Lung Cancer Histopathology Reporting Guide

International Collaboration on Cancer Reporting (ICCR)

Family/Last name

Given name(s)

Gender ☐ Male ☐ Female ☐ Intersex/indeterminate

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 ☐

Maximum tumour dimension (Note 2) mm

Macroscopic appearance of pleura overlying tumour(Note 3)

Atelectasis/obstructive pneumonitis (Note 4)

Present ◯ Absent ◯ Not assessable ◯
Involves entire lobe ◯ Involves entire lung ◯

Tumour involves main bronchus within 20 mm of carina

Involved ◯ Not involved ◯ Not assessable ◯ (Note 5)

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. (2004))

Squamous cell carcinoma ☐ Adenosquamous carcinoma ☐
Small cell carcinoma ☐ Sarcomatoid carcinoma ☐
Adenocarcinoma ☐ Carcinoid tumour ☐
Large cell carcinoma ☐ Other ☐

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 ⇒ %
- ☐ Acinar ⇒ %
- ☐ Papillary ⇒ %
- ☐ Micropapillary ⇒ %
- ☐ Solid ⇒ %

Other patterns (if present)

TYPE OF PATTERN %
TYPE OF PATTERN %
TYPE OF PATTERN %
TYPE OF PATTERN %

☐ Mucinous
☐ Colloid
☐ Fetal
☐ Enteric

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 tumor ◯
Greater than 10% residual viable tumor ◯
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 tumorlets, 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 ◯

Vascular margin

Involved ◯ Not involved ◯ Not applicable ◯

Other margin 1 eg parenchymal, chest wall

Involved ◯ Not involved ◯ Not applicable ◯

Other margin 2 eg parenchymal, chest wall

Involved ◯ Not involved ◯ Not applicable ◯

LYMPH NODES STATUS (Note 15)

Station(s) examined (specify)

Involved ◯ Not involved ◯

Station(s) involved (specify)

ANCILLARY STUDIES

Immunohistochemical markers (Note 16)

Positive Abs	
Negative Abs	
Equivocal Abs	

Conclusions:

EGFR result (Note 17)

Other molecular data (Note 18)

Test	Result

Pathological staging (AJCC 7th edition)## (Note 19)

☐ m - multiple primary tumours ☐ r - recurrent

☐ y - posttreatment

Primary tumour (T)

- ○ 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 7cm or less or tumour with any of the following features (T2 tumours with these features are classified T2a if 5cm or less); Involves main bronchus 2cm or more distal to the carina; Invades visceral pleura (PL1 or PL2); Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
- ○ T2a Tumour more than 3 cm but 5cm or less in greatest dimension
- ○ T2b Tumour more than 5 cm but 7cm or less in greatest dimension
- ○ T3 Tumour more than 7cm or one that directly invades any of the following: parietal pleural (PL3) 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
- ○ 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

Regional lymph nodes (N)

- ○ 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)

Distant metastasis (M)

- ○ 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 (in extrathoracic organs)

* 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.

** 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.

Note 1 – Separate tumour nodules

Reason/Evidentiary Support:

Not infrequently, more than one discrete tumor nodule is identified in lung cancer resection specimens. It is important to distinguish synchronous primary tumors from a tumor displaying intrapulmonary metastases, as they have different prognoses and are staged differently.[1-2] Separate tumor 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 tumors in parentheses (e.g. T1b(m) or T1b(2)).[1] For multiple tumor nodules with similar histologies, the criteria of Martini and Melamed have long been used in this distinction.[3] According to these criteria, tumors 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 tumors share the same major histologic pattern, but also similarities in the percentages of other histologic patterns and cytologic and stromal features.

Patients with multiple tumor nodules deemed to not represent synchronous primaries in the same lobe have survival outcomes similar to patients with solitary tumors 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 tumor nodules deemed to not represent synchronous primaries in different lobes of the same lung and patients with solitary tumors that fulfill T4 criteria, has led the AJCC to recommend staging such patients similarly.

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Note 2 - Maximum tumour dimension

Reason/Evidentiary Support:

Tumor size has long been recognized as an important prognostic indicator in lung cancer.[5] Based on survival data, the 7th edition of the TNM system has further subdivided the T category by tumor size.[1] The maximum diameter of a tumor, measured to the nearest millimeter, should ideally be assessed on the unfixed specimen to avoid the possibility of size underestimation resulting from formalin fixation-induced shrinkage.[6] In specimens harboring multiple synchronous primaries, assignment of the T category is based on the size of the largest tumor.

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

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Note 3 - Macroscopic appearance of pleura overlying tumor

The macroscopic appearance of the visceral pleural overlying a tumor 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.[7] The presence of visceral pleural invasion must be confirmed histologically.

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Note 4 - Atelectasis/obstructive pneumonitis

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 tumors 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 radiographic findings.[8] In certain instances, the lack of availability of radiologic information renders this parameter not assessable. Cases in which atelectasis/obstructive pneumonia is determined to be present, the extent to which the lung (entire lobe or entire lung) is involved should be specified.

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Note 5 – Main bronchus within 20 mm of carina

Reason/Evidentiary Support:

Assuming the margins are negative and the tumor 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 tumor to the carina is a concern in pneumonectomy specimens with central tumors, 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 tumor from the carina requires integration of clinicoradiographic 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 resection margin

Reason/Evidentiary Support:

Although level III-2 and above evidence supporting inclusion of distance of tumor to the closest resection margin as a required element is not available, the panel agreed that this information should be required to facilitate post-operative treatment planning. Documentation of the macroscopic distance between a tumor 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

Reason/Evidentiary Support:

All lung carcinomas should be typed according to the 2004 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 (see below).

It is anticipated that the classification of lung adenocarcinoma recently proposed by the IASLC/ATS/ERS will in large part be incorporated in the next WHO Classification, and have therefore been included in this dataset as a recommended element (refer to the dataset below. [10]

Lung carcinomas should be adequately sampled in order to ensure defining features are satisfactorily represented in the sections examined histologically. For cases in which the newly proposed entities of 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 tumors, 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 tumors.[11]

World Health Organization classification of lung neoplasms

- Squamous cell carcinoma
  - Papillary
  - Clear cell
  - Small cell
  - Basaloid
- Small cell carcinoma
  - Combined small cell carcinoma
- Adenocarcinoma
  - Adenocarcinoma, mixed subtype
  - Acinar adenocarcinoma

- Bronchioloalveolar carcinoma
  - Non-mucinous
  - Mucinous
  - Mixed non-mucinous and mucinous or indeterminate
- Solid adenocarcinoma with mucin production
- Foetal adenocarcinoma
- Mucinous ('colloid') carcinoma
- Mucinous cystadenocarcinoma
- Signet ring adenocarcinoma
- Clear cell adenocarcinoma

Large cell carcinoma
- Large cell neuroendocrine carcinoma
  - Combined large cell neuroendocrine carcinoma
- Basaloid carcinoma
- Lymphoepithelioma-like carcinoma
- Clear cell carcinoma
- Large cell carcinoma with rhabdoid phenotype

Adenosquamous carcinoma

Sarcomatoid carcinoma
- Pleomorphic carcinoma
- Spindle cell carcinoma
- Giant cell carcinoma
- Carcinosarcoma
- Pulmonary blastoma

Carcinoid tumour
- Typical carcinoid
- Atypical carcinoid

Salivary gland tumours
- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Epithelial-myoepithelial carcinoma

Pre-invasive lesions
- Squamous carcinoma in situ
- Atypical adenomatous hyperplasia
- Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

The IASLC/ATS/ERS classification of adenocarcinoma[10]

- Preinvasive lesions
  - Atypical adenomatous hyperplasia
  - Adenocarcinoma in situ (≤3 cm formerly BAC)
    - Nonmucinous
    - Mucinous
    - Mixed mucinous/nonmucinous
- Minimally invasive adenocarcinoma (≤3 cm lepidic predominant tumor with ≤5 mm invasion)
  - Nonmucinous
  - Mucinous
  - Mixed mucinous/nonmucinous
- Invasive adenocarcinoma
  - Lepidic predominant (formerly nonmucinous BAC pattern, with >5mm invasion)
  - Acinar predominant

    - Papillary predominant
    - Micropapillary predominant
    - Solid predominant with mucin production
- Variants of invasive adenocarcinoma
    - Invasive mucinous adenocarcinoma (formerly mucinous BAC)
    - Colloid
    - Fetal (low and high grade)
    - Enteric

BAC, bronchioloalveolar carcinoma

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Note 8 – Histological grade

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, histological grading is qualitative assessment of tumour differentation and for adenocarcinoma is based on conventional histological criteria (i.e. the extent to which the architectural pattern of the tumour resembles normal lung tissue and the degree of cytologic atypia).[9] In tumours that exhibit more than one grade of differentiation, the grade of the least differentiated component should be reported as the histological grade. Recently, a system of grading tumors based on histologic pattern has shown that tumors can be separated into prognostically distinct groups.[13] Validation of this proposed system will require additional studies.

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Note 9 - Response to neoadjuvant therapy

Reason/Evidentiary Support:

Quantification of the extent of tumor regression in patients who have received neoadjuvant chemotherapy and/or radiation therapy is prognostically useful.[14-15] An estimation of whether greater or less than 10% residual viable tumor 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

Reason/Evidentiary Support:

Extension of tumor into extrapulmonary structures is an adverse prognostic factor, the degree to 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

Reason/Evidentiary Support:

Lymphovascular invasion has been demonstrated to be an independent prognostic factor in lung carcinoma.[16-19] A number of studies have evaluated the prognostic impact of large vessel (arterial and/or venous) invasion independent of lymphatic invasion with somewhat conflicting results.[20-22] 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

Reason/Evidentiary Support:

The presence of tumor at the surface of the visceral pleura has been recognized as an independent adverse prognostic factor for quite some time.[5] More recently, penetration through the visceral pleural elastic layer was shown to have the same prognostic impact.[23-24] 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.[7] For tumors 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 tumor 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.[7] Occasionally, tumor cells are intermingled with fibers 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 are indeterminate for VPI. Occasionally, the visceral pleural elastic layer is imperceptible, even on elastic stains, in cases where tumor 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. tumors 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 tumor 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 tumor and it is simply not possible to assess VPI.

Data on tumors that cross an interlobar fissure into an adjacent ipsilateral lobe but are not present on the visceral pleural surface is limited, but under current staging recommendations, are categorized as T2.[7]

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Note 13 - Extent of pleural involvement

Although tumor penetration beyond the visceral pleural elastic layer has been shown to have the same prognostic significance as tumor 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 tumor put forth by Hammar, which has been recognized 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, tumor penetration beyond the visceral pleural elastic layer;

PL2, tumor extension to the visceral pleural surface; and

PL3, extension into the parietal pleura.[7,25]

PL0 is categorized as VPI absent, while both PL1 and PL2 types of VPI change the category of otherwise T1 tumors to T2. Tumors that would otherwise be categorized as T1 or T2 are changed to T3 in the presence of type PL3 pleural involvement.[7]

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Note 14 – Surgical margin status

Reason/Evidentiary Support:

Completeness of resection is not only an important prognostic factor, but also influences post-operative management, including decisions about adjuvant therapy.[26] 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 comprised of an arterial and venous margin) or multiple.

A positive bronchial or vascular margin is widely considered to represent tumor within the lumen that is densely adherent to and/or involving the wall. According to several studies, tumor 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.[27-30] Recently, however, the significance of peribronchial soft tissue involvement without mucosal involvement has been called into question.[31] Data on the impact of intraluminal tumor alone at the margin are too limited to draw meaningful conclusions. When reporting the presence of tumor at the bronchial or vascular margin, the pathologist should provide a comment delineating the nature of the involvement.

The significance of carcinoma in situ (CIS) at the bronchial margin remains unresolved due to its rare occurrence.[32] Results of several studies suggest the presence of CIS at the margin is not an independent prognostic factor.[32-33] 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 insure 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

Reason/Evidentiary Support:

Lymph node metastases are an adverse prognostic factor, the extent to which is dependent on the location of the involved lymph nodes.[34] The lymph node status should be reported as the number of lymph nodes involved and the total number of lymph nodes submitted, specifying the site(s) of involvement (lymph node stations) 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, when a determination of the actual number of nodes is not possible, it is permissible to report the sites of nodal metastases without specifying the number involved.

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Note 16 – Immunohistochemical markers

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.[35-36] p40, an antibody against an isoform of p63, has recently been reported to be a highly specific marker for squamous cell carcinoma.[37]

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.[38] In such cases, exclusion of metastasis from an extrapulmonary primary is best achieved by careful correlation with the radiographic distribution of disease.

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Note 17 – EGFR result

A small proportion of lung adenocarcinomas harbor mutations in the epidermal growth factor receptor (EGFR) gene that make them susceptible to the EGFR tyrosine kinase inhibitors (EGFR-TKIs) erlotinib and gefitinib.[39-40] Originally reported to occur most frequently in young female East Asian never-smokers whose tumors had a prominent lepidic (designated at the time as bronchioloalveolar) growth pattern, TKI-responsive EGFR mutations have also been demonstrated in patients with other demographic and clinicopathologic characteristics.[10] 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.[41] For this reason, the IASLC/ATS/ERS has recommended that patients with advanced stage lung adenocarcinoma have their tumors tested for the presence of EGFR mutations, with DNA sequencing as the preferred method of analysis.[10] It is anticipated that forthcoming guidelines jointly 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) will expand the recommendation for EGFR mutational testing to include all lung adenocarcinomas.[42] The eGFR methodology should follow local/regional or national recommendations.

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Note 18 – Other molecular data

KRAS mutations, ERCC1, RRM1, and TS expression, and EML4-ALK translocations 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 are associated with a lack of response to EGFR-TKIs.[43] High expression of the enzyme excision repair complementing factor 1 (ERCC1) predicts resistance to platinum therapy and shorter survival.[44-45] Low expression of RRM1 is associated with improved survival with gemcitabine/platin therapy.[44] High expression of (TS) confers a less favorable response to a class of drugs that includes 5-FU.[46] At present, testing for these molecular alterations is at the discretion of the reporting institution and/or preference of the treating physician.

EML4-ALK translocations, like EGFR mutations, occur in a small subset of lung cancers patients, most typically never or light smokers with pulmonary adenocarcinoma, and are the target of a selective chemotherapeutic agent.[47] The recently discovered drug, crizotinib, significantly improves progression-free survival in patients with EML4-ALK-translocated lung carcinoma.[48] EML4-ALK translocations are nearly always mutually exclusive of EGFR and KRAS mutations.[49] Given the efficacy of crizotinib, it appears likely that testing for EML4-ALK translocations in lung adenocarcinomas that lack EGFR and KRAS mutations will become standard of care in the near future. The National Comprehensive Cancer Network (NCCN) has in fact recommended that patients with advanced stage nonsquamous non-small cell carcinoma be tested not only for EGFR mutations, but also for ALK translocations.[50] The preferred and only Food and Drug Administration (FDA)-approved method for EML4-ALK translocation testing is a fluorescence in situ hybridization (FISH) assay that employs a break-apart probe.[51] Studies of other detection techniques, such as using an immunohistochemical marker that is specific for EML4-ALK, are ongoing.[52]

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Note 19 – Pathological staging (AJCC 7th edition)

The reference document: TNM Supplement: A commentary on uniform use, 4th Edition (C Wittekind editor) may be of assistance when staging.[53]

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References

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