3–4 cm) cancers by size had similar prognosis to those of pT2b (4–5 cm), and those that were pT2b (4–5 cm) by size with visceral pleural invasion had a prognosis similar to those that were pT3 by size (5–7 cm), although this was not as clear in clinical staging so is not part of the 8th edition.[14] There is no difference in staging between PL1 and PL2, although this should be documented, as cancers with neoplastic cells on the visceral pleural surface (PL2) have higher recurrence and poorer prognosis.[39–42] Invasion of the parietal pleura (with or without chest wall involvement) warrants staging as pT3. The anatomic border between visceral pleura and parietal pleura may be difficult to identify in the context of a cancer and its desmoplastic reaction, and discussion with the surgeon may be of value. Again, elastic van Gieson staining may also help, as there is a discontinuous layer of elastin in the parietal pleura that may remain despite tumoral fibrosis.

Staging of Subsolid Nodules and Early-Stage Disease.—In 2011, new entities of adenocarcinoma in situ, minimally invasive adenocarcinoma, and lepidic predominant adenocarcinoma were defined[43] and subsequently incorporated into the 2015 World Health Organization classification of lung cancer.[44] To fit these entities into the T classification (UICC) of the staging system, there is now a Tis classification for adenocarcinoma in situ, with Tis (adenocarcinoma in situ) specified to distinguish it from squamous cell carcinoma in situ, which is classified as Tis (squamous cell carcinoma in situ). Minimally invasive adenocarcinoma is classified as T1mi.

Furthermore, given the addition of minimally invasive adenocarcinoma and the general acceptance that lepidic growth, particularly when predominant, represents in situ growth, only the invasive size of the tumor should be used for the T size (Figure 2, A and B), following a recommendation made in 3 editions of the UICC TNM supplement since 2003,[37] as well as data showing improved stratification and downstaging in early-stage disease. At clinical staging, for part-solid lesions suspected to be nonmucinous lung adenocarcinomas, the size of the solid component on high-resolution computed tomography using the lung window is the measurement to be used to define clinical (c) T.[37]

As the amount of lepidic tumor may potentially be underestimated grossly, evaluation of cancer size may require reexamination of the specimen and careful correlation with microscopic and radiographic findings. The limitations of radiology are addressed below; however, the UICC TNM supplement recommends that in the situation of a discrepancy between the clinically and pathologically detected tumor size, the clinical measurement should also be used for pathologic (p) T.[45]

In nonmucinous lung adenocarcinomas with a lepidic component, if the size of the invasive component cannot be measured in a single discrete focus, it can be estimated by multiplying the total size by the percentage of the invasive components. Further guidance on the challenges and practical approaches to applying these new principles are summarized in detail in the paper by Travis et al.[37]

Neoadjuvant Therapy.—If there has been neoadjuvant therapy, pathologic staging should be prefixed by the letters yp. If size cannot be measured in a single discrete focus, ypT size should be estimated by multiplying the percentage of viable tumor by the tumor bed size. The most important point is to recognize when the percentage of treatment effect is 90% or greater.

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Table 2. Criteria for the T, N, and M Categories for Staging of Lung Cancer[a]

TX	Primary tumor cannot be assessed or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ; Tis (AIS) for AIS, Tis (SCIS) for SCIS
T1	Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus[b]
T1mi	Minimally invasive adenocarcinoma[c]
T1a	Tumor 1 cm or less in greatest dimension[b]
T1b	Tumor more than 1 cm but not more than 2 cm in greatest dimension[b]
T1c	Tumor more than 2 cm but not more than 3 cm in greatest dimension[b]
T2	Tumors more than 3 cm but not more than 5 cm in greatest dimension, or tumor with any of the following features[d]: Involves the main bronchus Invades visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, either involving part of the lung or the whole lung T2 tumors with these features are classified as T2a if 4 cm or less, or cannot be determined, or T2b if more than 4 cm but not more than 5 cm
T2a	Tumor more than 3 cm but not more than 4 cm in greatest dimension
T2b	Tumor more than 4 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm but not more than 7 cm in greatest dimension, or one that directly invades one of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or associated separate tumor nodule(s) in the same lobe as the primary
T4	Tumor more than 7 cm or one of any size that directly invades one of the following: diaphragm, mediastinum, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, vertebra; or separate tumor nodule(s) in different ipsilateral lobe to that of the primary
NX	Regional lymph nodes cannot be assessed
N0	No regional node involvement
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar nodes and/or intrapulmonary nodes (node stations 10–14), including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal node(s) (node stations 2–9)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular nodes
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural/pericardial nodules or malignant pleural or pericardial effusion[e]
M1b	Single extrathoracic metastasis in a single organ[f]
M1c	Multiple extrathoracic metastases in one or several organs

Abbreviations: AIS, adenocarcinoma in situ; M, metastasis; N, node; SCIS, squamous cell carcinoma in situ; T, tumor.

[a] With permission from the International Association for the Study of Lung Cancer (IASLC) Staging Manual of Thoracic Oncology. Reprinted courtesy of the International Association for the Study of Lung Cancer. Copyright ©2016, IASLC. For small cell carcinomas, staging via 8th TNM is recommended, especially for those with limited disease. For carcinoid tumors, staging via 8th TNM is recommended for all cases.

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

[c] Solitary adenocarcinoma (not more than 3 cm in greatest dimension), with a predominantly lepidic pattern and not more than 5 mm invasion in greatest dimension in any one focus.

[d] T2 tumors with these features are classified T2a if 4 cm or less or if size cannot be determined and T2b if larger than 4 cm but not larger than 5 cm.

[e] Most pleural (pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements on clinical judgement dictate that the effusion is not related to tumor, the effusion should be excluded as a staging descriptor.

[f] This includes involvement of a single nonregional node.

Lung Cancers Comprising Multiple Lesions.—Lung cancers with multiple lesions are seen with increasing frequency, and the existing rules for their classification are ambiguous. For the 8th edition, these lung cancers continue to be classified into 2 main disease patterns, and specific recommendations on their classification have been recommended to facilitate homogenous staging. For separate primary lung cancers, each cancer is staged separately. For separate tumor nodules (intrapulmonary metastasis), the classification (UICC) recommended in the 7th edition has not changed: T3 for ipsilateral separate cancer nodules in the same lobe, T4 for ipsilateral separate cancer nodules in a different lobe, and M1a for a separate cancer nodule(s) in a contralateral lobe(s). However, additional subdivision that recognizes (1) separate primary lung cancers presenting as predominantly ground-glass opacities on imaging with typically nonmucinous adenocarcinoma showing lepidic predominant morphology on histopathology and (2) pneumonic presentation on imaging that typically correlates with invasive mucinous adenocarcinoma has been proposed for future data collection in order to further define this controversial area of staging. For the former, the existing rule of recording the highest T followed by the number of lesions or "m" for multiple in parentheses and adding an N and an M that apply to all lesions has been recommended. For the latter, their classification will be based on the lobar location of the tumor: T3 if in the same lobe, T4 if in another ipsilateral lobe, and M1a if in the contralateral lung. Criteria to facilitate the clinical (cTNM) and pathologic (pTNM) classification of these 4 patterns of lung cancer have been provided based on the best evidence or consensus.[46–49]

N: Regional Lymph Nodes

The anatomical location of lymph node involvement is defined by either the Naruke[50] (for Japanese data), Mountain-Dressler[51] (for some non-Japanese data), or IASLC nodal chart. Although the last of these was the result of an international and multidisciplinary consensus,

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Table 3. Changes in T Categories in 8th Edition Compared With the 7th Edition
To subclassify T1 into T1a (≤1 cm), T1b (>1 to ≤2 cm), and T1c (>2 to ≤3 cm)
To subclassify T2 into T2a (>3 to ≤4 cm) and T2b (>4 to ≤5 cm)
To reclassify tumors greater than 5 to less than or equal to 7 cm as T3
To reclassify tumors greater than 7 cm as T4
To group involvement of main bronchus as T2 regardless of distance from carina
To group partial and total atelectasis/pneumonitis that extends to the hilar region T2
To reclassify diaphragm invasion as T4
To delete mediastinal pleura invasion as a T descriptor
Addition of Tis (AIS) for adenocarcinoma in situ in distinction from Tis (SCIS) for squamous cell carcinoma in situ, T1mi for MIA
To use invasive size for T staging of nonmucinous lung adenocarcinomas

Abbreviations: AIS, adenocarcinoma in situ; M, metastasis; MIA, minimally invasive adenocarcinoma; N, node; SCIS, squamous cell carcinoma in situ; T, tumor.

has well-defined anatomic landmarks for each nodal station, and is the recommended lymph node map, the IASLC nodal map has been used inconsistently since its publication in 2009.[52] N0 to N3 consistently separates patients into prognostically distinct groups and remains unchanged from the 7th edition. Additional analyses were performed by further dividing N1 into N1 at a single station (N1a) and N1 at multiple stations (N1b); N2 into N2 at a single station without N1 involvement ("skip" metastasis, N2a1), N2 at a single station with N1 involvement (N2a2), and N2 at multiple stations (N2b). Although survival differences were demonstrated with the addition of this schema (N1a, N1b, N2a, N2b), it was not adopted because data were derived exclusively from pathologic staging and could not be validated clinically. It is recommended that these data be recorded and used for future analyses because they have prognostic relevance.[15]

M: Distant Metastases

No significant survival differences were found among M1a (metastases within the chest cavity) patients, and this definition remains unchanged from the 7th to the 8th edition. However, survival analysis of M1b (distant metastases outside the chest cavity) patients demonstrated survival differences according to the number of metastases; cancers with a single metastasis in a single organ had significantly better prognosis than those with multiple metastases in one or several organs. Therefore, although criteria for the M1a category remain unchanged from the 7th edition, single metastatic lesions in a single distant organ should be newly designated as M1b, whereas multiple lesions in a single organ or multiple lesions in multiple organs should be reclassified as M1c. This differentiation will hopefully serve as a first step into providing rational definitions for an oligometastatic disease (Table 2).[13]

Stage Groups

New TNM stage groups are shown in Table 4.[12]

STAGING OF MESOTHELIOMA

For nearly 40 years, there was no generally accepted staging system for malignant pleural mesothelioma. In 1994,

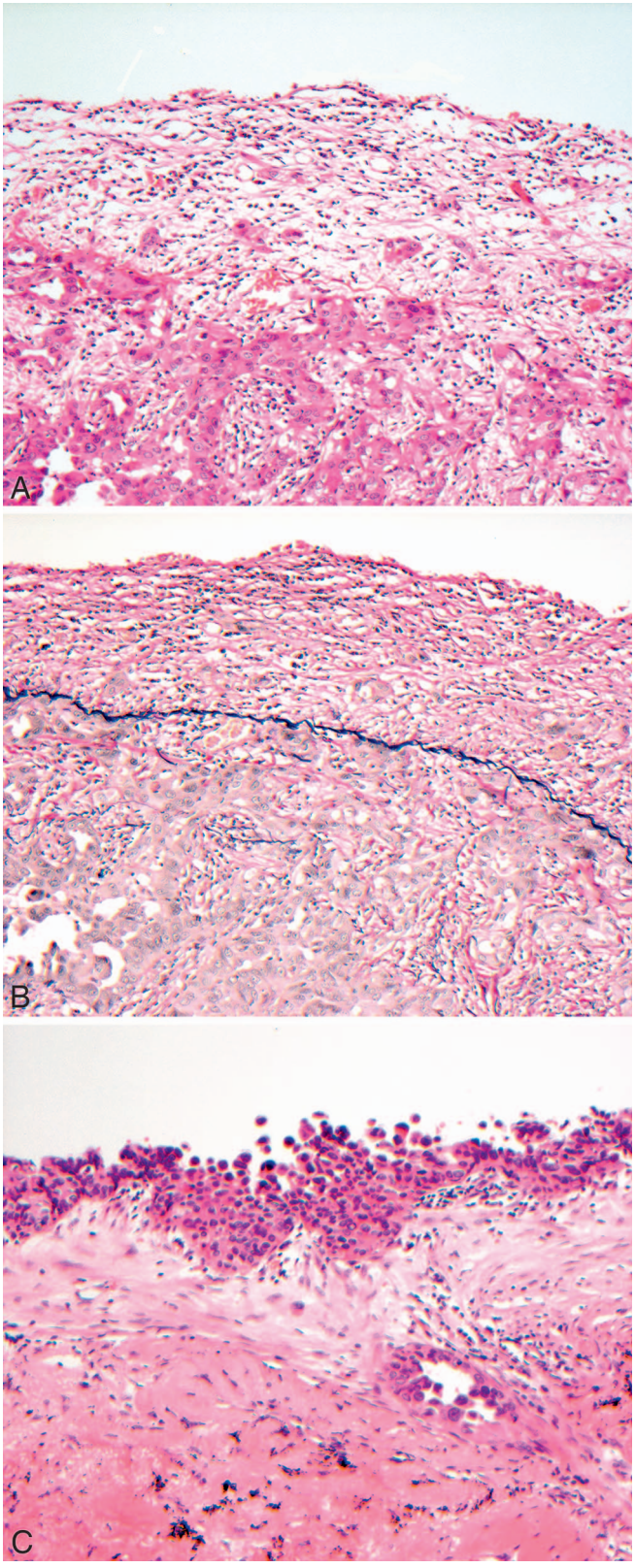

Figure 1. *Visceral pleural invasion. A and B, Tumor breaches the visceral pleura, made easier by elastic van Gieson staining (B), but does not reach the surface (PL1). C, Tumor diffusely involves the surface (PL2) (hematoxylin-eosin, original magnification ×100 [A and C]; original magnification ×100 [B]).*

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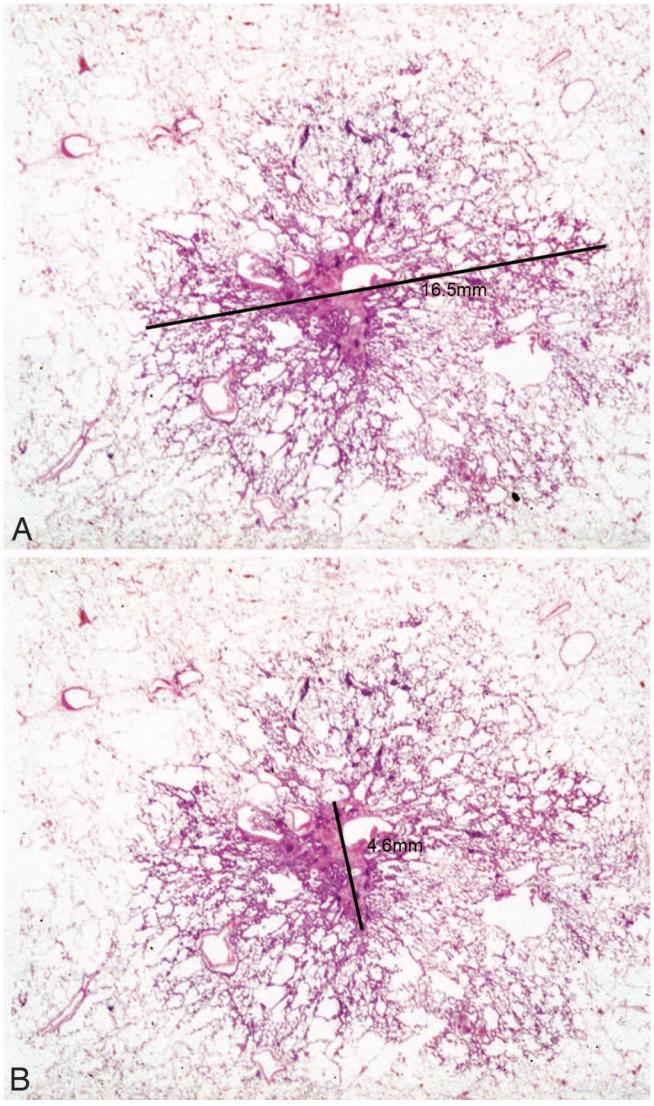

Figure 2. *pT staging in nonmucinous adenocarcinomas with a lepidic component. A, Using the seventh TNM, the greatest dimension of the tumor is 16.5 mm, with staging as pT1a. B, Using the eighth TNM staging system, the invasive component measures 4.6 mm, with staging as a minimally invasive adenocarcinoma (pT1mi). Lines indicate maximum tumor size (A) and maximum invasive tumor size (B) (hematoxylin-eosin, original magnification ×3.3).*

the International Mesothelioma Interest Group, in collaboration with the IASLC, proposed a TNM staging system based on analyses of outcomes in retrospective surgical series and small clinical trials. Subsequently accepted by the AJCC and the UICC, this became the international staging standard, although it had significant limitations. Therefore, through the development of an international data set (N = 3519), staging categories have been proposed for the 8th edition staging.[20]

T: Primary Tumor

Pathologic staging failed to demonstrate a survival difference between adjacent categories, with the exception of T3 versus T4. Performance improved with collapse of T1a and T1b into a single T1 classification (UICC); no T classification was shifted or eliminated. Tumor thickness and nodular or rindlike morphology were significantly associated with survival and are parameters recommended for further examination in relation to incorporation into future staging (Table 5).[22]

N: Regional Lymph Nodes

Clinical and pathologic 7th edition N1 and N2 classifications (UICC), comprising ipsilateral, intrathoracic nodal metastases, are combined into N1 in the 8th edition. Nodes previously classified as N3 in the 7th edition are reclassified as N2 in the 8th edition (Table 5).[21]

M: Distant Metastases

The M classification (UICC) remains unchanged.[23]

Stage Groups

Stage groups are provided in Table 6.[23]

STAGING OF THYMIC EPITHELIAL TUMORS

Until the 8th edition, no consensus staging system had been agreed upon for thymic epithelial tumors, with numerous systems proposed during the past decades and the revised Masaoka staging system being the most frequently applied.[53] With little progress in development of an official system, the ITMIG, in collaboration with the IASLC, assembled a retrospective database of more than 10 000 cases, from which thymic epithelial tumor staging was derived.[54]

T: Primary Tumor

T is divided into 4 categories (UICC), defined by level of invasion. T1 includes tumors localized to the thymus and anterior mediastinal fat, regardless of capsular invasion, up to and including infiltration through the mediastinal pleura. Invasion of the pericardium is designated as T2. T3 includes tumors with direct involvement of a group of mediastinal structures either singly or in combination: lung, brachiocephalic vein, superior vena cava, chest wall, and phrenic nerve. Invasion of more central structures constitutes T4: aorta and arch vessels, intrapericardial pulmonary artery, myocardium, trachea, and esophagus. Size did not emerge as a useful discriminator for T (Table 7).

N: Regional Lymph Nodes

Nodal involvement is divided into anterior (N1) and deep (N2) intrathoracic regions (Table 7). A nodal map has also been developed by ITMIG, defining the location of anterior and deep lymph nodes in the mediastinum.[24] In addition, ITMIG has recommended a revised version of the 3 mediastinal compartments separated by clear anatomic structures.[55]

M: Distant Metastases

Distant metastases can involve pleural or pericardial nodules (M1a) or intraparenchymal pulmonary nodules or metastases to distant sites (M1b) (Table 7).[25–27]

Stage Groups

Thymic epithelial tumor stage groups are shown in Table 8.

STAGING OF ESOPHAGEAL AND EGJ CANCERS

These recommendations were developed specifically for the AJCC. This section uses AJCC terminology, for ease of presentation and as an educational exercise (Table 1). Chief

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Table 4. Eighth Edition TNM Stage Groupings[a]

Descriptor in 7th Edition	T/M Category	N Category			
		N0	N1	N2	N3
Tis	Tis (SCIS)	**0**	NA	NA	NA
T1	Tis (AIS)	**0**	NA	**NA**	**NA**
T1	T1mi	**IA1** (IA)	NA	**NA**	**NA**
T1 ≤ 1 cm	T1a	**IA1** (IA)	**IIB** (IIA)	IIIA	IIIB
T1 > 1–2 cm	T1b	**IA2** (IA)	**IIB** (IIA)	IIIA	IIIB
T1 > 2–3 cm	T1c	**IA3** (IA)	**IIB** (IIA)	IIIA	IIIB
T2 > 3–4 cm	T2a	IB	**IIB** (IIA)	IIIA	IIIB
T2 > 4–5 cm	T2b	**IIA** (IB)	**IIB** (IIA)	IIIA	IIIB
T2 > 5–7 cm	T3	**IIB** (IIA)	**IIIA** (IIB)	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 structures	T3	IIB	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 > 7 cm	T4	**IIIA** (IIB)	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 diaphragm	T4	**IIIA** (IIB)	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 endobronchial: location/atelectasis 3–4 cm	T2a	**IB** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T3 endobronchial: location/atelectasis 4–5 cm	T2b	**IIA** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T4	T4	IIIA	IIIA	IIIB	**IIIC** (IIIB)
M1a	M1a	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1b single lesion	M1b	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1c multiple lesions	M1c	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)

Abbreviations: AIS, adenocarcinoma in situ; M, metastasis; N, node; NA, not applicable; SCIS, squamous cell carcinoma in situ; T, tumor.

[a] Changes in stage groupings proposed for the 8th edition are in bold, and the stage in the 7th edition is given in parentheses. Adapted from Goldstraw P, Chansky K, Crowley J, et al.[12] The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11(1):39–51 with permission from Elsevier.

Table 5. Eighth Edition T, N, and M Descriptors for Staging of Mesothelioma[a]

Category	Descriptor
T	Primary tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor limited to the ipsilateral parietal ± visceral ± mediastinal ± diaphragmatic pleura
T2	Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: Involvement of diaphragmatic muscle Extension of tumor from visceral pleura into the underlying pulmonary parenchyma
T3	Describes locally advanced but potentially resectable tumor Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: Involvement of the endothoracic fascia Extension into the mediastinal fat Solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall Nontransmural involvement of the pericardium
T4	Describes locally advanced technically unresectable tumor Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: Diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction Direct transdiaphragmatic extension of tumor to the peritoneum Direct extension of tumor to the contralateral pleura Direct extension of tumor to mediastinal organs Direct extension of tumor into the spine Tumor extending through to the internal surface of the pericardium with or without a pericardial effusion; or tumor involving the myocardium
N	Regional lymph nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary, hilar, or mediastinal (including the internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal lymph nodes) lymph nodes
N2	Metastases in the contralateral bronchopulmonary, hilar, or mediastinal lymph nodes or ipsilateral or contralateral supraclavicular lymph nodes
M	Distant metastasis
M0	No distant metastasis
M1	Distant metastasis

Abbreviations: M, metastasis; N, node; T, tumor.

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Table 6. Eighth Edition Stage Groupings for Mesothelioma[a]

	N0	N1	N2
T1	IA	II	IIIB
T2	IB	II	IIIB
T3	IB	IIIA	IIIB
T4	IIIB	IIIB	IIIB
M1	IV	IV	IV

Abbreviations: M, metastasis; N, node; T, tumor.

[a] Reprinted from *J Thorac Oncol*, 11, Rusch VW, Chansky K, Kindler HL, et al.[23] The IASLC mesothelioma staging project: proposals for the M descriptors and for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for mesothelioma. *J Thorac Oncol*. 2016;11(12):2112–2119 with permission from Elsevier.

among the terminology differences are the terms category and classification. Precise following of AJCC terminology is used throughout this section, including in figures and tables.

T: Primary Tumor

T category (AJCC) is defined by depth of cancer invasion (Table 9). Malignant cells confined to the esophageal epithelium are categorized as Tis (high-grade dysplasia). Cancers confined to the mucosa are T1a (intramucosal), and those that invade beyond, but are confined to the submucosa, are T1b (submucosal). Cancers confined to the muscularis propria are T2. Cancers invading the adventitia are T3. Cancers invading adjacent structures are T4 and are subcategorized into T4a and T4b.

Table 7. T, N, and M Descriptors for Staging of Thymic Epithelial Tumors[a]

Category	Descriptors
T	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor encapsulated or extending into the mediastinal fat, may involve the mediastinal pleura
	T1a No mediastinal pleural involvement
	T1b Direct invasion of the mediastinal pleura
T2	Tumor with direct invasion of the pericardium (either partial or full thickness)
T3	A tumor with direct invasion into any of the following: lung, brachiocephalic vein, superior vena cava (SVC), phrenic nerve, chest wall or extrapericardial pulmonary artery or vein
T4	A tumor with invasion into any of the following: aorta (ascending, arch or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus
N	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in anterior (perithymic) nodes
N2	Metastasis in deep intrathoracic or cervical nodes
M	
M0	No metastatic pleural, pericardial or distant sites
M1	
a	Separate pleural or pericardial nodule(s)
b	Distant metastasis beyond the pleura or pericardium (includes intraparenchymal lung nodules)

Abbreviations: M, metastasis; N, node; T, tumor.

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Table 8. TNM Categories for Thymic Epithelial Tumors[a]

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
IIIa	T3	N0	M0
IIIb	T4	N0	M0
IVa	T any	N1	M0
	T any	N0,1	M1a
IVb	T any	N2	M0, M1a
	T any	N any	M1b

Abbreviations: M, metastasis; N, node; T, tumor.

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N: Regional Lymph Nodes

The total number of regional lymph nodes containing metastases (positive nodes) is used to determine N category (Table 9). In categorizing N, data and analysis support coarse groupings of number of positive nodes (0, 1–2, 3–6, 7 or more) that harmonize with stomach N categories. These groups are N1 (1–2), N2 (3–6), and N3 (7 or more).

Table 9. Cancer Staging Categories for Cancer of the Esophagus and Esophagogastric Junction[a]

	Criteria
T category	
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a[b]	Tumor invades the lamina propria or muscularis mucosae
T1b[b]	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a[b]	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b[b]	Tumor invades other adjacent structures, such as aorta, vertebral body, or trachea
N category	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
M category	
M0	No distant metastasis
M1	Distant metastasis

Abbreviations: M, metastasis; N, node; T, tumor.

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[b] Subcategory.

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M: Distant Metastases

No evidence of metastasis to distant sites is categorized as M0. If metastases to distant sites are evident, these are categorized as M1 (Table 9).

Nonanatomic Categories

It is crucial to determine if histopathologic cell type is either squamous cell carcinoma or adenocarcinoma for all esophageal cancers, because cell type is a staging bifurcation point. Adenosquamous carcinoma, neuroendocrine cancers, and adenocarcinoma with neuroendocrine features are also staged using these criteria.

The nonanatomic cancer category *grade* (G) is critical in early-stage cancers (Table 9). Undifferentiated (G4) cancers will require additional pathologic analyses to expose histopathologic cell type. If glandular origin can be determined, the cancer is staged as a G3 adenocarcinoma; if a squamous origin can be determined or if the cancer remains undifferentiated after full analysis, it is staged as a G3 squamous cell carcinoma.

Cancer location is not important for adenocarcinoma staging, but in conjunction with grade it is necessary to subgroup pT3N0M0 squamous cell carcinoma (Table 9). The definition of the EGJ is revised such that cancers involving it with epicenters no more than 2 cm into the gastric cardia are staged as adenocarcinomas of the esophagus and those with more than 2 cm involvement of the gastric cardia are staged as stomach cancers. This was considered by the AJCC Upper Gastrointestinal Expert Panel as a placeholder until comprehensive genomic analysis could identify cell of origin rather than arbitrary measurement locations.[56,57]

Stage Groups

Clinical Stage Groups.—New to the 8th edition is the classification of cancers prior to treatment decision: clinical stage grouping (cTNM). Clinical staging is done with limited histologic cancer data in that the TNM categories are typically defined by imaging and by microscopic examination of biopsy specimens. Dissimilar stage group composition and survival profiles necessitated clinical stage groups (cTNM) separate from pathologic stage groups (pTNM).

Squamous Cell Carcinoma.—cStage 0 comprises cTis (Figure 3, A). cStage I consists exclusively of cT1N0–1M0. cStage II comprises cT2N0–1M0 and cT3N0M0 cancers. cStage III comprises cT3N1M0 and cT1–3N2M0 cancers. cT4N0–2M0 and all cN3M0 cancers are placed in cStage IVA. cStage IVB is reserved for cM1 cancers.

Adenocarcinoma.—cStage 0 comprises cTis (Figure 3, B). cStage I consists exclusively of cT1N0M0. cStage IIA is cT1N1M0 and cStage IIB is cT2N0M0. cStage III comprises cT2N1M0 and cT3–4aN0–1M0. cStage IVA consists of T4bN0–1M0 and all cN2–N3M0 cancers. cStage IVB comprises all cM1 cancers.

pTNM Stage Groups.—Historically, pathologic classification after esophagectomy alone (pTNM) has been the sole basis for all cancer staging. Today, pathologic staging is losing its clinical relevance for advanced-stage cancer as neoadjuvant therapy replaces esophagectomy alone. However, it remains relevant for early-stage cancers and as an important staging and survival reference point, but can no longer be shared with other classifications (ie, cTNM, ycTNM, ypTNM, etc).

Squamous Cell Carcinoma.—In the 8th edition, there is no net change in the number of stage subgroups; there is, however, significant rearrangement and renaming (Figure 4, A). pStage 0 is restricted to high-grade glandular dysplasia, pTis. Subcategorization of T1 combined with grade requires 2 pStage I subgroups: pStage IA (pT1aN0M0G1) and pStage IB (pT1aN0M0G2–3, pT1bN0M0, and pT2N0M0G1). pStage IIA comprises pT2N0M0G2–3 cancers, pT3N0M0 cancers of the lower thoracic esophagus, and pT3N0M0G1 cancers of the upper middle thoracic esophagus. pStage IIB comprises T3N0M0G2–3 cancers of the upper middle thoracic esophagus and pT1N1M0 cancers. pStage III and pStage IV are identical for both adenocarcinoma and squamous cell carcinoma.

Adenocarcinoma.—Stage subgroups increased from 9 in the 7th edition to 10 in the 8th edition. pStage 0 is restricted to high-grade glandular dysplasia, pTis (Figure 4, B). Subcategorization of T1 combined with grade requires 3 pStage I subgroups: pStage IA (pT1aN0M0G1), pStage IB (pT1aN0M0G2 and pT1bN0M0G1–2), and pStage IC (pT1N0M0G3 and pT2N0M0G1–2). pT2N0M0G3 remains the sole cancer in pStage IIA. pStage IIB comprises T3N0M0 and pT1N1M0. pStage III is reserved for advanced cancers with relatively good survival. pT2N1M0 and pT1N2M0 form pStage IIIA, whereas pT2N2M0, pT3N1–2M0, and pT4aN0–1M0 form pStage IIIB. pStage IV was subcategorized with the realization that the most locally advanced cancers have survival similar to that of cancers with metastasis to distant sites (M1). pT4aN2M0, pT4bN0–2M0, and pTanyN3M0 are pStage IVA. Cancers with metastasis to distant sites (M1) are restricted to pStage IVB.

Postneoadjuvant Pathologic Stage Groups (ypTNM)

New to the 8th edition (AJCC) is stage grouping of patients with esophageal cancers who have undergone postneoadjuvant therapy and had pathologic review of the resection specimen. Drivers of this addition include absence of equivalent pathologic (pTNM) categories for the peculiar postneoadjuvant pathologic categories (ypT0N0–3M0 and ypTisN0–3M0), dissimilar stage group compositions, and markedly different survival profiles. The UICC does not publish these recommendations.

The groups are identical for both histopathologic cell types (Figure 5). Grade is not included in postneoadjuvant pathologic staging. ypStage I comprises ypT0–2N0M0 cancers. ypStage II consists of the single entity ypT3N0M0. ypStage IIIA comprises cancers confined to the esophageal wall with ypN1 regional nodal category (ypT0–2N1M1). ypStage IIIB comprises ypT1–3N2M0, ypT3N1M0, and ypT4aN0M0 cancers. ypStage IVA includes ypT4aN1–2M0, ypT4bN0–2M0, and ypTanyN3M0. ypStage IVB comprises ypM1 cancers.

IMPLICATIONS FOR THE PATHOLOGIST

Although publications proposing changes for 8th edition staging have been published in 2015 and 2016, and these are incorporated in part in both UICC and AJCC manuals, the UICC has recommended implementation beginning January 2017, whereas the AJCC has deferred deployment of the eighth TNM until January 1, 2018, in order to ensure that appropriate infrastructure is in place for data collection. Pathologists therefore need to know what staging system is being used for data collection in their respective countries. To facilitate consistent worldwide data collection starting in

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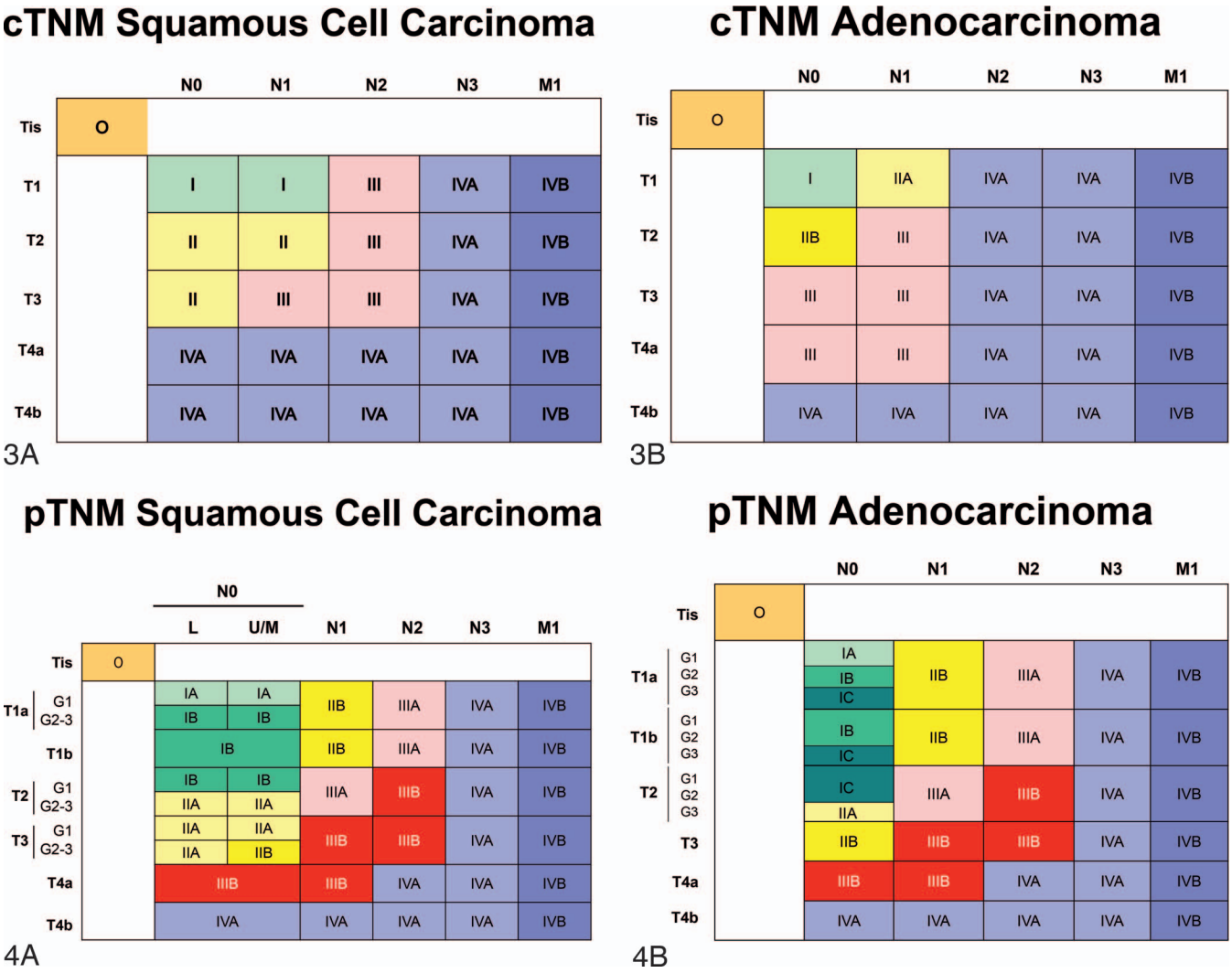

Figure 3. *Clinical stage groups (cTNM). A, Squamous cell carcinoma. B, Adenocarcinoma. Reprinted from Rice TW, Ishwaran H, Ferguson MK, Blackstone EH, Goldstraw P.*[34] *Cancer of the esophagus and esophagogastric junction: an eighth edition staging primer.* J Thorac Oncol. *2017;12:36–42 with permission from Elsevier.*

Figure 4. *Pathologic stage groups (pTNM). A, Squamous cell carcinoma. B, Adenocarcinoma. Reprinted from Rice TW, Ishwaran H, Ferguson MK, Blackstone EH, Goldstraw P.*[34] *Cancer of the esophagus and esophagogastric junction: an eighth edition staging primer.* J Thorac Oncol. *2017;12:36–42 with permission from Elsevier.*

2017, one solution is to document both the seventh and eighth TNM staging data for resected tumors, which allows the use of the eighth TNM system where desired and also allow pathologists to become familiar with the new system.

LUNG CANCER

With the move from the 7th to the 8th edition, there are several pathologic staging parameters that will require additional consideration by reporting pathologists, in particular tumor size. Appropriate measurement of size is especially important when dealing with mixed attenuation tumors, which are being found increasingly frequently as computed tomography screening for lung cancer becomes more widely adopted.[43,44] The relatively straightforward practice of documenting a single measurement of maximum diameter will require greater thoroughness, given that every centimeter now counts towards a higher T. There is often a lack of appreciation of the importance of accurate measurement, and some pathologists tend to approximate to the nearest 5 or 10 mm, so the importance of precise measurement needs to be stressed to all concerned. A cancer measuring 3 × 3 × 2 cm is very unlikely in reality and warrants immediate remeasurement, as the measurement probably represents liberal rounding off of the actual size.

Measurement of only the invasive component of adenocarcinomas will also require a greater degree of time and effort to ensure consistency and accuracy,[58] and reports will additionally require documentation of whole tumor size. Proposals for dealing with potential difficulties are discussed thoroughly in the paper by Travis et al,[37] emphasizing the importance of distinguishing the tumor from adjacent inflammatory/pneumonic changes, how to deal with irregular masses, and the importance of reevaluating the T size at the time of microscopic examination. For example, it is not infrequent that a lepidic component is not identified on initial gross examination, and will require a return to the specimen

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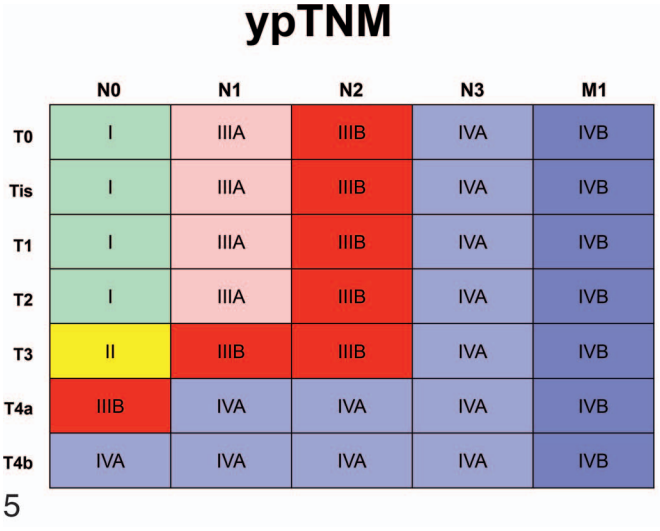

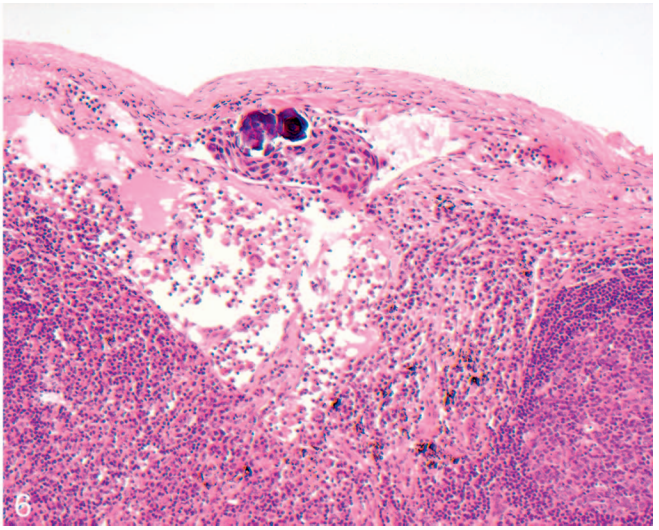

Figure 5. *Postneoadjuvant pathologic stage groups (ypTNM): squamous cell carcinoma and adenocarcinoma. Reprinted from Rice TW, Ishwaran H, Ferguson MK, Blackstone EH, Goldstraw P.*[34] *Cancer of the esophagus and esophagogastric junction: An eighth edition staging primer.* J Thorac Oncol. *2017;12:36–42 with permission from Elsevier.*

Figure 6. *An isolated cluster of tumor cells, including psammoma bodies, lies in a subcapsular sinus. This is staged as N0(i+) (hematoxylin-eosin, original magnification ×100).*

for further sampling and/or further measurement, as well as review of imaging. In relation to tumors containing localized areas of scarring, another infrequent occurrence, these are recommended to be included within the size measurement unless the tumor comprises solely small foci at the edge of the scar. Microscopic extensions at the edge of tumors, including spread through airspaces, additional nodules (see staging of multiple nodules) and lymphovascular invasion, are not to be included within the T size.

Even before dissection starts, specimens will have to be handled more carefully, ideally with inflation by the airways using formalin, or by direct injection into the parenchyma if the airways are obstructed. This will be especially important in subsolid and pure ground-glass nodules, where collapse of the specimen may affect measurement of cancer size. Fixation in formalin has also been shown to reduce the size of cancers,[59] although this predates the revised staging of adenocarcinomas. The actual impact of fixation on staging remains uncertain, given that the majority of laboratories undertake measurement after fixation by practical necessity. A gross photograph of the cancer at the time of initial cross section may now be of significant value, in order to allow correlation with microscopic findings, which might be difficult once dissection of the lobe is complete. Initial documentation may particularly be of critical importance should frozen section or removal of tumor for biobanking occur, thus compromising the ability to accurately determine size thereafter.

Finally, there have long been discussions among pathologists regarding whether all lepidic components are truly in situ, or whether some examples of lepidic growth represent the invasive component growing out from the central mass. It is likely that both scenarios occur, but the significance of the latter is unknown. Until prognostic data are presented, the current definition implies that any lepidic component should not be included in the measurement used for invasive tumor size for T. Elastic stains may again be of value in this setting.

It is also important to note that a degree of discordance between clinical staging via imaging and pathologic staging should be expected, as solid areas may simply reflect collapse within the tumor without invasion or the presence of mucin within alveolar spaces in a mucinous adenocarcinoma.[60] Additionally, computed tomography–pathologic correlation studies have shown that around 40% of purely ground-glass tumors measuring more than 10 mm contain invasive components.[61] Nevertheless, despite these inconsistencies, the practice of measuring invasive size should pave the way for better stratification of patients in relation to prognosis and adjuvant therapy, and it is up to the lung cancer community to continue to test and validate these recommendations and recommend refinements when appropriate.

In relation to regional lymph node staging, staging N classifications remain unchanged, although there are recommendations to collect additional data on the number of individual lymph node stations involved and the number of lymph nodes within individual stations.[15] Although the number of lymph node stations is relatively easy and reproducible data to collect, pathologists deciding to collect data on individual lymph nodes should liaise with their surgeons, as lymph nodes are often cut up into several pieces within the operating theatre in relation to frozen sections and intraoperative decisions. Pathologists also need to document extracapsular extension of tumor to the margin of samples from N1 and N2 stations, because, if these are present, the resection should be defined as microscopically incomplete (R1). Documenting N1 disease by direct extension rather than by lymphatic spread should also be considered, in relation to future studies on prognostication.[62,63] Also, isolated tumor cells (single tumor cells or small clusters less than 0.2 mm in greatest dimension) should be documented according to the staging recommendations (Figure 6).

A further issue to emphasize is ensuring that all lymph nodes are submitted for microscopic examination.[64,65] This is not just within separately submitted samples (where lymph

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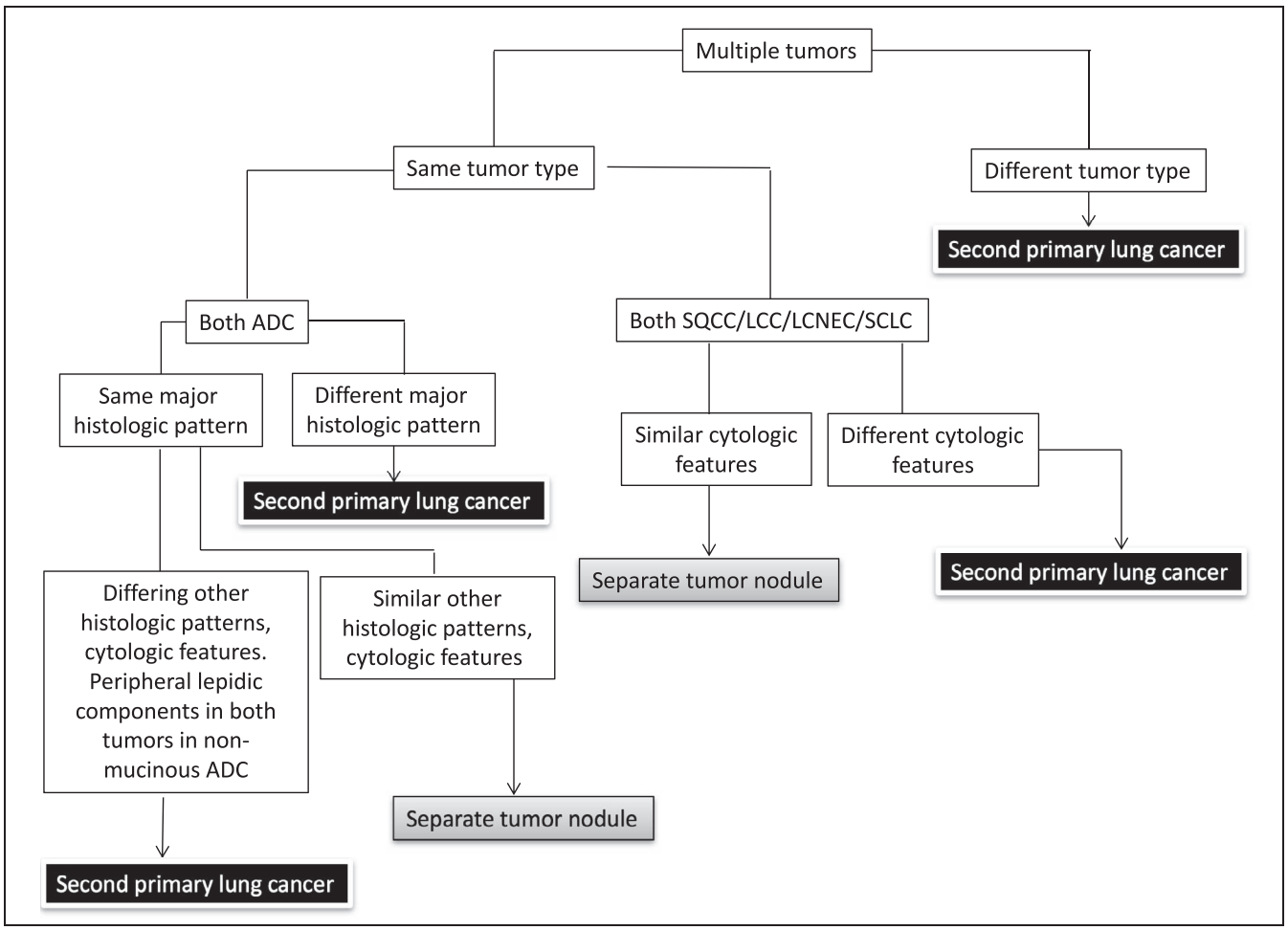

Figure 7. *Comprehensive histologic assessment: stepwise assessment of tumor type, histologic patterns in adenocarcinoma, and cytologic features allows more accurate and reproducible distinction between second primary lung cancers and separate tumor nodules. Abbreviations: ADC, adenocarcinoma; LCC, large cell carcinoma; LCNEC, large cell neuroendocrine carcinoma; SCLC, small cell lung carcinoma; SQCC, squamous cell carcinoma. Modified and used with permission by Wolters Kluwer Health, Inc, from Girard N, Deshpande C, Lau C, et al.*[70] *Comprehensive histologic assessment helps to differentiate multiple lung primary nonsmall cell carcinomas from metastases*. Am J Surg Pathol. *2009;33(12):1752–1764. Promotional and commercial use of the material in print, digital, or mobile device format is prohibited without the permission from the publisher Wolters Kluwer. Please contact healthpermissions@wolterskluwer.com for further details*.

nodes should be cut into slices 2–3 mm thick and placed in the appropriate number of cassettes, rather than crammed into one), but ensuring that more deeply sited lymph nodes within segmentectomies, lobectomies, and pneumonectomies are identified and submitted for microscopic examination. This latter practice improves the accuracy of staging and prognostication,[65] and there is also evidence that this practice reduces mortality.[66–68]

M classification remains a relatively rare occurrence in the handling of resection specimens. Pathologists should not conclude the reports as pM0, but rather leave this as blank unless there is evidence of metastatic disease, in which case pM1a and pM1b or pM1c should be assigned. When considering whether a separate nodule at the periphery of the same lung is intrapulmonary (pT3/pT4) or a pleural nodule (pM1a), the pathologist may be required to make a subjective judgment, although, as a rule of thumb, if more tumor lies outside the visceral pleura, pM1a is appropriate. If there is significant doubt, the general principle of staging is to apply the lower stage.

In relation to multiple tumors presenting in the lung, the criteria of Martini and Melamed[69] have been succeeded by the practice of a diagnostic algorithm of comprehensive histologic assessment, where assessment of tumor type, predominant pattern, additional pattern, and cytologic features are used sequentially to distinguish between separate primary lung cancers and intrapulmonary metastases (Figure 7).[70] The ability to undertake this has been shown to be reproducible among practicing pathologists, and it should be used in conjunction with other parameters such as imaging and, if required, molecular analysis. Best practice is most likely reviewing these cases in a multidisciplinary setting.[71]

MESOTHELIOMA

Pathologic staging of mesothelioma should be undertaken for larger specimens, such as decortications and extrapleural pneumonectomies. The 8th edition simplifies both T and N staging, and it is hoped that this will allow better stratification of patients for management decisions. Recent papers have suggested that tumor volume and maximal thickness of tumor samples may carry prognostic significance, and, although tumor volume will likely remain the domain of the imaging community, measurement of tumor

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thickness may become increasingly important as a parameter as more data are collected.[72] Further research into this area is encouraged. Moreover, recent data describing differences in immune-genomic phenotyping within resected mesothelioma specimens should encourage pathologists to save and evaluate multiple areas of the resected specimen.[73] Pathologists need to be aware of mesothelioma involving the lung filling airspaces in discohesive fashion, mimicking desquamative interstitial pneumonia, as cases will be understaged if this is not recognized. Care also needs to be taken to ensure that mesothelial cells within lymph nodes represent metastatic disease and are not benign mesothelial inclusions.[74]

THYMIC EPITHELIAL TUMORS

Unlike lung cancer, where staging has undergone several iterations that have allowed precise definition of anatomic parameters (such as invasion of the visceral pleura), definitions of T, N, and M classifications in thymic malignancies relied heavily on expert consensus for this first version. For example, when ITMIG initially held meetings to assess the Masaoka-Koga staging system, it became apparent that pathologists from various countries defined involvement of the pericardium in completely different ways (from "adhesion only" to "partial involvement" to "infiltration to the internal surface").[75] This is now defined as infiltration into the fibrous layer (partial) and through the entire pericardium (complete). Thymic epithelial tumors are staged as pT3 when there is infiltration into the lung, which is defined as infiltration into or through the visceral pleura into the parenchyma (Figure 8, A through C). There were no data to support distinction between visceral pleural–only involvement and involvement of the lung parenchyma itself by direct spread. Of particular note, although size has become increasingly important for T in lung cancers, this parameter showed no prognostic effect, apart from in incompletely resected thymic tumors at 10 cm, although this did not predict the probability of achieving a complete resection.[26] Measurement of size is therefore not part of T, but it is still recommended that pathologists document the maximum diameter in at least 1 dimension, as this can guide histologic sampling in relation to the number of blocks and may be relevant in future analysis.

ESOPHAGEAL AND EGJ CANCERS

Clinical Categories and Grouping

Nonanatomic Clinical Categories.—Biopsy is mandatory and necessary for determination of clinical histologic cell type and clinical histologic grade (cG). Because obliterative endoscopic ablation/resection or neoadjuvant therapy may exclude future assessment of the primary cancer, this biopsy may provide the only assessment of the primary cancer.

In most instances, differentiation of cancers as squamous cell carcinoma or adenocarcinoma relies on identifying features of squamous differentiation (keratin pearl formation, intercellular bridges, and cells with abundant glassy eosinophilic cytoplasm) versus gland formation for adenocarcinoma. However, this distinction can be challenging in specimens with limited diagnostic material and in higher cG cancers. Ancillary markers, such as p63, p40, and cytokeratin 5/6 for squamous differentiation and Alcian blue–periodic acid-Schiff stain to demonstrate subtle intracellular mucin, for adenocarcinoma can be helpful.

cG is important for treatment decisions (cT1–2N0M0 adenocarcinoma and cT2N0M0 squamous cell carcinoma) and a predictor of clinical outcome. Unfortunately, it is inconsistently reported in biopsy specimens, because superficial biopsy samples may provide limited material to accurately grade the cancer. Additionally, reporting cG has not been previously required for biopsy specimens. Every attempt should be to made grade cancers using criteria outlined by the World Health Organization.[76] Low-grade (G1) and moderately differentiated cancers (G2) are likely subject to significant interobserver variability. Poor differentiation or signet-ring cell morphology (G3) are associated with poor outcome,[77] and therefore must be documented in the pathology report of this biopsy (cG) (Figure 9).

cTNM Categories.—Endoscopic mucosal resection specimens may permit microscopic determination of cT. Similarly, EUS-FNA may provide cytologic confirmation of cN+. Cytologic or histologic confirmation of cM1 is recommended by the AJCC.[36] If there is pathologic confirmation of distant metastatic cancer, categorization of this classification is pM1, not cM1, in contradistinction to cT and cN.[36]

Pathologic Categories and Grouping

Accurate pathologic staging requires careful examination of the gross specimen for cancer size, shape, configuration, location, distance from margins (proximal, distal, and radial), and nodal dissection. Inking the adventitial aspect of the specimen facilitates microscopic assessment of pT and residual tumor (R).

Lymph node dissection is a major component of pathologic staging. Optimal lymph node categorization depends on the surgeon's ability to resect adequate amounts of nodal tissue and the dissecting skills of the pathologist. First, full-thickness sections of the primary cancer and deepest extent of invasion into the adventitia are obtained. Lymph node retrieval by complete adventitial dissection can now be performed. Lack of adherence to this practice leads to false-positive radial margins. In cases where lymph node tissue is submitted as separate specimens, the number of lymph nodes, including the presence of matted lymph nodes, should be documented in the pathology report. In specimens received in multiple fragments, accurate lymph node count is not possible if the surgeon has not documented count. The surgeon must provide the number of regional lymph nodes in the fragmented specimen and document this in the operative note.

The American College of Gastroenterology has endorsed endoscopic mucosal resection as a modality for both diagnosis and treatment of mucosal nodularity in patients with Barrett esophagus.[78] Endoscopic mucosal resection specimens provide larger, intact specimens containing submucosal tissue for accurate pathologic assessment of pG, pT, and lymphovascular invasion in patients with superficial esophageal adenocarcinoma (Figure 10). In order to facilitate accurate categorization and stage grouping, specimens should be oriented and fixed by pinning to a cork board and serially sectioned after inking the lateral and deep margins of the specimen. Assessing endoscopic mucosal resection specimens is challenging because specimen edges often exhibit significant thermal artifact and tend to curl. This precludes accurate assessment of lateral mucosal margins. Duplication of muscularis muco-

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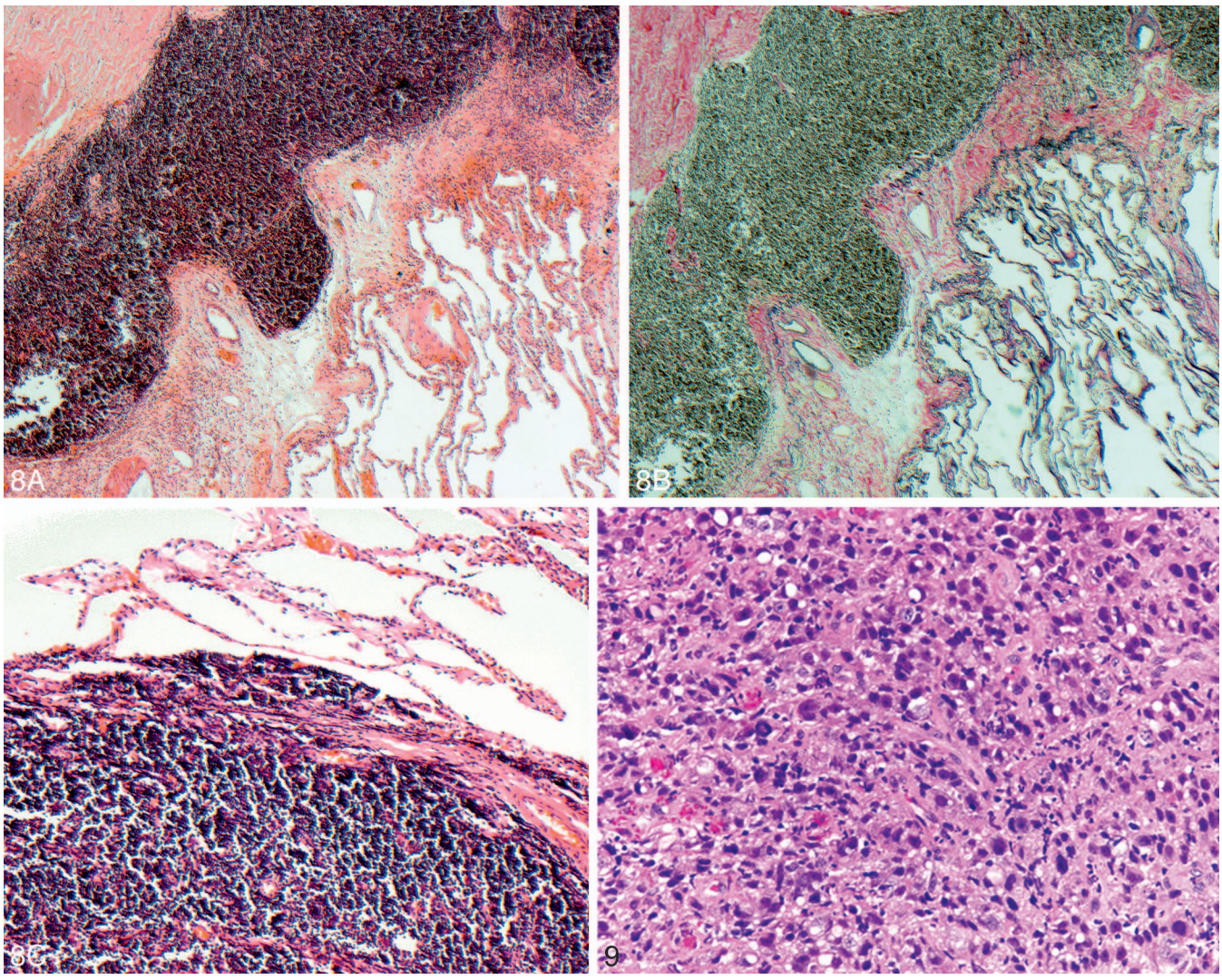

Figure 8. *A and B, Invasion through the elastin layer of the visceral pleura is highlighted by elastic van Gieson staining. C, At higher power in a different field, thymoma directly infiltrates lung parenchyma (pT3 using the eighth TNM system) (original magnification ×20 [A and B]; hematoxylin-eosin, original magnification ×40 [C]).*

Figure 9. *A biopsy from esophageal mass showing poorly differentiated adenocarcinoma with focal signet ring cell features (hematoxylin-eosin, original magnification ×200).*

sae, often seen in Barrett-related adenocarcinomas, can result in misinterpreting invasion into the space between duplicated muscularis mucosae as submucosal invasion.[79] Cancers should be categorized as pT1b only when neoplastic glands infiltrate beyond the duplicated muscularis mucosal layer, involve the plane containing submucosal glands, or are located adjacent to large-caliber arterial branches not normally found in the mucosa.

Endoscopic submucosal dissection is emerging as an endoscopic technique for en bloc resection of lesions that are likely to demonstrate submucosal invasion, lesions larger than 15 mm in size, and poorly "lifting" tumors.[80] Similar to endoscopic mucosal resection specimens, the tissue orientation in endoscopic submucosal dissection specimens facilitates the crucial distinction between pT1a and pT1b cancer.[81]

Postneoadjuvant Categories and Grouping

Gross appearance of a cancer varies depending on response to neoadjuvant therapy. With minimal response, the cancer is readily visualized and is sampled similar to a nontreated cancer. With a good response, the cancer may only show ulceration or mucosal irregularity. The cancer bed should be completely submitted for histologic evaluation.

Obliteration of anatomic landmarks poses significant diagnostic challenges in assigning ypT, especially for EGJ cancers.[82] In some institutions, for EGJ cancers, the esophageal adventitial surface and gastric serosa are inked with different colors to determine exact anatomic location and ypT.[83] This practice will be obviated with genetic signature determination of cancer cell of origin.

Neoadjuvant therapy induces several histologic changes, including ulceration, mural fibrosis, acellular mucin pools, and dystrophic calcification (Figure 11, a). Cancer cells must be distinguished from reactive stromal cells and macrophages. Regardless of the cell type, residual cancer cells usually demonstrate enlarged, irregular, and hyperchromatic nuclei with a dense homogeneous nuclear chromatin pattern and abundant eosinophilic or vacuolat-

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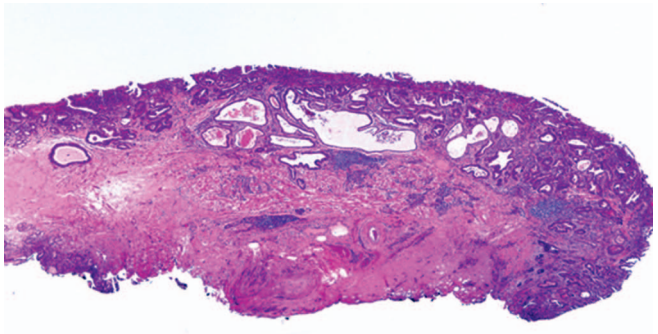

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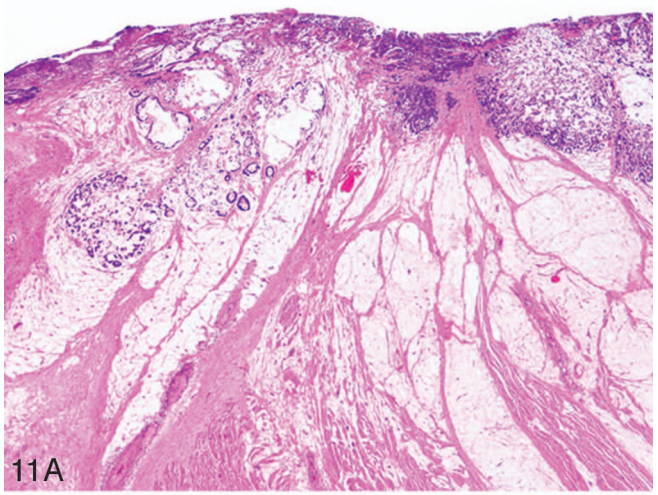
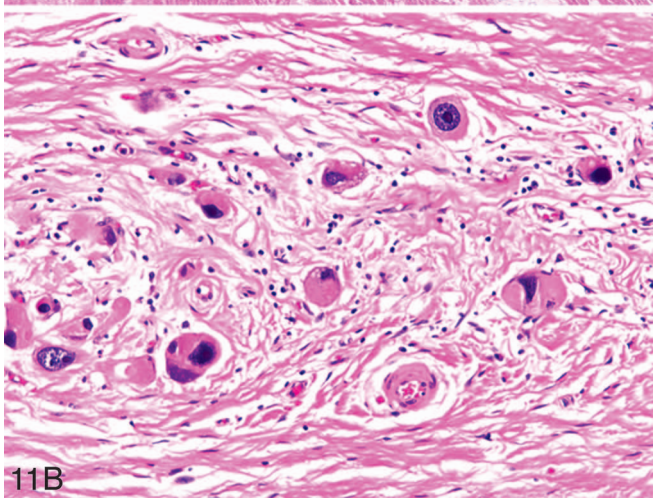


11A



11B

Figure 10. *An endoscopic mucosal resection specimen that was performed for a mucosal nodule. The specimen shows atypical glands infiltrating the inner layer of duplicated muscularis mucosae, consistent with intramucosal adenocarcinoma (hematoxylin-eosin, original magnification ×20).*

Figure 11. *A, Esophageal adenocarcinoma resection with therapy effect. The esophageal wall shows residual signet ring cell adenocarcinoma along with pools of acellular mucin (lower right). B, Residual cancer cells often show dense eosinophilic cytoplasm with irregular, hyperchromatic nuclei, and cytoplasmic vacuolation (hematoxylin-eosin, original magnifications ×20 [A] and ×200 [B]).*

ed cytoplasm (Figure 11, B). Occasionally, residual cancer cells show neuroendocrine phenotype or squamous features. These foci should be considered when determining ypT.[84]

Neoadjuvant histopathologic changes may preclude accurate grading of cancer, especially in cases with minimal residual cancer. This underscores the importance of grading cancers on preoperative biopsy. Acellular mucin pools should not be used to determine pT or R.[84]

Cancer regression grading, described by Mandard et al,[85] is the most widely used system to assess response to therapy. The 3-tiered cancer regression grading system outlined by Ryan et al[86] for assessing treated rectal cancer has shown good interobserver reproducibility among pathologists, and is incorporated in the College of American Pathologists' templates.

In patients receiving neoadjuvant therapy, lymph nodes can atrophy and may be difficult to recognize macroscopically. In these cases, histologic assessment of the majority of the periesophageal soft tissue is helpful to retrieve grossly impalpable lymph nodes. Following treatment, lymph node parenchyma often shows fibrosis, lymphoid depletion, and acellular mucin lakes. Lymph nodes with these changes and without any viable cancer cells should be considered negative for metastasis (ypN0). Immunohistochemical stains such as cytokeratin AE1/AE3 may be used to confirm the presence of rare residual cancer cells. However, as false-positive results may occur, they should be interpreted in conjunction with morphologic findings.

CONCLUSIONS

The 8th edition staging of thoracic malignancies is the result of work during a decade encompassing more than 100 000 patients. This has allowed creation of robust staging systems that need to be deployed by practicing pathologists to ensure consistent collection of data, not just for patient management in terms of prognostication and treatment decisions, but also in the context of cancer registration, epidemiology, drug trials, and research.

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APPENDIX

International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee

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