Lung Cancer Histopathology Reporting Guide

International Collaboration on Cancer Reporting (ICCR)

Family/Last name

Given name(s)

Gender ☐ Male ☐ Female

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are REQUIRED. Elements in **grey text** are RECOMMENDED.

OPERATIVE PROCEDURE

Wedge resection ☐ Lobectomy ☐
Segmentectomy ☐ Bilobectomy ☐
Other ☐ Pneumonectomy ☐

SPECIMEN LATERALITY

Left ◯ Right ◯ Not provided ◯

ATTACHED ANATOMICAL STRUCTURES

None submitted ◯ Submitted ◯

ACCOMPANYING SPECIMENS

None submitted ◯ Lymph nodes ☐ Other ☐

TUMOUR SITE

Upper lobe ☐ Middle lobe ☐ Lower lobe ☐
Bronchus *(specify site)* ☐

SEPARATE TUMOUR NODULES (Note 1)

Cannot be assessed ◯ Absent ◯
Synchronous primaries ◯ *(REQUIRED elements should be reported for each synchronous primary)*

Present ◯
Number of tumours
Site
Same lobe ☐
Different ipsilateral lobe ☐
Contralateral lung ☐

MACROSCOPIC APPEARANCE OF PLEURA (Note 2) OVERLYING TUMOUR

ATELECTASIS/OBSTRUCTIVE PNEUMONITIS (Note 3)

Present ◯ Absent ◯ Not assessable ◯

◯ Involves entire lung
◯ Involves entire lobe

MAXIMUM TUMOUR DIMENSION (Note 4)

mm

TUMOUR INVOLVES MAIN BRONCHUS AND/OR CARINA (Note 5)

Not applicable ◯ Not identified ◯
Not assessable ◯ Present ◯

◯ ≥20 mm from carina
◯ <20 mm from carina
◯ At carina

DISTANCE OF TUMOUR TO CLOSEST RESECTION MARGIN (Note 6)

mm

BLOCK IDENTIFICATION KEY

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

HISTOLOGICAL TUMOUR TYPE (Note 7)

(Value list from the World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. (2015))

Adenocarcinoma ☐
Squamous cell carcinoma ☐
Small cell carcinoma ☐
Other (*specify*) ☐

Classification of Adenocarcinoma *(Select all that apply)*

☐ Adenocarcinoma in situ (AIS)
- ☐ Non-mucinous
- ☐ Mucinous

☐ Minimally invasive adenocarcinoma (MIA)
- ☐ Non-mucinous
- ☐ Mucinous

☐ Invasive adenocarcinoma

PREDOMINANT PATTERN

◯ Lepidic ◯ Invasive mucinous
◯ Acinar ◯ Colloid
◯ Papillary ◯ Fetal
◯ Micropapillary ◯ Enteric
◯ Solid

OTHER PATTERNS *(if present)*

TYPE OF PATTERN
TYPE OF PATTERN
TYPE OF PATTERN

HISTOLOGICAL GRADE (Note 8)

Well differentiated ◯ Poorly differentiated ◯
Moderately differentiated ◯ Undifferentiated ◯
Not applicable ◯

RESPONSE TO NEOADJUVANT THERAPY (Note 9)

Not applicable ◯ Less than 10% residual viable tumour ◯
Greater than 10% residual viable tumour ◯
Treatment history not known ◯

DIRECT INVASION OF ADJACENT STRUCTURES (Note 10)

(Select all that apply)

Not identified ☐
Not applicable ☐
Trachea ☐
Chest wall ☐
Diaphragm ☐
Oesophagus ☐
Heart ☐
Great vessels ☐
Vertebral body ☐
Phrenic nerve ☐
Mediastinum ☐
Mediastinal fat ☐
Mediastinal pleura ☐
Parietal pericardium ☐
Recurrent laryngeal nerve ☐

LYMPHOVASCULAR INVASION (Note 11)

Present ◯ Not identified ◯ Indeterminate ◯

VISCERAL PLEURAL INVASION (Note 12)

Present ◯ Not identified ◯ Indeterminate ◯
Cannot be assessed ◯

⇩

Extent of pleural involvement (Note 13) PL1 ◯ PL2 ◯ PL3 ◯

PERINEURAL INVASION

Present ◯ Not identified ◯ Indeterminate ◯

OTHER NEOPLASTIC PROCESSES

(eg tumourlets, NEH, AAH, dysplasia)

NON-NEOPLASTIC LUNG DISEASE

SURGICAL MARGIN STATUS (Note 14)

Bronchial margin

Involved by invasive carcinoma ◯ Not involved ◯
Involved by CIS only ◯ Not applicable ◯
Only peribronchial soft tissue involved ◯

Vascular margin

Involved ◯ Not involved ◯ Not applicable ◯
Only perivascular soft tissue involved ◯

Other margin 1 *(specify eg parenchymal, chest wall)*

Involved ◯ Not involved ◯ Not applicable ◯

Other margin 2 *(specify eg parenchymal, chest wall)*

Involved ◯ Not involved ◯ Not applicable ◯

LYMPH NODES STATUS (Note 15)

Station(s) examined *(specify)*

Not involved ◯
Involved by micrometastasis only ◯
Involved ◯

Involved station 1
Number of involved lymph nodes
Total number of lymph nodes from this site
◯ Number cannot be determined

Involved station 2
Number of involved lymph nodes
Total number of lymph nodes from this site
◯ Number cannot be determined

Involved station 3
Number of involved lymph nodes
Total number of lymph nodes from this site
◯ Number cannot be determined

ANCILLARY STUDIES

Immunohistochemical markers (Note 16)

Positive Abs	
Negative Abs	
Equivocal Abs	

Conclusions:

Molecular data (Note 17)

EGFR result

Mutation absent ◯ Result indeterminate ◯
Mutation present ◯

Describe

EML4-ALK result

Rearrangement absent ◯ Result indeterminate ◯

Rearrangement present ◯

Describe

Other *(specify)*

Test	Result

PATHOLOGICAL STAGING (TNM 7th edition)## (Note 18)

☐ m - multiple primary tumours at a single site
☐ r - recurrent tumours after a disease free period
☐ y - classification is performed during or following multimodality treatment

T - Primary tumour

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

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

** T2 tumours with these features are classified T2a if 5 cm or less, or if size cannot be determined and T2b if greater than 5 cm but not larger than 7 cm.

N - Regional lymph nodes

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

M - Distant metastasis

◯ Not applicable
◯ M0 No distant metastasis
◯ M1 Distant metastasis
◯ M1a Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural or pericardial effusion***
◯ M1b Distant metastasis

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

Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 7th Edition, eds Leslie H. Sobin, Mary K. Gospodarowicz, Christian Wittekind. 2009, Publisher Wiley-Blackwell

Note 1 – Separate tumour nodules (Required)

Reason/Evidentiary Support:

Not infrequently, more than one discrete tumour nodule is identified in lung cancer resection specimens. It is important to distinguish synchronous primary tumours from a tumour displaying intrapulmonary metastases, as they have different prognoses and are staged differently.[1,2] Separate tumour nodules of different histologic types are considered synchronous primaries and should be recorded as such in the pathology report with the highest T category followed by the suffix "m", indicating multiplicity, or the number of tumours in parentheses (e.g. T1b(m) or T1b(2)).[1] For multiple tumour nodules with similar histologies, the criteria of Martini and Melamed have long been used in this distinction.[3] According to these criteria, tumours of similar histology are categorized as synchronous primaries if they are in different segments, lobes, or lungs, originate from carcinoma in situ, and there is neither carcinoma in lymphatics common to both nor extrapulmonary metastases at the time of diagnosis.[3] More recently, comprehensive histologic assessment has been proposed as a reliable method of separation.[4] Although a detailed discussion of this technique is beyond the scope of this document, comprehensive histologic assessment examines not only whether multiple tumours share the same major histologic pattern, but also similarities in the percentages of other histologic patterns and cytologic and stromal features.

Patients with multiple tumour nodules deemed not to represent synchronous primaries in the same lobe have survival outcomes similar to patients with solitary tumours that by size or other criteria fall into the T3 category and for this reason are staged similarly.[1] Analogously, the similarity in survival between patients with multiple tumour nodules deemed not to represent synchronous primaries in different lobes of the same lung and patients with solitary tumours that fulfil T4 criteria, has led the AJCC to recommend staging such patients similarly.

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Note 2 - Macroscopic appearance of pleura overlying tumour (Recommended)

Reason/Evidentiary Support:

The macroscopic appearance of the visceral pleural overlying a tumour can help to guide the submission of tissue blocks and gauge the index of suspicion for visceral pleural invasion. It is important to note, however, that macroscopic visceral pleural puckering is not itself diagnostic of visceral pleural invasion.[5] The presence of visceral pleural invasion must be confirmed histologically.

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Note 3 - Atelectasis/obstructive pneumonitis (Required)

Reason/Evidentiary Support:

The presence and extent of atelectasis/obstructive pneumonia factor into assignment of the T category. While most likely to be seen in association with central tumours that obstruct either the main or proximal lobar bronchi, this staging parameter can be difficult to accurately assess in resected specimens and often requires correlation with the radiological findings.[6] In certain instances, the lack of availability of radiologic information renders this parameter not assessable. In cases in which atelectasis/obstructive pneumonia is determined to be present, involvement of the entire lobe or entire lung should be specified as this has staging implications

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Note 4 - Maximum tumour dimension (Required)

Reason/Evidentiary Support:

Tumour size has long been recognized as an important prognostic indicator in lung cancer.[7] Based on survival data, the 7th edition of the TNM system has further subdivided the T category by tumour size.[1] The maximum diameter of a tumour, measured to the nearest millimetre, should ideally be assessed on the unfixed specimen to avoid the possibility of size underestimation resulting from formalin fixation-induced shrinkage.[8] In specimens harbouring multiple synchronous primaries, assignment of the T category is based on the size of the largest tumour.

Care should be taken not to overestimate tumour size by including areas of adjacent obstructive pneumonia in the tumour measurement. The gross assessment of tumour size should be confirmed microscopically and in cases where adjacent obstructive pneumonia has been mistakenly incorporated into the tumour measurement, tumour size should be adjusted accordingly.

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Note 5 – Tumour involves main bronchus and/or carina (Required)

Reason/Evidentiary Support:

Assuming the margins are negative and the tumour is not of the superficial spreading type, this staging element is generally not a factor for wedge resections and lobectomies as such specimens do not incorporate the main bronchus. The proximity of tumour to the carina is a concern in pneumonectomy specimens with central tumours, particularly those which involve the right main bronchus, as it is shorter than the left main bronchus. In such cases, accurate determination of distance of tumour from the carina requires integration of clinicoradiological data and/or consultation with the surgeon, radiologist, and/or bronchoscopist. When this information is not available, particularly as may occur in the setting of external consultation, it is permissible to indicate this staging parameter is not assessable.

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Note 6 – Distance of tumour to closest resection margin (Required)

Reason/Evidentiary Support:

Although level III-2 and above evidence supporting inclusion of distance of tumour to the closest resection margin as a required element is not available, this information should be required to facilitate post-operative treatment planning. Documentation of the macroscopic distance between a tumour and the nearest resection margin and specifying the closest margin is invaluable in cases where the distance is greater than that which could be encompassed in a tissue block. For cases in which the distance can be visualized on a microscopic slide, it is recommended that the macroscopic measurement be confirmed histologically.

The types of margins will vary according to the specimen received. For wedge resections, the only resection margin is the parenchymal margin, which is represented by the staple line. Larger resections may include parenchymal margins (e.g. lobectomies from patients with incomplete fissures) in addition to bronchial and vascular margins.

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Note 7 – Histological tumour type (Required)

Reason/Evidentiary Support:

All lung carcinomas should be typed according to the 2015 World Health Organization (WHO) Classification (see list below).[9] Accurate typing of lung carcinoma is becoming increasingly important, as histology impacts on decisions to proceed with molecular testing (see below) and the most appropriate chemotherapy regimen for patients in whom adjuvant therapy is indicated. Given the essential role that histologic type plays in patient management, a designation of non-small cell lung carcinoma, not otherwise specified (NSCLC, NOS), is not acceptable in resection specimens.[10] While it is beyond the scope of this document to provide a detailed discussion of the pathologic features of various histologic types of lung carcinoma, in poorly differentiated cases, immunohistochemistry can greatly aid in classification.

Lung carcinomas should be adequately sampled in order to ensure defining features are satisfactorily represented in the sections examined histologically. For cases in which adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA) are being considered, the IASLC/ATS/ERS requires that lesions be entirely submitted for histopathologic examination.[10]

It should be noted that the recommendations put forth in this document apply to small cell carcinoma and carcinoid tumours, as well as non-small cell types of lung carcinoma. While originally used primarily for non-small cell lung carcinoma, the TNM staging system has since also been scientifically validated for small cell carcinoma and carcinoid tumours.[11]

World Health Organization classification of tumours of the lung[9]

Epithelial tumours	
Adenocarcinoma	8140/3
Lepidic adenocarcinoma	8250/3*****
Acinar adenocarcinoma	8551/3*****
Papillary adenocarcinoma	8260/3
Micropapillary adenocarcinoma	8265/3
Solid adenocarcinoma	8230/3
Invasive mucinous adenocarcinoma	8253/3*****
Mixed invasive mucinous and non-mucinous adenocarcinoma	8254/3*****
Colloid adenocarcinoma	8480/3
Fetal adenocarcinoma	8333/3
Enteric adenocarcinoma	8144/3
Minimally invasive adenocarcinoma	
Non-mucinous	8256/3*
Mucinous	8257/3*****
Preinvasive lesions	
Atypical adenomatous hyperplasia	8250/0*****
Adenocarcinoma in situ	8140/2
Non-mucinous	8250/2*
Mucinous	8253/2*
Squamous cell carcinoma	8070/3
Keratinizing squamous cell carcinoma	8071/3
Non-keratinizing squamous cell carcinoma	8072/3
Basaloid squamous cell carcinoma	8083/3
Preinvasive lesion	
Squamous cell carcinoma in situ	8070/2
Neuroendocrine tumours	
Small cell carcinoma	8041/3
Combined small cell carcinoma	8045/3
Large cell neuroendocrine carcinoma	8013/3
Combined large cell neuroendocrine carcinoma	8013/3

Carcinoid tumours	
Typical carcinoid	8240/3
Atypical carcinoid	8249/3
Preinvasive lesion	
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia	8040/0*
Large cell carcinoma	8012/3
Adenosquamous carcinoma	8560/3
Pleomorphic carcinoma	8022/3
Spindle cell carcinoma	8032/3
Giant cell carcinoma	8031/3
Carcinosarcoma	8980/3
Pulmonary blastoma	8972/3
Other and unclassified carcinomas	
Lymphoepithelioma-like carcinoma	8082/3
NUT carcinoma	8023/3*
Salivary gland-type tumours	
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Epithelial- myoepithelial carcinoma	8562/3
Pleomorphic adenoma	8940/0

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Note 8 – Histological grade (Recommended)

Although a tiered grading scheme for lung cancer is specified by the AJCC, its reproducibility and prognostic significance has not been rigorously tested.[12] According to the WHO, sarcomatoid carcinomas (pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, and carcinosarcoma) and pulmonary blastoma are classified as high grade (poorly differentiated) and large cell carcinoma is classified as undifferentiated. However, a definitive grading system for resected lung adenocarcinomas has yet to be established and there are insufficient data to determine how to grade squamous and adenosquamous carcinoma and as such, these tumours can be assigned the 'not applicable' category.[9] Alternatively, for lung adenocarcinoma one grading system that has been proposed by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS) and European Respiratory Society (ERS) but has not yet been formally adopted is based on the predominant histologic subtype and has been show to correlate with prognosis.[13-15] In this scheme, lepidic-predominant tumours (grade 1) correspond to well-differentiated tumours, acinar or papillary-predominant tumours (grade 2) behave as moderately differentiated tumours, and solid or micropapillary-predominant tumours (grade 3) would be considered poorly differentiated tumours.[9] Cribriform predominant tumours are currently classified alongside acinar predominant tumours as G2, but may show worse prognosis. Invasive mucinous adenocarcinoma and colloid adenocarcinoma are classified as G3. In tumours that exhibit more than one grade of differentiation, the grade of the least differentiated component should be reported as the histological grade. The WHO Classification of Lung, Pleura, Thymus and Heart should be consulted for the applicability and/or assignment of histologic grade for tumours not discussed here.

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Note 9 - Response to neoadjuvant therapy (Required)

Reason/Evidentiary Support:

Quantification of the extent of tumour regression in patients who have received neoadjuvant chemotherapy and/or radiation therapy is prognostically useful.[16,17] An estimation of whether greater or less than 10% residual viable tumour is present in the resection specimen should be reported and the "y" prefix included as part of the TNM pathologic stage.

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Note 10 – Direct invasion of adjacent structures(Required)

Reason/Evidentiary Support:

Extension of tumour into extrapulmonary structures is an adverse prognostic factor, the degree of which depends on the structures involved.[2] Occasionally, lung cancer resections will include extrapulmonary structures either en bloc or separately. The presence or absence of invasion into extrapulmonary structures in such cases should be reported and the involved structures should be specified.

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Note 11 – Lymphovascular invasion (Required)

Reason/Evidentiary Support:

Lymphovascular invasion has been demonstrated to be an independent prognostic factor in lung carcinoma and is an exclusionary criterion for the new entities of adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA).[9,18-21] A number of studies has evaluated the prognostic impact of large vessel (arterial and/or venous) invasion independent of lymphatic invasion with somewhat conflicting results.[22-24] For this reason, it is permissible to report the presence of vascular and/or lymphatic invasion under the single heading of lymphovascular invasion.

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Note 12 – Visceral pleural invasion (Required)

Reason/Evidentiary Support:

The presence of tumour at the surface of the visceral pleura has been recognized as an independent adverse prognostic factor for quite some time.[7] More recently, penetration through the visceral pleural elastic layer was shown to have the same prognostic impact.[25,26] With the release of the current staging classification, criteria for visceral pleural invasion (VPI) have been more clearly defined to encompass both invasion beyond the visceral pleural elastic layer and extension to the visceral pleural surface.[5] For tumours that are in contact with the visceral pleura and do not clearly extend to the visceral pleural surface, elastic stains can aid in the detection of tumour cells beyond the visceral pleural elastic layer.

Often, there is not one, but two perceptible visceral pleural elastic layers. In most individuals, the elastic layer that is closer to the surface of the visceral pleura, typically referred to as the outer or external elastic layer, is thicker and more continuous, while within the visceral pleural connective tissue adjacent to the alveolar parenchyma lies a less prominent and/or somewhat fragmented internal (inner)

elastic layer. It is the recommendation of the International Staging Committee that the thickest elastic layer be used to assess VPI.[5] Occasionally, tumour cells are intermingled with fibres of the visceral pleural elastic layer without unequivocally penetrating beyond the visceral pleural elastic layer. This should not be interpreted as evidence of VPI.

A small percentage of cases is indeterminate for VPI. Occasionally, the visceral pleural elastic layer is imperceptible, even on elastic stains, in cases where tumour is in contact with the visceral pleura but does not extend to the visceral pleural surface. In such circumstances, the TNM classification dictates that the lower category be assigned (i.e. tumours should not be upstaged on the basis of equivocal VPI).[2] So too is the case when the visceral pleura in the vicinity of a tumour is fibrotic or elastotic to the point of obscuring the normal visceral pleural elastic landmarks so that elastin stains are difficult if not impossible to interpret. Rarely, due to adhesions or other technical factors, a specimen is received devoid of visceral pleura overlying a tumour and it is simply not possible to assess VPI.

Data on tumours that cross an interlobar fissure into an adjacent ipsilateral lobe but are not present on the visceral pleural surface are limited, but under current staging recommendations, are categorized as T2.[5]

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Note 13 - Extent of pleural involvement (Recommended)

Although tumour penetration beyond the visceral pleural elastic layer has been shown to have the same prognostic significance as tumour extending to the visceral pleural surface (see above), the pathologist may wish to provide greater detail in the report by documenting the extent of pleural invasion. A scheme for classifying pleural involvement by tumour put forth by Hammar, which has been recognised by the Japan Lung Society and recently undergone slight modification by the International Staging Committee, is as follows:

PL0, no penetration beyond the visceral pleural elastic layer;

PL1, tumour penetration beyond the visceral pleural elastic layer;

PL2, tumour extension to the visceral pleural surface; and

PL3, extension into the parietal pleura.[5,27]

PL0 is categorized as VPI absent, while both PL1 and PL2 types of VPI change the category of otherwise T1 tumours to T2. Tumours that would otherwise be categorized as T1 or T2 are changed to T3 in the presence of type PL3 pleural involvement.[5]

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Note 14 – Surgical margin status (Required)

Reason/Evidentiary Support:

Completeness of resection is not only an important prognostic factor, but also influences post-operative management, including decisions about adjuvant therapy.[28] The status of the surgical resection margin(s) should be reported for all resections, but the number and types of margins varies according to the specimen received. For wedge resections, the only resection margin is the parenchymal margin, which is represented by the staple line. Larger resections may include parenchymal margins (e.g. lobectomies from patients with incomplete fissures) in addition to bronchial and vascular margins. Depending on the anatomy and extent of resection, these may be singular (one bronchial margin and one vascular margin composed of an arterial and venous margin) or multiple.

A positive bronchial or vascular margin is widely considered to represent tumour within the lumen that is densely adherent to and/or involving the wall. According to several studies, tumour restricted to the peribronchial or perivascular soft tissue at the margin or the presence of lymphatic permeation alone at the margin is also prognostically important.[29-32] Recently, however, the significance of peribronchial soft tissue involvement without mucosal involvement has been called into question.[33] Data on the impact of intraluminal tumour alone at the margin are too limited to draw meaningful conclusions. When reporting the presence of tumour at the bronchial or vascular margin, the pathologist should delineate the nature of the involvement.

The significance of carcinoma in situ (CIS) at the bronchial margin remains unresolved due to its rare occurrence.[34] Results of several studies suggest the presence of CIS at the margin is not an independent prognostic factor.[34,35] Nevertheless, it is important to report CIS at the margin so that additional data might permit a more conclusive assessment of its role in prognosis.

En bloc resections contain additional margins (e.g. rib, chest wall soft tissue), the nature of which is dependent on the type and extent of extrapulmonary structures resected. Ideally, the surgeon will designate the location of the resection margin(s) of extrapulmonary structures prior to submission of the specimen, but in ambiguous cases, direct communication will help to ensure appropriate handling and submission of tissue for histopathologic examination. The status of additional margin(s) and their location(s) should be specified in the pathology report.

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Note 15 – Lymph node status (Required)

Reason/Evidentiary Support:

Lymph node metastases are an adverse prognostic factor, the extent of which is dependent on the location of the involved lymph nodes.[36] The site(s) of involvement (lymph node stations) should be recorded according to the IASLC lymph node map.[2] Given the nature of the procedure, lymph nodes obtained by mediastinoscopy are often received fragmented and unless specified by the surgeon, it may not be possible to distinguish a single fragmented lymph node from fragments of multiple lymph nodes. For this reason, only if the actual number of nodes is known or provided should it be quantified. Otherwise, it is permissible to report the sites of nodal metastases without specifying the number involved. Cases with only micrometastasis (greater than 0.2 mm but less than or equal to 0.2 cm) to lymph nodes can be classified as involved by micrometastasis only. Isolated tumour cells (ITC) in lymph nodes (less than 0.2 mm in greatest dimension) do not impact the pN designation and cases with only ITC are classified as pN0.

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Note 16 – Immunohistochemical markers (Recommended)

A concerted effort should be made to classify poorly differentiated lung cancers in resection specimens. There have been a number of studies examining the best means for doing so using an immunohistochemical approach, which have shown TTF-1, napsin, CK5/6 and p63 to be among the most reliable markers.[37,38] p40, an antibody against an isoform of p63, has recently been reported to be a highly specific marker for squamous cell carcinoma.[39]

Mucinous adenocarcinomas of the lung can exhibit aberrant staining for markers that are more commonly associated with carcinomas of the gastrointestinal tract, such as CK20 and CDX-2, and/or fail to stain with markers typically associated with pulmonary carcinoma, such as CK7 and TTF-1.[40] In such cases, exclusion of metastasis from an extrapulmonary primary is best achieved by careful correlation with the radiological distribution of disease.

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Note 17 – Molecular data (Recommended)

EGFR result

A proportion of lung adenocarcinomas harbours mutations in the epidermal growth factor receptor (EGFR) gene that makes them susceptible to the EGFR tyrosine kinase inhibitors (EGFR-TKIs) erlotinib and gefitinib.[41,42] EGFR-TKIs have been shown to improve progression-free survival in patients with EGFR-mutated lung adenocarcinoma and these agents are being considered as first line therapy in advanced stage disease in many countries.[43] For this reason, the IASLC/ATS/ERS has recommended that patients with advanced stage lung adenocarcinoma have their tumours tested for the presence of EGFR mutations, with DNA sequencing as the preferred method of analysis.[10] The guidelines proposed by the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) expand the recommendation for EGFR mutational testing to include all lung adenocarcinomas.[44,45] The EGFR methodology should follow local/regional or national recommendations.

Other molecular data

KRAS mutations, and EML4-ALK rearrangements are but a few of the continuously expanding array of molecular alterations other than EGFR that have prognostic and/or therapeutic implications in lung cancer.

Mutations in KRAS may be associated with a lack of response to EGFR-TKIs.[46]
ALK rearrangements occur in a small subset of lung cancer patients, typically never or light smokers with pulmonary adenocarcinoma, and are associated with response to ALK inhibitors such as crizotinib.[47,48] ALK rearrangements are nearly always mutually exclusive of EGFR and KRAS mutations.[49] Similar to ALK rearrangements c-ros oncogene 1 (ROS1) rearrangements have been identified in a small subset of patients and also show response to crizotinib.[50] The National Comprehensive Cancer Network (NCCN) has recommended that patients with advanced stage non-squamous non-small cell carcinoma be tested not only for EGFR mutations, but also for ALK rearrangements.[51] In the U.S., the Food and Drug Administration (FDA)-approved methods for EML4-ALK rearrangement testing include fluorescence in situ hybridization (FISH) using a break-apart probe and most recently, Ventana ALK D5F3 immunohistochemistry to aid in the identification of patients eligible for crizotinib.[52,53] Although the package insert for crizotinib indicates that as an FDA-approved method, ALK D5F3 can be used alone to determine patient eligibility for treatment, a common practice is to screen cases with immunohistochemistry and proceed to FISH only in cases that are equivocal or positive by immunohistochemistry for confirmation of the ALK status.

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Note 18 – Pathological staging (TNM 7th edition) (Required)

The reference document: TNM Supplement: A commentary on uniform use, 4th Edition (C Wittekind editor) may be of assistance when staging.[54]

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References

1 Rami-Porta R, Ball D, Crowley J, Giroux DJ, Jett J, Travis WD, Tsuboi M, Vallieres E and Goldstraw P (2007). The IASLC Lung Cancer Staging Project: proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2(7):593–602.

2 Edge SE, Byrd DR, Compton CC, Fritz AG, Greene FL and Trotti A (eds) (2010). *AJCC Cancer Staging Manual 7th ed.*, New York, NY.: Springer.

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