LUNG CANCER

STRUCTURED REPORTING PROTOCOL

(2nd Edition 2013)

Core Document versions:

- AJCC Cancer Staging Manual 7th edition (including errata corrected with 5th reprint 10th Aug 2010).
- *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart*, Volume 10, 3rd edition, 2004

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Contents

Scope

This protocol contains standards and guidelines for the preparation of structured reports for resection specimens of lung cancer. It is not applicable for endoscopic biopsy specimens.

Structured reporting aims to improve the completeness and usability of pathology reports for clinicians, and improve decision support for cancer treatment. The protocol provides the framework for the reporting of any lung cancer, whether as a minimum dataset or fully comprehensive report.

Abbreviations

AJCC	American Joint Committee on Cancer
CK	cytokeratin
EGFR	epidermal growth factor receptor
EML4-ALK	EML4 (Echinoderm microtubule associated protein like 4)-ALK (anaplastic lymphoma kinase)
ERCC1	Excision repair cross-complementation group 1 protein
FISH	fluorescence in-situ hybridization
IASLC	International Association for the Study of Lung Cancer
ICCR	International Collaboration on Cancer Reporting
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
NSCLC	non-small cell lung cancer
LIS	laboratory information system
PBS	Pharmaceutical Benefits Scheme
PL	pleura
R	residual tumour
RCPA	Royal College of Pathologists of Australasia
RRM	RNA recognition motif
TTF-1	thyroid transcription factor-1
TNM	tumour–node–metastasis (a staging system)
TS	thymidylate synthase
UICC	Union Internationale Contre le Cancer (International Union Against Cancer)
VPI	visceral pleural invasion
WHO	World Health Organization

Definitions

The table below provides definitions for general or technical terms used in this protocol. Readers should take particular note of the definitions for 'standard', 'guideline' and 'commentary', because these form the basis of the protocol.

Ancillary study	An ancillary study is any pathology investigation that may form part of a cancer pathology report but is not part of routine histological assessment.
Clinical information	Patient information required to inform pathological assessment, usually provided with the specimen request form. Also referred to as 'pretest information'.
Commentary	Commentary is text, diagrams or photographs that clarify the standards (see below) and guidelines (see below), provide examples and help with interpretation, where necessary (not every standard or guideline has commentary). Commentary is used to: • define the way an item should be reported, to foster reproducibility • explain why an item is included (eg how does the item assist with clinical management or prognosis of the specific cancer). • cite published evidence in support of the standard or guideline • clearly state any exceptions to a standard or guideline. • In this document, commentary is prefixed with 'CS' (for commentary on a standard) or 'CG' (for commentary on a guideline), numbered to be consistent with the relevant standard or guideline, and with sequential alphabetic lettering within each set of commentaries (eg CS1.01a, CG2.05b).
General commentary	General commentary is text that is not associated with a specific standard or guideline. It is used: • to provide a brief introduction to a chapter, if necessary • for items that are not standards or guidelines but are included in the protocol as items of potential importance, for which there is currently insufficient evidence to recommend their inclusion. (Note: in future reviews of protocols, such items may be reclassified as either standards or guidelines, in line with diagnostic and prognostic advances, following evidentiary review).

Guideline	Guidelines are recommendations; they are not mandatory, as indicated by the use of the word 'should'. Guidelines cover items that are not essential for clinical management, staging or prognosis of a cancer, but are recommended. Guidelines include key observational and interpretative findings that are fundamental to the diagnosis and conclusion. Such findings are essential from a clinical governance perspective, because they provide a clear, evidentiary decision-making trail. Guidelines are not used for research items. In this document, guidelines are prefixed with 'G' and numbered consecutively within each chapter (eg G1.10).
Predictive factor	A *predictive factor* is a measurement that is associated with response or lack of response to a particular therapy.
Prognostic factor	A *prognostic factor* is a measurement that is associated with clinical outcome in the absence of therapy or with the application of a standard therapy. It can be thought of as a measure of the natural history of the disease.
Macroscopic findings	Measurements, or assessment of a biopsy specimen made by the unaided eye.
Microscopic findings	In this document, the term 'microscopic findings' refers to histo-morphological assessment.
Standard	Standards are mandatory, as indicated by the use of the term 'must'. Their use is reserved for core items essential for the clinical management, staging or prognosis of the cancer and key information (including observations and interpretation) which is fundamental to the diagnosis and conclusion. These elements must be recorded and at the discretion of the pathologist included in the pathology report according to the needs of the recipient of the report. The summation of all standards represents the minimum dataset for the cancer. In this document, standards are prefixed with 'S' and numbered consecutively within each chapter (eg **S1.02**).
Structured report	A report format which utilizes standard headings, definitions and nomenclature with required information.
Synoptic report	A structured report in condensed form (as a synopsis or precis).

Synthesis	Synthesis is the process in which two or more pre-existing elements are combined, resulting in the formation of something new. The Oxford dictionary defines synthesis as "the combination of components or elements to form a connected whole". In the context of structured pathology reporting, synthesis represents the integration and interpretation of information from two or more modalities to derive new information.

Introduction

Lung cancer

Lung cancer has a high mortality rate and is the commonest cause of cancer death in Australia, accounting for 19.4% of cancer-related deaths.[1-2] While lung cancer accounts for most deaths, it is only the fifth most common cancer in Australia after colorectal cancer, breast cancer, prostate cancer and melanoma.[1] The incidence and mortality from lung cancer has increased in Australian females over the last decade but decreased in males, similar to trends observed in the USA.[3] These variations have been attributed to alterations in smoking habits between the sexes over time.[4]

The average 5-year relative survival rate for non-small cell lung cancer (NSCLC) in Australia is only 12% for males and 16% for females and the 1-year relative survival rate is 36–38%.[5] While the overall survival rate for lung cancer is low, early stage NSCLC has 5 year survival rates of about 60–70% for Stage I disease and 40-55% for Stage II disease[6] and for those patients who survive 3 years from the time of diagnosis, the 5-year relative survival rate rises to 75%.[7] The treatment of choice and foremost potential for cure of Stage I–II (and some Stage IIIA) NSCLC is complete surgical resection.[8] In addition, there is evidence of a survival benefit in patients receiving adjuvant chemotherapy if they have Stage II disease or higher.[9-10]

Pathological reporting

Pathological assessment of resection specimens provides important information on the salient features of lung cancer such as tumour type, size, local extent, lymph node status and stage. This diagnostic and prognostic information forms the basis of clinical decision making by multidisciplinary management teams. Tumour typing, especially the distinction between small cell carcinoma and non-small cell carcinoma[11] is crucial in directing appropriate management. More recently, subtyping of histological types of NSCLC has also been demonstrated to play a role in determining which tumours are likely to respond to different chemotherapeutic agents. For example, adenocarcinomas are more likely to harbour genetic mutations amenable to treatment with targeted molecules.[12] Pathological staging of tumours assists in directing appropriate clinical management by helping to determine which patients are suitable for adjuvant treatment.[9] This data also provides a prediction of prognosis and a means of evaluating the outcome of different therapies among comparable groups of patients in clinical trials.[13]

Benefits of structured reporting

Given the integral role of pathology in helping to determine best management of lung cancer patients, it is imperative that the relevant information is provided in all pathology reports of lung cancer cases. Best practice requires consistent reporting of key elements in pathological assessment of tumours in a clear and comprehensive manner, to enable fully informed clinical decision making. The use of standardised structured/synoptic pathology reports assists in achieving consistency in pathology reporting, which facilitates optimal patient care. Synoptic reporting of tumours has proved to be of benefit in ensuring relevant information is included in pathology reports of numerous tumour types[14-18] and it is anticipated that this approach will also be of benefit in lung cancer.

In this document, standards and guidelines for pathology reporting of lung cancer have been devised based on best available evidence and input of consensus expert opinion from a multidisciplinary group. The aim is to provide a checklist to help pathologists to include all important data required by the treating clinician in an organised format. The synoptic report also provides easily extractible information for cancer registries and clinical audit as well as for research purposes. Importantly, free text can be used to provide additional information in the synoptic report. This is particularly important when a pathologist needs to communicate complex or unusual findings.

Our ultimate goal is to achieve the highest standards of care for patients with lung cancer. A nationally accepted system of pathology reporting will be a vital step towards this goal.

Design of this protocol

This protocol defines the relevant information to be assessed and recorded in a pathology report for lung cancer. Mandatory elements (standards) are differentiated from those that are not mandatory but are recommended (guidelines). Also, items suited to tick boxes are distinguished from more complex elements requiring free text or narrative. The structure provided by the following chapters, headings and subheadings describes the elements of information and their groupings, but does not necessarily represent the format of either a pathology report (Chapter 7) or checklist (Chapter 6). These, and the structured pathology request form (Appendix 1) are templates that represent information from this protocol, organised and formatted differently to suit different purposes.

It should be noted that if the resection specimen contains two or more primary carcinomas (as indicated by the term 'synchronous carcinomas' on the reporting checklist) then a separate reporting checklist must be completed for each primary carcinoma.

Key documents

- *Guidelines for Authors of Structured Cancer Pathology Reporting Protocol*, Royal College of Pathologists of Australasia, 2009.[19]
- *The Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Providers*, Royal College of Pathologists of Australasia, 2004.[20]
- *AJCC Cancer Staging Manual*, 6th and 7th editions, American Joint Committee on Cancer 2002 and 2010.[13,21]
- *Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart*, World Health Organization Classification of Tumours, Volume 10, 2004.[11]

Updates since last edition

- Rework of chapter 1 and appendix 1 in line with new framework
- Removal of numbering for specimen handling in Ch 2, with subsequent renumbering
- Inclusion of a new S5.02 and subsequent renumbering of this chapter
- Edits to G6.01

- Addition of G6.03
- Rework of the checklist in Ch 6.
- Inclusion of ICCR agreed REQUIRED and RECOMMENDED elements as follows:
    - Operative procedure
    - Specimen laterality
    - Attached anatomical structures
    - Accompanying specimens
    - Block identification key
    - Tumour site
    - Separate tumour nodules
    - Maximum tumour dimension
    - Macroscopic appearance of pleura overlying tumour
    - Distance of tumour to closest resection margin
    - Tumour involves main bronchus within 20 mm of carina
    - Atelectasis/obstructive pneumonitis
    - Histological tumour type
    - Histological grade
    - Visceral pleural invasion
    - Extent of pleural involvement
    - Lymphovascular invasion
    - Perineural invasion
    - SURGICAL MARGIN STATUS
        - Bronchial resection margin
        - Vascular resection margin
        - Other margins
    - Direct invasion of adjacent structures
    - Response to neoadjuvant therapy
    - LYMPH NODE STATUS
        - Station(s) examined
        - Lymph node involvement by tumour
        - Station(s) involved
    - Non-neoplastic lung disease
    - Other neoplastic processes (eg tumourlets, NEH, AAH, Dysplasia)
    - IMMUNOHISTOCHEMICAL MARKERS
        - Antibodies
        - Conclusions
    - EGFR result
    - Other molecular data
    - PATHOLOGICAL TUMOUR STAGE

Authority and development

This section provides details about the process undertaken in developing this protocol.

This edition of the protocol is an amalgam of two separate but interwoven processes.

a) The first edition of the Lung Cancer protocol was published in Feb 2010. It was developed by an expert committee as follows:

Dr Jenny Ma Wyatt (Chair and lead author), Pathologist

Associate Professor David Ball, Radiation Oncologist

Dr Belinda Clarke, Pathologist

Associate Professor Wendy Cooper, Pathologist

Associate Professor David Ellis, Pathologist

Professor Douglas Henderson, Pathologist

Professor Brian McCaughan, Surgeon

Professor Michael Millward, Medical Oncologist

That edition of the protocol was developed following the nine-step process set out in *Guidelines for Authors of Structured Cancer Pathology Reporting Protocols* [19]

b) In 2011 the International Collaboration of Cancer Reporting (ICCR) was established and developed an international cancer dataset for Lung Cancer published to :

www.rcpa.edu.au/Publications/StructuredReporting/ICCR.htm

The ICCR dataset was developed by an international group of expert pathologists and clinicians. Representation of the international committee is as follows:

Dr Kay Washington	Team Lead, Pathologist CAP
Dr Jenny Ma Wyatt	Pathologist, RCPA
Prof Douglas Henderson	Pathologist, RCPA
Dr Andrew Nicholson	Pathologist, Royal College of Pathologists, UK
Dr Alexandra Rice	Pathologist, Royal College of Pathologists, UK
Dr Kelly Butnor	Pathologist, College of American Pathologists
Dr Kirk Jones	Pathologist, College of American Pathologists
Dr Andrew Churg	Pathologist, CAP-ACP
Dr David Hwang	Pathologist, CAP-ACP

The protocols developed by the ICCR member countries, including Australia's 1st edition Lung Cancer protocol, were used as the basis for discussion of the ICCR dataset.

This edition of the Lung Cancer protocol includes all of the ICCR cancer dataset elements as well as those elements and commentary from the first edition of the Lung Cancer protocol which complement but do not overlap with the ICCR elements. The ICCR elements are identified in each chapter with the ICCR logo placed before the Standard or

Guideline number or bullet and the ICCR element description and commentary boarded by a grey box as shown below:

S2.07	**The maximum tumour dimension must be recorded.**

Additional commentary by the RCPA may be added to an ICCR element but is not included in the grey bordered area eg

S2.10	**The distance of the tumour to the closest resection margin must be recorded.**	
	CS2.10a	Although level III-2 and above evidence[22] supporting inclusion of distance of tumour to the closest resection margin as a core element is not available, the international panel agreed that 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.
	CS2.10b	The distance from the bronchial resection margin is useful information for surgical audit and for assessing the completeness of surgical resection of the tumour.

Stakeholders

ACT Health
Anatomical Pathology Advisory Committee (APAC)
Australasian Lung Cancer Trials Group (ALTG)
Australasian Society of Cardiac & Thoracic Surgeons (ASCTS)
Australian Association of Pathology Practices Inc (AAPP)
Australian Cancer Network
Australian Commission on Safety and Quality in Health Care
Australian Lung Foundation Lung Cancer Consultative Group
Cancer Australia
Cancer Council ACT
Cancer Council NSW
Cancer Council Queensland
Cancer Council SA
Cancer Council Tasmania
Cancer Council Victoria
Cancer Council Western Australia
Cancer Institute NSW
Cancer Services Advisory Committee (CanSAC)
Cancer specific expert groups – engaged in the development of the protocols
Cancer Voices
Clinical Oncology Society of Australia (COSA)
Colorectal Cancer Research Consortium
Department of Health and Ageing
Grampians Integrated Cancer Services (GICS)
Health Informatics Society of Australia (HISA)
Independent group of pathologists
Medical Software Industry Association (MSIA)
National Breast and Ovarian Cancer Centre (NBOCC)
National Coalition of Public Pathology (NCOPP)
National E-Health Transition Authority (NEHTA)
National Pathology Accreditation Advisory Council (NPAAC)
National Round Table Working Party for Structured Pathology Reporting of Cancer.
New Zealand Guidelines Group (NZGG)
NSW Department of Health
Peter MacCallum Cancer Institute
Queensland Cooperative Oncology Group (QCOG)

Representatives from laboratories specialising in anatomical pathology across Australia

Royal Australasian College of Physicians (RACP)

Southern Cancer Network, Christchurch, New Zealand

Southern Melbourne Integrated Cancer Service (SMICS)

Standards Australia

The Medical Oncology Group of Australia

The Royal Australasian College of Surgeons (RACS)

The Royal Australian and New Zealand College of Radiologists (RANZCR)

The Royal Australian College of General Practitioners (RACGP)

The Royal College of Pathologists of Australasia (RCPA)

The Thoracic Society of Australia & New Zealand (TSANZ)

Victorian Cooperative Oncology Group (VCOG)

Western Australia Clinical Oncology Group (WACOG)

Secretariat

Meagan Judge, Royal College of Pathologists of Australasia.

Development process

This protocol has been developed following the seven-step process set out in *Guidelines for Authors of Structured Cancer Pathology Reporting Protocols*.[19]

Where no reference is provided, the authority is the consensus of the expert group.

1 Pre-analytical

This chapter relates to information that should be recorded on receipt of the specimen in the laboratory.

The pathologist is reliant on the quality of information received from the clinicians or requestor. Some of this information may be received in generic pathology request forms, however, the additional information required by the pathologist specifically for the reporting of lung cancer is outlined in Appendix 1. Appendix 1 also includes a standardised request information sheet that may be useful in obtaining all relevant information from the requestor**.**

Surgical handling procedures affect the quality of the specimen and recommendations for appropriate surgical handling are included in Appendix 1.

S1.01 All demographic information provided on the request form and with the specimen must be recorded.

CS1.01a The Royal College of Pathologists of Australasia (RCPA) *The Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Providers* must be adhered to.[23] This document specifies the minimum information to be provided by the requesting clinician for any pathology test.

CS1.01b The patient's ethnicity must be recorded, if known. In particular whether the patient is of aboriginal or Torres Strait islander origin. This is in support of a government initiative to monitor the health of indigenous Australians particularly in relation to cancer.

CS1.01c The patient's health identifiers may include the patient's Medical Record Number as well as a national health number such as a patient's Medicare number (Australia), Individual Healthcare Identifier (IHI) (Australia) or the National Healthcare Identifier (New Zealand).

S1.02 All clinical information as documented on the request form must be recorded verbatim.

CS1.02a The request information may be recorded as a single text (narrative) field or it may be recorded atomically.

S1.03 The pathology accession number of the specimen must be recorded.

S1.04 The principal clinician involved in the patient's care and responsible for investigating the patient must be recorded.

CS1.04a Knowledge of the clinical presentation is an essential part of the WHO classification yet it may not be available for a number of reasons:

- The clinical assessment and staging may be incomplete at the time of biopsy.
- The pathology request is often authored by the clinician

performing the biopsy rather than the clinician who is investigating and managing the patient.

- The identity of this clinician is often not indicated on the pathology request form

In practice therefore, it is important in such cases that the reporting pathologist should be able to communicate with the managing clinician for clarification.

G1.01 Any clinical information received in other communications from the requestor or other clinician should be recorded together with the source of that information.

2 Specimen handling and macroscopic findings

This chapter relates to the procedures required after the information has been handed over from the requesting clinician and the specimen has been received in the laboratory.

Specimen handling

- Tissue banking.

  Pathologists may be asked to provide tissue samples from fresh lung specimens for tissue banking or other research purposes. The decision to provide tissue should only be made when the pathologist is sure that the diagnostic process and pathological evaluation will not be compromised. As a safeguard, research use of the specimen may be put on hold until the diagnostic process is complete so that the specimen can be retrieved if necessary.

- **Fixation – adequate fixation is required to ensure high quality pathological assessment.**

  - The resection specimen must be inflated with formalin and fixed, preferably overnight via cannulation of the bronchus at the medial resection line.[24-26]

  - For wedge resection specimens, the lung can be inflation-fixed by injection through the visceral pleura. This technique can also be used for lobectomy and pneumonectomy specimens where occlusion of the relevant bronchus by tumour prevents inflation through the bronchial lumen.

- **Specimen inspection - the specimen must be handled in a systematic and thorough fashion to ensure completeness and accuracy of pathological data.**

  - Basic aspects of the cut-up procedures and macroscopic assessment of lung cancer are described in standard texts, particularly Westra et al.[24]

  - Assessment of tumour location.

    The relevant main, lobar or segmental bronchi (if present in the specimen) must be opened seeking evidence of bronchial origin.

    Although bronchial metastases can occur, identification of a bronchial origin for the tumour is important in discriminating between a primary bronchopulmonary carcinoma and metastatic disease.

    If necessary, a metal probe can be inserted along the lumen of the bronchial system, directed towards the segment(s) where the cancer is located, and then slicing along the probe using a long-bladed knife.[24,27]

- Marking of resection margins.

  Resection margins must be inked when this may aid in assessing possible microscopic tumour involvement of surgical margins. It may be necessary to ink the hilar soft tissue surgical margin, chest wall margin or wedge biopsy surgical margin in relevant specimens with tumours close to margins. It may be useful to ink the pleural surface in areas of pleural puckering overlying the tumour.

- **The following areas must be examined and thoroughly sampled for microscopic examination:**

  a. **tumour tissue**

  b. **central scar if present**

  c. **visceral pleura overlying a peripheral tumour (and parietal pleura/chest wall if present)**

  d. **bronchial resection margin**

  e. **vascular resection margin**

  f. **all lymph nodes**

  g. **non-neoplastic lung.**

  - In view of the well recognized heterogeneity of lung cancers, the tumour should be adequately sampled to identify any different tumour types within a single macroscopic tumour.

Macroscopic findings

S2.01	**The operative procedure must be recorded.**	
	CS2.01a	Types of specimens include wedge resection, segmentectomy, lobectomy, bilobectomy or pneumonectomy.
S2.02	**The specimen laterality must be recorded.**	
S2.03	**Any attached anatomical structures must be recorded.**	
S2.04	**Any accompanying specimens must be recorded.**	
S2.05	**A block identification key must be recorded.**	
S2.06	**The tumour site must be recorded.**	

	CS2.06a	For example, upper lobe, middle lobe, lower lobe, main bronchus. If main bronchus specify the site.

G2.01 The tumour location (central or peripheral) should be recorded.

CG2.01a For a central tumour, state whether it involves mainstem, lobar or segmental bronchus.

S2.07	**The presence or absence of separate tumour nodules must be recorded.**	
	CS2.07a	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.[21,28] 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)).[28] For multiple tumour nodules with similar histologies, the criteria of Martini and Melamed have long been used in this distinction.[29] 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.[29] More recently, comprehensive histologic assessment has been proposed as a reliable method of separation.[30] 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.
	CS2.07b	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.[28] Analogously, the similarity in survival between patients with multiple tumour nodules deemed to not represent synchronous primaries in different lobes of the same lung and patients with solitary tumours that fulfill T4 criteria, has led the AJCC to recommend staging such patients similarly.
S2.08	**The maximum tumour dimension must be recorded.**	
	CS2.08a	Tumour size has long been recognized as an important prognostic indicator in lung cancer.[31] Based on survival data, the 7th edition of the TNM system has further subdivided the

		T category by tumour size.[28] The maximum diameter of a tumour, 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.[32] In specimens harboring multiple synchronous primaries, assignment of the T category is based on the size of the largest tumour.
	CS2.08b	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.
S2.09	**The macroscopic appearance of pleura overlying tumour must be described.**	
	CS2.09a	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.[33] The presence of visceral pleural invasion must be confirmed histologically.

S2.10 **The extent of direct spread of the primary tumour to other tissues must be recorded.**

CS2.10a Extrapulmonary tissues eg hilar soft tissues, parietal pleura, chest wall, mediastinal tissue, pericardium, diaphragm must be assessed and sampled if they are present.

S2.11	**The distance of the tumour to the closest resection margin must be recorded.**	
	CS2.11a	Although level III-2 and above evidence[22] supporting inclusion of distance of tumour to the closest resection margin as a core element is not available, the international panel agreed that 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.
	CS2.11b	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.

CS2.11c The distance from the bronchial resection margin is useful information for surgical audit and for assessing the completeness of surgical resection of the tumour.

S2.12	**Record whether the tumour involves main bronchus within 20 mm of the carina.**	
	CS2.12a	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 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.

S2.13 The site of all lymph nodes must be recorded and they must be assessed for possible involvement by tumour.

CS2.13a Lymph node involvement is essential for staging. Therefore, all lymph nodes must be submitted for microscopic examination.

CS2.13b Lymph nodes included in the N1 category of TNM staging may be identified by pathologists (peribronchial, hilar, intrapulmonary lymph nodes — see Appendix 7). However, N2 (and more distal) lymph nodes from specific mediastinal and subcarinal lymph node stations[34] require separate specimen identification by the referring surgeon.

S2.14	**The presence or absence of atelectasis/obstructive pneumonitis must be recorded.**	
	CS2.14a	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 radiological findings.[35] 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, the extent to which the lung (entire lobe or entire lung) is involved should be specified.

CS2.14b Tumours with partial involvement of the lung by atelectasis/obstructive pneumonitis are designated T2; involvement of the entire lung is designated T3. Small central tumours may be 'upstaged' by the presence of total atelectasis/obstructive pneumonitis into the T3 category.

S2.15 The non-neoplastic lung must be described.

CS2.15a Examination of lung tissue away from the tumour may reveal lymphatic spread of tumour, satellite nodules and other conditions (eg emphysema, fibrosis).

G2.02 Any additional relevant comments should be recorded. A descriptive or narrative field should be provided to record any macroscopic information that is not recorded in the above standards and guidelines, and that would normally form part of the macroscopic description.

CG2.02a The traditional macroscopic narrative recorded at the time of specimen dissection is often reported separately from the cancer dataset. Although this remains an option, it is recommended that macroscopic information be recorded within the overall structure of this protocol.

CG2.02b Much of the information recorded in a traditional macroscopic narrative is covered in the standards and guidelines above and in many cases, no further description is required.

3 Microscopic findings

Microscopic findings relates to purely histological assessment. Information derived from multiple investigational modalities, or from two or more chapters, are described in Chapter 5.

S3.01	**The histological tumour type must be recorded.**	
	CS3.01a	All lung carcinomas should be typed according to the 2004 World Health Organization (WHO) Classification (see Appendix 4)[11] 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.[36] 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 has therefore been included in this dataset as a recommended element (refer to the dataset below).[36] 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.[36] 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.[37]
G3.01	If adenocarcinoma, the IASLC/ATS/ERS classification should be recorded.	
	CG3.01a	The IASLC/ATS/ERS classification of adenocarcinoma is included in Appendix 5.[36]

S3.02	**The histological grade must be recorded.**	
	CS3.02a	Although a tiered grading scheme for lung cancer is specified by the AJCC, its reproducibility and prognostic significance has not been rigorously tested.[38] 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).[11] 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 tumours based on histologic pattern has shown that tumours can be separated into prognostically distinct groups.[39-40] Validation of this proposed system will require additional studies.
	CS3.02b	Several studies have shown that comprehensive histological classification of adenocarcinomas provides prognostic information. Adenocarcinoma in situ, minimally invasive adenocarcinoma and lepidic predominant patterns are associated with the best survival. Solid and micropapillary predominant patterns usually have the worse prognosis.[39-44] Acinar and papillary predominant patterns have an intermediate prognosis. However, it should be noted that there are fairly wide survival differences in histological groups when comparing the different studies. There is good reproducibility among pulmonary pathologists in determining the predominant histological pattern of adenocarcinomas although distinction of purely lepidic non-invasive growth patterns from those with invasion remains controversial.[45]
	CS3.02c	If there are variations of grade within the tumour, grading should be classified on the least differentiated area.[11]
	CS3.02d	Although the stage of disease and the performance status at diagnosis are the most powerful prognostic indicators for survival, histological grading is also an independent prognostic indicator in some studies.[46]
	CS3.02e	Grading may not be applicable for some lung neoplasms.[11] Carcinoid tumours are classified as typical or atypical, according to criteria outlined in the WHO classification of lung neoplasms.
S3.03	**Visceral pleural invasion must be recorded as present or absent.**	
	CS3.03a	The presence of tumour at the surface of the visceral pleura has been recognized as an independent adverse prognostic factor for quite some time.[31] More recently, penetration through the visceral pleural elastic layer was shown to have the same prognostic impact.[47-48] 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.[33] 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.
	CS3.03b	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.[33] Occasionally, tumour 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.
	CS3.03c	A small percentage of cases are 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).[21] 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.
	CS3.03d	Data on tumours 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.[33]
	CS3.03e	An elastic stain must be performed for all blocks where the tumour is close to the pleura and when the presence of pleural invasion is indeterminate by examination of H&E sections alone.[33,49-50] It may be necessary to perform the elastic stain on multiple blocks, especially in areas of pleural puckering. Assessment of the elastic stain may be difficult in some cases where there is reduplication or alteration of the elastic layers resulting from local fibroinflammatory changes.
G3.02	The extent of pleural involvement should be recorded.	

	CG3.02a	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 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, tumour penetration beyond the visceral pleural elastic layer; • PL2, tumour extension to the visceral pleural surface; and • PL3, extension into the parietal pleura.[33,51] 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.[33]

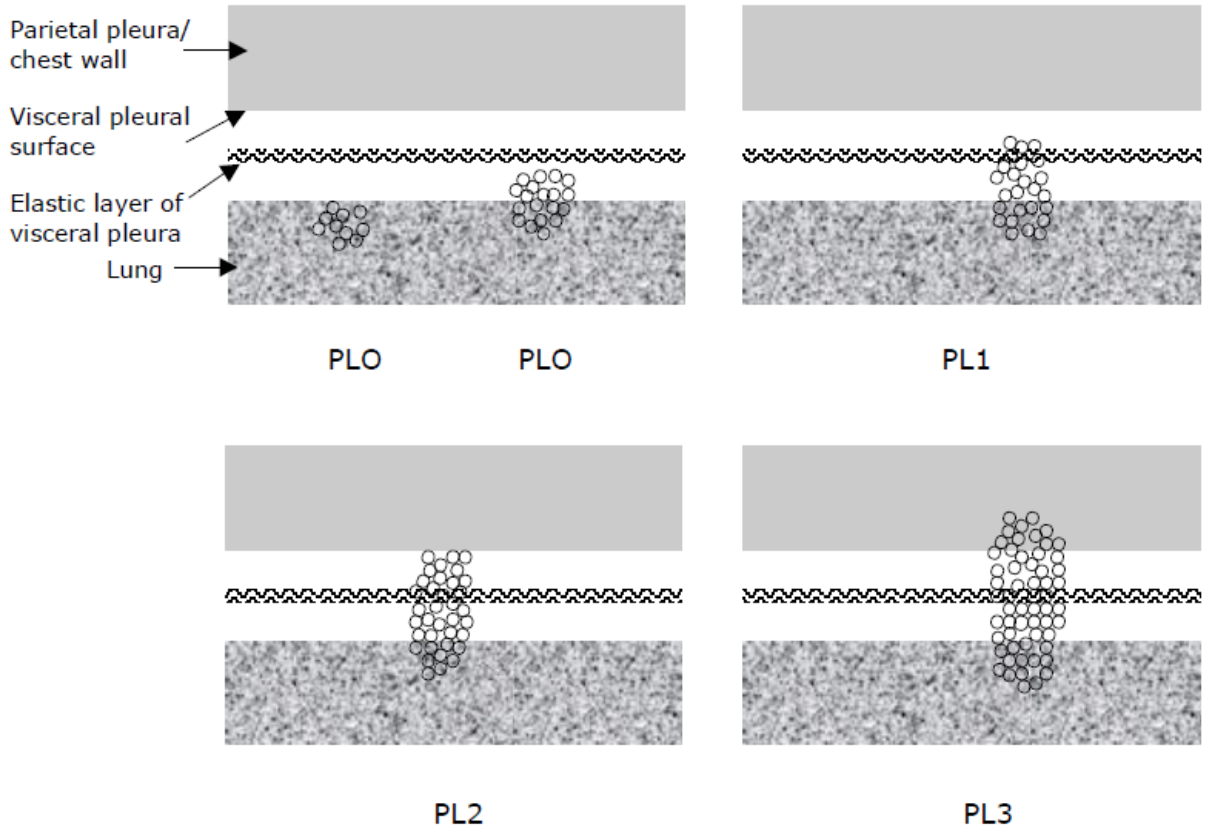
CG3.02b See Table G3.02b, Figure G3.02b and Appendix 7.

Table G3.02b Definition of visceral pleural invasion and corresponding T category[a]

PL status	Explanation	T category
Visceral pleural invasion (VPI) absent		
PL0	Tumour confined to subpleural lung parenchyma *or* Tumour invades superficially into connective tissue or intermingles with elastic fibres of visceral pleura but does not invade beyond the thick elastic layer	T1 or higher (T category determined by features other than VPI such as size etc)
Visceral pleural invasion (VPI) present		
PL1	Tumour invades ***beyond*** the elastic layer	At least T2
PL2	Tumour invades to the visceral pleural surface	At least T2
PL3	Tumour invades into parietal pleura or chest wall	At least T3

PL = pleura; VPI = visceral pleural invasion
a Modified from Travis 2009[52]

Figure G3.02b Diagram of visceral pleural invasion



S3.04	**The presence or absence of lymphovascular invasion must be recorded.**	
	CS3.04a	Lymphovascular invasion has been demonstrated to be an independent prognostic factor in lung carcinoma.[53-56] 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.[57-59] For this reason, it is permissible to report the presence of vascular and/or lymphatic invasion under the single heading of lymphovascular invasion.
	CS3.04b	Although the presence of vascular or lymphatic invasion does not change the pT staging, it is an unfavourable prognostic finding in some studies[53-56,60-61] and may influence the selection of treatment by some clinicians.

G3.03 If lymphovascular invasion is present, state whether involvement of artery, vein or lymphatic if possible and the extent of invasion (eg extensive, focal).

G3.04	The presence or absence of perineural invasion should be recorded.	
S3.05	**The status of the surgical margins must be recorded.**	
	CS3.05a	Completeness of resection is not only an important prognostic factor, but also influences post-operative management, including decisions about adjuvant therapy.[62] 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.[63-66] Recently, however, the significance of peribronchial soft tissue involvement without mucosal involvement has been called into question.[67] 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 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.[68] Results of several studies suggest the presence of CIS at the margin is not an independent prognostic factor.[68-69] 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.

CS3.05b For the bronchial resection margin, if invasive tumour is present, state whether the tumour involves bronchial tissue only or infiltrates peribronchial soft tissue.[70] For tumours involving a major bronchus and where the tumour extends close to the surgical margin on gross inspection, the microscopic clearance should be measured in millimetres.

CS3.05c For the vascular resection margin, if involved by tumour, state the nature of involvement: Tumour thrombus present in the lumen of the vessel; vessel wall involved by tumour etc.

CS3.05d Any other surgical margin such as the parenchymal margin of a wedge resection specimen, must be assessed for tumour clearance.

S3.06	**Direct invasion of adjacent structures must be recorded.**	
	CS3.06a	Extension of tumour into extrapulmonary structures is an adverse prognostic factor, the degree of which depends on the structures involved.[21] 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.

CS3.06b State whether the tumour is absent or present at the inked resection margin for any structures mentioned.

CS3.06c Measure and record the distance of tumour from the closest

margin in millimetres.

S3.07 *In situ* carcinoma must be recorded as present or absent.

CS3.07a Note presence or absence of *in situ* component (eg squamous cell carcinoma *in situ*). This is important information for follow-up of patients.

S3.08	**The response to neoadjuvant therapy must be recorded.**	
	CS3.08a	Choose from the following values: • Not applicable • Less than 10% residual viable tumour • Greater than 10% residual viable tumour • Treatment history not known
	CS3.08b	Quantification of the extent of tumour regression in patients who have received neoadjuvant chemotherapy and/or radiation therapy is prognostically useful.[71-72] 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.
S3.09	**Lymph node status must be recorded.**	
	CS3.09a	Record the stations examined, whether there is involvement by tumour or not; and where there is involvement specify the stations involved.
	CS3.09b	Lymph node metastases are an adverse prognostic factor, the extent to which is dependent on the location of the involved lymph nodes.[73] 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.[21] 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.

CS3.09c Refer to Appendix 6 for the IASLC Lymph node map.

G3.05 The extent of lymph node replacement by tumour should be recorded.

CG3.05a State whether tumour involvement of nodes is focal, extensive or complete. It should also be stated if the nodal involvement appears to be by direct invasion rather than metastatic spread even though this does not affect staging.

G3.06 The presence or absence of extracapsular extension should be recorded.

CG3.06a Although extracapsular extension does not change the pN staging, it is an important prognostic finding and may influence the selection of treatment by some clinicians. Lack of extracapsular extension is one of the requirements for a tumour to be considered as having "completeness of surgical resection", a recently developed clinicopathological concept[70] (see G5.02).

	G3.07	Any non-neoplastic lung disease should be recorded.
	G3.08	Other neoplastic processes (eg tumourlets, NEH, AAH, dysplasia) should be recorded.

CG3.08a Microscopic examination is used to confirm macroscopic impression of atelectasis/obstructive pneumonitis.

CG3.08b Microscopic examination of lung tissue away from the tumour may reveal lymphatic spread of the tumour, satellite nodules, preneoplastic lesions (eg, atypical adenomatous hyperplasia) or other conditions (eg, emphysema, respiratory bronchiolitis, interstitial lung disease, asbestosis).

G3.09 Any additional relevant comments should be recorded.

4 Ancillary studies findings

Ancillary studies may be used for a number of purposes including

- to assist in disease classification,
- to provide prognostic information or
- to predict the likelihood of patient response to specific biologic therapies.

G4.01	Results of any immunohistochemical markers used to assist in diagnosis should be recorded.	
	CG4.01a	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 A, CK5/6 and p63 to be among the most reliable markers.[74-75] p40, an antibody against an isoform of p63, has recently been reported to be a highly specific marker for squamous cell carcinoma.[76] 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.[77] In such cases, exclusion of metastasis from an extrapulmonary primary is best achieved by careful correlation with the radiological distribution of disease.
	CG4.01b	The WHO classification of lung tumours (2004)[11] relies predominantly on light microscopy for classification but immunohistochemistry may be helpful in some instances for precise subclassification in poorly differentiated tumours and exclusion of metastasis. Immunohistochemical assessment is therefore not necessary in routine diagnosis of most cases of resected lung cancer.[11] However, immunohistochemical stains may be useful in some instances to assess rarer types of lung tumours (eg large cell neuroendocrine carcinoma, spindle cell neoplasms), to distinguish between primary and metastatic lung cancers and at times, to help reach a diagnosis in small biopsy samples when there is only limited material available for morphological assessment.
	CG4.01c	Pathologists are advised to refer to available literature for greater detail regarding the most appropriate use of immunohistochemical stains in lung cancer.[11,74-76,78-82] The immunohistochemical profile of thyroid transcription factor-1 (TTF-1), cytokeratin 7 and 20 (CK7 and CK20) can be particularly useful in helping to distinguish between primary and metastatic lung adenocarcinomas (in addition to attention to tumour morphology and the clinical and radiological findings).[83] TTF-1 is a fairly specific marker for a variety of lung (and thyroid) tumours. However, its sensitivity is only high for adenocarcinomas (~75%) and small cell carcinomas (~90%), with less sensitivity observed in large cell carcinomas

(~50%) and squamous cell carcinomas (~10%) of lung origin.[78-79] TTF-1 is less useful in small cell carcinomas, as specificity is low with about 1/3–1/2 of small cell carcinomas from extrapulmonary sites also expressing this marker.[84]

While the majority of primary lung adenocarcinomas are CK7+/CK20-/TTF-1+ (~75%), CK20 may also be positive, particularly in cases with mucinous or enteric-type differentiation.[79,83-84] Immunohistochemical markers are not useful in distinguishing between primary and metastatic squamous cell carcinoma where attention to clinical scenario as well as the number and the site of lesions is more useful.

The current view of many Clinical Oncological groups[85-94] is that precise evaluation of histological subtype is now mandatory, and will be increasingly relevant to later molecular target therapy, i.e. a simple division into small cell carcinoma and non-small cell carcinoma is no longer sufficient to determine current complex treatment regimes. Immunohistochemistry may therefore become more important in the examination of lung resection specimens, as well as small bronchial biopsies, fine needle biopsies, and cytology cell block material.

CG4.01d Subtyping NSCLC in small biopsy and cytology samples

The jointly proposed guidelines from the College of American pathologists (CAP), International Association for the Study of Lung Cancer (IASLC) and Association for Molecular Pathology (AMP)[95] recommend that consideration should be given to cutting multiple additional unstained sections "up front" when the sample is first processed in the laboratory. These unstained sections could then be used for deeper levels or additional histochemical/immunohistochemical stains as required to establish the diagnosis and for subsequent molecular testing, without having to reface and recut the blocks which may result in loss of substantial tissue.

For small biopsy and cytology samples that lack clear adenocarcinoma or squamous cell carcinoma (SCC) morphology, the IASLC/ATS/ERS Multidisciplinary Classification of Lung Adenocarcinoma recommends that the use of special stains should be minimal to preserve tissue for molecular testing. The most commonly used markers for adenocarcinoma are TTF1, Napsin A or CK7 and for SCC, p63, CK5/6 or p40.[74-76,80-82]

Pathologists are advised to use the minimal number of markers to preserve tissue for molecular testing and potentially avoid the need for repeat biopsies.

In resection specimens, approximately 10% of cases will have a morphological diagnosis of undifferentiated large cell carcinomas, some of which will display an immunophenotype suggestive of adenocarcinoma or SCC but the significance of this immunophenotype in this setting is not known.

G4.02	EGFR results should be recorded if performed.	
	CG4.02a	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.[96-97] Originally reported to occur most frequently in young female East Asian never-smokers whose tumours 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.[36] 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.[92] 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.[36] The EGFR methodology should follow local/regional or national recommendations.

	CG4.02b	The jointly proposed guidelines from the College of American pathologists (CAP), International Association for the Study of Lung Cancer (IASLC) and Association for Molecular Pathology (AMP) have now been published.[95] They recommend that resected tumours which are adenocarcinomas and mixed lung cancers with an adenocarcinoma component should be tested for EGFR mutation to select patients for EGFR-targeted tyrosine kinase inhibitor therapy. For more limited lung cancer specimens (biopsies, cytology), they recommend testing of tumours where an adenocarcinoma component cannot be completely excluded.
	CG4.02c	The molecular test will often be oncologist-initiated and requires discussion between the oncologist and the pathologist, preferably in the setting of a multidisciplinary meeting. For the purposes of medicare reimbursement, EGFR mutation testing must currently be requested by, or on behalf of, a specialist or consultant physician.
	CG4.02d	The purpose of pathological evaluation of lung cancer includes the determination of molecular abnormalities that can guide patient selection for appropriate therapy.[98] Testing should be done when it is considered that the information provided will be of clinical value. This may be because of an immediate need to consider therapy, or to plan therapeutic options in the future. Currently, this is restricted to testing for abnormalities that are associated with sensitivity or resistance to small molecule inhibitors of the epidermal growth factor receptors (EGFRs) — gefitinib and erlotinib. The presence of an EGFR gene mutation in tumour tissue is required for patients to receive gefitinib under the Pharmaceutical Benefits Scheme (PBS) in Australia. Erlotinib is PBS funded but not based on

mutation testing. As yet there are no published direct trials of gefitinib and erlotinib to conclude they are equally active, although this may eventually prove to be the case.

CG4.02e The commonest activating somatic mutations in the EGFR gene are associated with favourable outcomes from treatment with such therapy,[99] while some mutations are associated with resistance to the current generation of EGFR tyrosine kinase inhibitors. The mutations are limited to exons 18–21 of EGFR and occur in non-small cell lung cancer (NSCLC) in 10–15% of Caucasians[100] and 30–40% of Asians. As well as ethnicity, the frequency of mutations is higher in NSCLC from never smokers, women, and in adenocarcinomas. Greater than 80% of mutations are either short in frame deletions in exon 19 or single point mutations in exon 21 (L858R).

CG4.02f Mutations in the KRAS gene are associated with lack of benefit from EGFR inhibitors.[101] Mutations occur in exon 2 at codon 12 or 13 and are single point mutations. Mutations in the EGFR and KRAS genes are virtually never both present in the same tumour.[101]

CG4.02g Mutation testing can be performed on fresh tissue but in routine practice is mostly performed on paraffin-embedded tissue blocks including cell blocks from cytological preparations. The diagnosis of lung cancer is often made on small biopsy or cytology samples. The small volume of tumour material available in these cases can be a limiting factor in molecular testing. The role of the anatomical pathologist, following diagnostic assessment, is primarily to select and forward the block for mutation testing. Factors to consider in selecting the most appropriate block to detect a somatic mutation by conventional DNA sequencing based techniques include the greatest volume of viable tumour material and the highest proportion of tumour cells. Specimens that have been decalcified should be avoided if possible.

CG4.02h The mutation test result should be included as a supplementary report in the original pathology report if the test has been performed by the same laboratory. However, it may be performed some years later by a completely different laboratory. In that case the test result from the molecular diagnostic laboratory may be considered a stand-alone report.

G4.03	Other molecular pathology testing result(s) should be recorded if performed.	
	CG4.03a	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.[102] High expression of the enzyme excision repair cross complementation group 1 protein (ERCC1) predicts resistance to platinum therapy and shorter survival.[103-104] Low expression of RRM1 is associated with improved survival

		with gemcitabine/platin therapy.[103] High expression of TS confers a less favorable response to a class of drugs that includes 5-FU.[105] 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 cancer patients, most typically never or light smokers with pulmonary adenocarcinoma, and are the target of a selective chemotherapeutic agent.[106] The recently discovered drug, crizotinib, significantly improves progression-free survival in patients with EML4-ALK-translocated lung carcinoma.[107] EML4-ALK translocations are nearly always mutually exclusive of EGFR and KRAS mutations.[108] 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.[109] 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.[110] Studies of other detection techniques, such as using an immunohistochemical marker that is specific for EML4-ALK, are ongoing.[111]
	CG4.03b	There is recent evidence that sensitive ALK IHC may be a useful screening tool for assessment of ALK gene rearrangements using both the 5A4 clone[112-114] and the newly available D5F3 clone[115-116], providing careful validation is undertaken.[95]

5 Synthesis and overview

Information that is synthesized from multiple modalities and therefore cannot reside solely in any one of the preceding chapters is described here. For example, tumour stage is synthesized from multiple classes of information – clinical, macroscopic and microscopic.

Overarching case comment is synthesis in narrative form. Although it may not necessarily be required in any given report, the provision of the facility for overarching commentary in a cancer report is essential.

By definition, synthetic elements are inferential rather than observational, often representing high-level information that is likely to form part of the 'diagnostic summary' section in the final formatted report.

S5.01	**The pathological staging must be recorded.**	
	CS5.01a	The reference document: TNM Supplement: A commentary on uniform use, 4th Edition (C Wittekind editor) may be of assistance when staging.[117]

CS5.01b Staging is a classification system that provides information regarding the anatomical extent of a tumour based on attributes that encompass the natural behaviour of the tumour. The AJCC/UICC classification is based on three main attributes — extent of local tumour spread (T), regional lymph node involvement (N) and distant metastases (M).

Clinical staging (cTNM) is based on information obtained before the initial treatment and may include physical examination, radiology, endoscopy, biopsy and surgical findings.

Pathological staging (pTNM) is based on information obtained from pathological examination in addition to clinical information. Pathological examination of the resected primary tumour and regional lymph nodes is used to ascertain the highest pT and pN categories.

For cases in which pathological staging is performed subsequent to initial treatment (eg neoadjuvant chemotherapy), the prefix 'y' can be used to indicate that staging has not been performed prior to multimodality therapy (eg ypTNM).

CS5.01c See Appendix 7 for details of the AJCC/UICC staging for lung cancer. Please note the changes to the TNM Classification of Lung Cancer in 2010.[21 ,34,118]

S5.02 The year of publication and edition of the cancer staging system

used in S5.01 must be included in the report.

G5.01 Residual tumour status should be recorded.

CG5.01a Residual tumour (R) is a TNM descriptor used to categorise the absence or presence of residual tumour after treatment.

CG5.01b The R categories are:

RX: Presence of residual tumour cannot be assessed
R0: No residual tumour
R1: Microscopic residual tumour.

Residual tumour at the bronchial margin may be:
R1: Invasive mucosal carcinoma or peribronchial infiltration
R1(is): Carcinoma in situ
R2: Macroscopic residual tumour.

G5.02 "Completeness of surgical resection" should be recorded if known.

CG5.02a "Completeness of surgical resection" is a recently developed clinicopathological concept.[70]

The International Association for the Study of Lung Cancer (IASLC) Staging Committee created the Complete Resection Subcommittee in 2001 to work on an international definition of complete resection in lung cancer surgery.

"Completeness of surgical resection" is recognised as an important determinant of prognosis and important information for treatment. Unlike residual tumour (R) status, it cannot be established by pathological examination alone and requires correlation with clinical information and intraoperative findings. The assessment of the status is best achieved via discussion at the multidisciplinary meeting.

CG5.02b The resection is defined as:

- complete
- incomplete
- uncertain

CG5.02c The resection is defined as complete when it meets all of the following criteria: free resection margins proved microscopically; systematic nodal dissection or lobe-specific systematic nodal dissection; no extracapsular nodal extension of the tumour; and the highest mediastinal node removed must be negative.

Systematic nodal dissection consists of excision of the mediastinal fat and enclosed lymph nodes as well as

excision of hilar and intrapulmonary lymph nodes.[70]

CG5.02d The resection is defined as incomplete if there is involvement of resection margins, extracapsular nodal extension, unremoved positive lymph nodes or positive pleural or pericardial effusions.

CG5.02e The resection is defined as uncertain when the resection margins are free and no residual tumour is left but the resection does not fulfil the criteria for complete resection for one or more of the following factors: intraoperative lymph node evaluation less rigorous than systematic nodal dissection or lobe-specific systematic nodal dissection; the highest mediastinal node removed is positive; there is carcinoma in situ at the bronchial margin; pleural lavage cytology is positive.

G5.03 The 'diagnostic summary' section of the final formatted report should include:

a. Operative procedure (S2.01)

b. Specimen laterality (S2.02)

c. Tumour site (S2.06)

d. Tumour type (S3.01)

e. Tumour stage (S5.01)

f. Residual tumour status (G5.01)

g. Completeness of surgical resection (G5.02).

S5.03 The reporting system must provide a field for free text or narrative in which the reporting pathologist can give overarching case comment.

CS5.03a This field may be used, for example, to:

- discuss the significance of ancillary tests
- discuss any noteworthy prognostic features
- express any diagnostic subtlety or nuance that is beyond synoptic capture
- document further consultation or results still pending.

CS5.03b Use of this field is at the discretion of the reporting pathologist.

6 Structured checklist

The following checklist includes the standards and guidelines for this protocol which must be considered when reporting, in the simplest possible form. The summation of all 'Standards' is equivalent to the 'minimum dataset' for lung cancer. For emphasis, standards (mandatory elements) are formatted in bold font.

S6.01 The structured checklist provided may be modified as required but with the following restrictions:

a. **All standards and their respective naming conventions, definitions and value lists must be adhered to.**

b. **Guidelines are not mandatory but are recommendations and where used, must follow the naming conventions, definitions and value lists given in the protocol.**

G6.01 The order of information and design of the checklist may be varied according to the laboratory information system (LIS) capabilities and as described in *Functional Requirements for Structured Pathology Reporting of Cancer* Protocols.[119]

CG6.01a Where the LIS allows dissociation between data entry and report format, the structured checklist is usually best formatted to follow pathologist workflow. In this situation, the elements of synthesis or conclusions are necessarily at the end. The report format is then optimised independently by the LIS.

CG6.01b Where the LIS does not allow dissociation between data entry and report format, (for example where only a single text field is provided for the report), pathologists may elect to create a checklist in the format of the final report. In this situation, communication with the clinician takes precedence and the checklist design is according to principles given in Chapter 7.

G6.02 Where the checklist is used as a report template (see G6.01), the principles in Chapter 7 and Appendix 2 apply

CG6.02a All extraneous information, tick boxes and unused values should be deleted

G6.03 Additional comment may be added to an individual response where necessary to describe any uncertainty or nuance in the selection of a prescribed response in the checklist. Additional comment is not required where the prescribed response is adequate.

Values in italics are conditional on previous responses.

Values in all caps are headings with sub values.

S/G	Item description	Response type	Conditional
Pre-analytical			
S1.01	**Demographic information provided**		
S1.02	**Clinical information provided on request form**	**Text** OR **Structured entry as below:**	
	Nature of the resection	**Single selection value list:** • Wedge resection • Segmentectomy • Bilobectomy • Lobectomy • Pneumonectomy • Other	**If other is selected, record type**
	Type	***Text***	
	Additional extrapulmonary tissue	**Single selection value list:** • No • Yes	**If yes, specify type of extrapulmonary tissue**
	Type of extrapulmonary tissue	***Text***	

	Site and laterality of tumour	**Multi select value list (choose all that apply)** • Right upper lobe • Right middle lobe • Right lower lobe • Left upper lobe • Left lower lobe • Main bronchus	
	Results of previous cytological investigations or biopsies	**Text**	
	Details of any previous treatment of the current tumour	**Text**	
	Details of previous cancer diagnosis	**Text**	
	Risk factors for lung cancer (eg smoking history, ethnicity and asbestos exposure)	**Text**	
	Clinical tumour stage	**Text**	
	New primary cancer or recurrence	**Single selection value list:** • New primary • Recurrence – regional • Recurrence – distant • Not stated	
S1.03	**Pathology accession number**	Alpha-numeric	

S1.04	**Principal clinician caring for the patient**	Text	
G1.01	Other clinical information received	Text	
Macroscopic findings			
S2.01	**Operative procedure**	**Single selection value list:** • Wedge resection • Segmentectomy • Bilobectomy • Lobectomy • Pneumonectomy • Other	**If other is selected, record type**
	Type	***Text***	
S2.02	**Specimen laterality**	**Single selection value list:** • Left • Right • Not provided	
S2.03	**Attached anatomical structures**	**Single selection value list:** • None submitted • Submitted	**If submitted, describe**
	Describe	***Text***	

S2.04	**Accompanying specimens**	**Multi select value list (choose all that apply)** • None submitted • Lymph nodes • Other	**If other, describe**
	Describe	***Text***	
S2.05	**Block identification key**	**Text**	
S2.06	**Tumour site**	**Multi select value list (choose all that apply)** • Upper lobe • Middle lobe • Lower lobe • Bronchus	**If Bronchus, specify site**
	Bronchus site	***Text***	
G2.01	Tumour location	**Single selection value list:** • Central • Peripheral	**If central record where it is involved**
	Involved	**Multi select value list (choose all that apply)** • Mainstem • Lobar • Segmental bronchus	

S2.07	**Separate tumour nodules**	**Single selection value list:** • Cannot be assessed • Absent • Present • Separate primaries Notes A separate checklist is required for each synchronous primary	**If present, record the number of tumours and site.**
	Number of tumours	***Numeric:*** ___	
	Site	**Multi select value list (choose all that apply)** • Same lobe • Different ipsilateral lobe • Contralateral lung	
S2.08	**Maximum tumour dimension**	**Numeric: ___mm**	
S2.09	**Macroscopic appearance of pleura overlying tumour**	**Text**	
S2.10	**Extent of direct spread of tumour to other tissues**	**Text**	
S2.11	**Distance of tumour to closest resection margin**	**Numeric: ___mm**	

S2.12	**Tumour involves main bronchus within 20 mm of carina**	**Single selection value list:** • Not assessable • Not involved • Involved	
S2.13	**Lymph nodes**	**Single selection value list:** • Absent • Present	**If present record, site and number of lymph nodes**
	Site(s) and number of lymph nodes	***Text:*** *Site* ***AND*** ***Numeric:*** *Number of LN's* *<u>Note:</u> that the site and number of LN's for that site may need to be repeated for each specimen site received.*	
S2.14	**Atelectasis/obstructive pneumonitis**	**Single selection value list:** • Not assessable • Absent • Present	**If present, record extent**
	Extent	***Single selection value list:*** • *Involves entire lobe* • *Involves entire lung*	
S2.15	**Non-neoplastic lung**	**Text**	
G2.02	Other relevant information and comments	**Text**	

Microscopic findings			
S3.01	**Histological tumour type**	**Single selection value list:** • Squamous cell carcinoma • Small cell carcinoma • Adenocarcinoma • Large cell carcinoma • Adenosquamous carcinoma • Sarcomatoid carcinoma • Carcinoid tumour • Other	**If other describe other type** **If adenocarconoma consider reporting G3.01**
	Other type	***Text***	
G3.01	***Adenocarcinoma classification*** ***(See Appendix 5)***	***Multi select value list (select all that apply):*** • Adenocarcinoma in situ (AIS) o Non-mucinous o Mucinous • Minimally invasive adenocarcinoma (MIA) o Non-mucinous o Mucinous • Invasive adenocarcinoma *Predominant pattern* o Lepidic ___% o Acinar ___% o Papillary ___% o Micropapillary ___%	

		o Solid ___% Other patterns (if present) (specify each with a percentage) • Mucinous • Colloid • Fetal • Enteric	
S3.02	**Histological grade**	**Single selection value list:** • Well differentiated • Moderately differentiated • Poorly differentiated • Undifferentiated • Not applicable	
S3.03	**Visceral pleural invasion**	**Single selection value list:** • Cannot be assessed • Indeterminate • Not identified • Present	**If present, consider recording the extent of pleural involvement G3.02.**
G3.02	*Extent of pleural involvement*	***Single selection value list:*** • *PL1* • *PL2* • *PL3*	

S3.04	**Lymphovascular invasion**	**Single selection value list:** • Not identified • Indeterminate • Present	**If present, consider reporting the type of vessels involved G3.03**
G3.03	*Vessel(s) involved*	***Multi select value list (select all that apply):*** • *Artery* • *Vein* • *Lymphatics*	**For each vessel type involved, indicate the type of involvement.**
	Type of involvement	***Single selection value list:*** • *Focal* • *Extensive* *Notes* *The type of involvement will need to be recorded for each vessel type involved recorded above.*	
G3.04	Perineural invasion	**Single selection value list:** • Not identified • Indeterminate • Present	
S3.05	**SURGICAL MARGIN STATUS**		

	Bronchial resection margin	**Single selection value list:** • Not applicable • Not involved • Involved by invasive carcinoma • Involved by CIS only	**If involved by invasive carcinoma, record the tissues involved.** **If not involved record the microscopic clearance.**
	Tissues involved	***Single selection value list:*** • *Bronchial* • *Peribronchial soft tissue* • *Both*	
	Microscopic clearance	***Numeric: ___mm***	
	Vascular resection margin	**Single selection value list:** • Not applicable • Not involved • Involved	**If involved, record nature of involvement**
	Nature of involvement	***Text***	
	Other margins	**Text: List margin** **AND** **Single selection value list:** • Not applicable • Not involved • Involved	**If not involved, record microscopic clearance.**

	Microscopic clearance	***Numeric: ___mm***	
S3.06	**Direct invasion of adjacent structures**	**Multi select value list (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	**If any structures selected, record if there is tumour at the resection margin for involved structures**
	Tumour at resection margin(s) for involved structures	***Single selection value list:*** • *Absent* • *Present*	***If present, specify the involved margin(s).*** ***If absent, record closest microscopic clearance.***
	Involved margin(s)	***Text***	
	Closest microscopic clearance	***Numeric: ___mm***	

S3.07	**In situ carcinoma**	**Single selection value list:** • Absent • Present	
S3.08	**Response to neoadjuvant therapy**	**Single selection value list:** • Not applicable • Less than 10% residual viable tumour • Greater than 10% residual viable tumour • Treatment history not known	
S3.09	***LYMPH NODES***		***Conditional on lymph nodes being received in S2.13***
	Station(s) examined	***Text***	
	Lymph node status	**Single selection value list:** • Not involved • Involved	
	Station(s) involved	***Text***	
	Number of positive nodes	***Numeric:*** _____/_____ ***(number of positive nodes/total number of nodes per station)*** ***Notes:*** For each station involved record the number of positive nodes over the total number of nodes at this station.	

G3.05	Lymph node replacement	**Single selection value list:** • Focal • Extensive • Complete	
	Nodal involvement due to	**Single selection value list:** • Metastatic spread • Direct invasion	
G3.06	Extracapsular extension	**Single selection value list:** • Absent • Present	
G3.07	Non-neoplastic lung disease	**Text**	
G3.08	Other neoplastic processes (eg tumourlets, NEH, AAH, dysplasia)	**Text**	
G3.09	Other relevant comments	**Text**	
Ancillary test findings			
G4.01	**IMMUNOHISTOCHEMICAL MARKERS**		
	Antibodies	**List (as applicable):** • Positive antibodies • Negative antibodies • Equivocal antibodies	
	Conclusions	**Text**	

G4.02	EGFR result	**Text**	
G4.03	Other molecular data	Note: repeat for each other test performed.	
	Test	**Text**	
	Results	**Text**	
Synthesis and overview			
S5.01	**PATHOLOGICAL STAGING (AJCC 7TH EDITION)**		
	Suffixes	**Choose if applicable:** • m - multiple primary tumours • r - recurrent • y - posttreatment	
	Primary tumour (T)	**Single selection value list:** 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	

		* 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.	
	Regional lymph nodes (N)	**Single selection value list:** 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)	**Single selection value list:** 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) ** Most pleural (and pericardial) effusion 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.	
S5.02	**Year and edition of staging system**	**Numeric:** year **AND** **Text:** Edition eg 1st, 2nd etc	
G5.01	Residual tumour status	**Single selection value list:** RX: Presence of residual tumour cannot be assessed R0: No residual tumour R1: Microscopic residual tumour. Residual tumour at the bronchial margin may be: R1: Invasive mucosal carcinoma or peribronchial infiltration R1(is): Carcinoma in situ R2: Macroscopic residual tumour.	
G5.02	Completeness of surgical resection	**Single selection value list:** • Complete • Incomplete • Uncertain	

G5.03	Diagnostic summary Include: a. Operative procedure (S2.01) b. Specimen laterality (S2.02) c. Tumour site (S2.06) d. Tumour type (S3.01) e. Tumour stage (S5.01) f. Residual tumour status (G5.01) g. Completeness of surgical resection (G5.02)	**Text**	
S5.03	**Overarching comment**	**Text**	

7 Formatting of pathology reports

Good formatting of the pathology report is essential to optimise communication with the clinician, and will be an important contributor to the success of cancer reporting protocols. The report should be formatted to provide information clearly and unambiguously to the treating doctors, and should be organised with their use of the report in mind. In this sense, the report differs from the structured checklist, which is organised with the pathologists' workflow as a priority.

Uniformity in the format as well as in the data items of cancer reports between laboratories makes it easier for treating doctors to understand the reports; it is therefore seen as an important element of the systematic reporting of cancer.

Please see Appendix 2 for further guidance.

Appendix 1 Pathology request and surgical handling procedures

This appendix describes the information that should be collected before the pathology test. Some of this information can be provided on generic pathology request forms; any additional information required specifically for the reporting of lung cancer may be provided by the clinician on a separate request information sheet.

An example request information sheet is included below.

Elements which are in bold text are those which pathologists consider to be required information. Those in non-bold text are recommended.

Also included in this appendix are the procedures that are recommended before handover of specimens to the laboratory.

Patient information

- **Adequate demographic and request information should be provided with the specimen.**
  - Items relevant to cancer reporting protocols include:
    - patient name
    - date of birth
    - sex
    - identification and contact details of requesting doctor
    - date of request
  - The patient's ethnicity should be recorded, if known. In particular whether the patient is of aboriginal or Torres Strait islander origin. This is in support of a government initiative to monitor the health of indigenous Australians particularly in relation to cancer.
- The patient's health identifiers should be provided.
  - The patient's health identifiers may include the patient's Medical Record Number as well as a national health number such as a patient's Medicare number (Australia), Individual Healthcare Identifier (IHI) (Australia) or the National Healthcare Identifier (New Zealand).

Clinical information

- **The nature of the resection should be recorded.**
  - Examples include wedge resection, lobectomy or pneumonectomy.
  - If additional extrapulmonary tissue has been resected due to possible involvement by tumour (eg pericardium, adherent parietal pleura), this should be stated to assist in appropriate

pathological examination of relevant areas and pathological staging.

- **The site and laterality of the tumour should be recorded.**

  - If multiple lobes are involved this must be stated.

- The result(s) of previous cytological investigations or biopsy of the tumour should be recorded.

  - Previous biopsy or cytology results may include bronchial biopsy, fine needle aspiration biopsy, positive sputum cytology, bronchial brushings or washings. If possible, details of the laboratory that reported on these cases should also be provided.

  - The results of these investigations may affect the handling of the specimen (eg sampling for ancillary studies may be indicated in the case of an unusual tumour with uncertain biopsy/cytology diagnosis). Sampling for microbiology may be indicated if the differential diagnosis includes infection.

  - The results of previous investigations may also affect tumour staging; for example, cytological diagnosis of malignant pleural effusion in a lung cancer is categorised as M1a (2010 revision of the TNM staging system – see Appendix 7).

- The details of any previous treatment of the current tumour should be recorded.

  - Information about previous neoadjuvant chemotherapy and/or radiotherapy may assist in morphological interpretation of the current pathology specimen. More extensive sampling of the specimen may also be necessary to identify any residual viable tumour.

- Relevant details of previous cancer diagnosis should be recorded.

  - Information regarding previous malignancies (pulmonary or extrapulmonary) and, if necessary, review of previous specimens may assist in reaching the correct diagnosis on the current pathology specimen. If possible, details of the laboratory that reported on the potentially relevant malignancies should also be provided.

- Any risk factors should be recorded.

  - Risk factors for lung cancer include a history of smoking, asbestos exposure and interstitial lung disease. Information regarding a patient's smoking history can be important to the pathologist as some types of lung cancer rarely occur in life-long nonsmokers. Ethnicity should be recorded where relevant. Some forms of lung cancer are more common in certain ethnic groups (please see CG4.02a). A history of significant asbestos exposure would be useful to ensure adequate sampling of non-neoplastic lung tissue for asbestos bodies or fibres.

- The clinical tumour stage should be recorded.

  - Details of the surgeon's opinion of tumour stage based on radiological and surgical findings (see Appendix 7) will assist in accurate pathological staging. For instance, invasion of adjacent structures such as parietal pleura or mediastinum are important determinants of tumour stage.

- **Record if this is a new primary cancer or a recurrence of a previous cancer, if known.**

  - The term recurrence defines the return, reappearance or metastasis of cancer (of the same histology) after a disease free period.

    Recurrence should be classified as distant metastases or regional (local) recurrence.

    Regional (local) recurrence refers to the recurrence of cancer cells at the same site as the original (primary) tumour or the regional lymph nodes.

    Distant metastasis refers to the spread of cancer of the same histologic type as the original (primary) tumour to distant organs or distant lymph nodes.

  - This information will provide an opportunity for previous reports to be reviewed during the reporting process, which may provide valuable information to the pathologist. This information also has implications for recording cancer incidence and evidence based research.

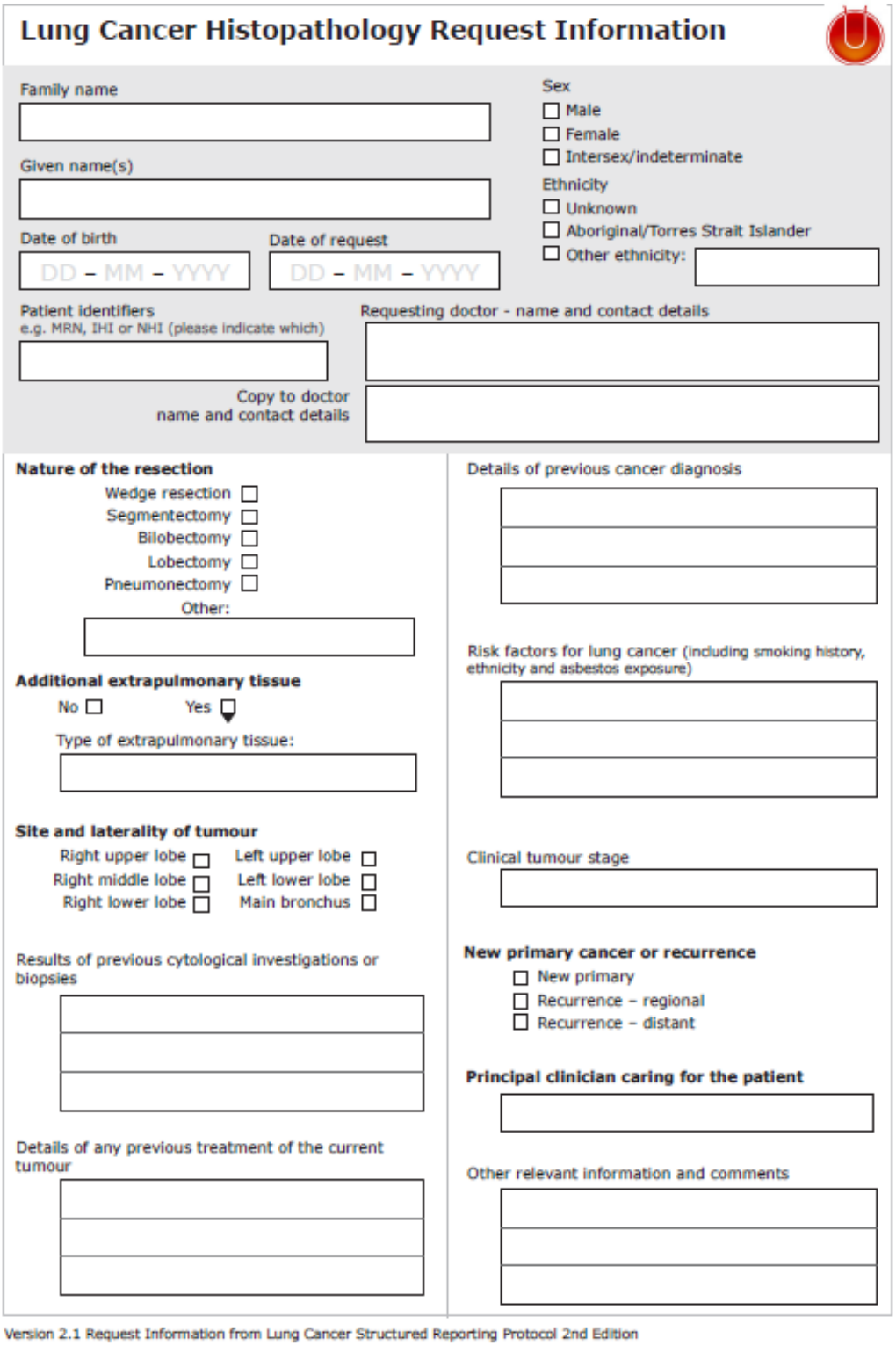
- Any other relevant information and comments should be recorded.

Surgical handling

- The specimen should be sent to the laboratory in the fresh state without delay.

  - The laboratory should be informed if the specimen is likely to arrive out of normal working hours.

Example Request Information Sheet



Lung Cancer Histopathology Request Information

Family name

Given name(s)

Date of birth DD – MM – YYYY

Date of request DD – MM – YYYY

Sex
- Male
- Female
- Intersex/indeterminate

Ethnicity
- Unknown
- Aboriginal/Torres Strait Islander
- Other ethnicity:

Patient identifiers
e.g. MRN, IHI or NHI (please indicate which)

Requesting doctor - name and contact details

Copy to doctor name and contact details

Nature of the resection
- Wedge resection
- Segmentectomy
- Bilobectomy
- Lobectomy
- Pneumonectomy
- Other:

Additional extrapulmonary tissue

No Yes

Type of extrapulmonary tissue:

Site and laterality of tumour
- Right upper lobe
- Right middle lobe
- Right lower lobe
- Left upper lobe
- Left lower lobe
- Main bronchus

Results of previous cytological investigations or biopsies

Details of any previous treatment of the current tumour

Details of previous cancer diagnosis

Risk factors for lung cancer (including smoking history, ethnicity and asbestos exposure)

Clinical tumour stage

New primary cancer or recurrence
- New primary
- Recurrence – regional
- Recurrence – distant

Principal clinician caring for the patient

Other relevant information and comments

Version 2.1 Request Information from Lung Cancer Structured Reporting Protocol 2nd Edition

The above Request Information Sheet is published on the RCPA website.

Appendix 2 Guidelines for formatting of a pathology report

Layout

Headings and spaces should be used to indicate subsections of the report, and heading hierarchies should be used where the LIS allows it. Heading hierarchies may be defined by a combination of case, font size, style and, if necessary, indentation.

- Grouping like data elements under headings and using 'white space' assists in rapid transfer of information.[120]

Descriptive titles and headings should be consistent across the protocol, checklist and report.

When reporting on different tumour types, similar layout of headings and blocks of data should be used, and this layout should be maintained over time.

- Consistent positioning speeds data transfer and, over time, may reduce the need for field descriptions or headings, thus reducing unnecessary information or 'clutter'.

Within any given subsection, information density should be optimised to assist in data assimilation and recall.

- Configuring reports in such a way that they 'chunk' data elements into a single unit will help to improve recall for the clinician.[120]
- 'Clutter' should be reduced to a minimum.[120] Thus, information that is not part of the protocol (eg billing information, Snomed codes, etc) should not appear on the reports or should be minimised.
- Injudicious use of formatting elements (eg too much bold, underlining or use of footnotes) also increases clutter and may distract the reader from the key information.

Where a structured report checklist is used as a template for the actual report, any values provided in the checklist but not applying to the case in question must be deleted from the formatted report.

Reports should be formatted with an understanding of the potential for the information to 'mutate' or be degraded as the report is transferred from the LIS to other health information systems.

As a report is transferred between systems:

- text characteristics such as font type, size, bold, italics and colour are often lost
- tables are likely to be corrupted as vertical alignment of text is lost when fixed font widths of the LIS are rendered as proportional fonts on screen or in print
- spaces, tabs and blank lines may be stripped from the report, disrupting the formatting
- supplementary reports may merge into the initial report.

Appendix 3 Example of a pathology report for lung cancer

Robbin, Chris W.
C/O Paradise Close
Wineglass Bay Resort
Tasmania

Male

DOB 1/7/1998
MRN FMC1096785

Lab Ref: **13/P28460**
Referred: 30/2/2013

Managing Clinician: Dr G. Fortune
Rainforest Cancer Centre.
46 Smith Road,
Woop Woop, 3478

Referred by: Mr V. Butler
Suite 3, AJC Medical Centre,
Bunyip Crescent
Nar Nar Goon West, 3182

LUNG CANCER STRUCTURED REPORT

Diagnostic Summary

Right lower lobe of lung (lobectomy):

Squamous cell carcinoma,
AJCC (7th edition 2010) Stage IB (pT2a, pN0, MX)
R1(is) Carcinoma in-situ at bronchial resection margin

Supporting Information

CLINICAL

Nature of the resection:	Lobectomy
Additional extrapulmonary tissue:	No
Site and laterality of tumour:	Right lower lobe
Previous biopsies:	
FNA:	Squamous cell carcinoma (RPAH,18/2/2013)
Right pleural effusion:	Negative (RPAH, 14/2/2013)
Previous treatment:	Nil
Risk factors:	Nil known
Clinical tumour stage:	cT1, NX, M0
New primary or recurrence:	New primary

MACROSCOPIC

Operative procedure:	Lobectomy
Specimen laterality:	Right
Attached anatomical structures:	None submitted
Accompanying specimens:	None submitted
Tumour site:	Lower lobe
Tumour location:	Central, Lobar
Separate tumour nodules:	Absent
Maximum tumour dimension:	50mm
Macro. appearance of pleura:	Pleural puckering
Extent of direct spread to other tissues:	Not applicable
Dist. to closest resection margin:	12mm
Tumour involves main bronchus within 20 mm of carina:	Not assessable
Lymph nodes:	Present 6 peribronchial, 1 mediastinal

Atelectasis/obstruct. pneumonitis:	Absent
Non-neoplastic lung:	Emphysema

MICROSCOPIC

Histological tumour type:	Squamous cell carcinoma
Histological grade:	Moderately differentiated
Visceral pleural invasion:	Present
Extent of involvement:	PL1. The tumour has invaded beyond the elastic layer of the visceral pleura (confirmed by elastic stain) but not to the visceral pleural surface.
Lymphovascular invasion:	Present
Vessels involved:	Artery
Type of involvement:	Extensive

SURGICAL MARGIN STATUS

Bronchial resection margin:	Involved by CIS only. Focal involvement only. Not involved by invasive carcinoma, 7mm clearance
Vascular resection margin:	Not involved
Direct invasion of adj. structures:	Not identified
In-situ Carcinoma:	Present
Response to neoadjuvant therapy:	Not applicable

LYMPH NODES

Stations examined:	6 peribronchial, 1 mediastinal
Lymph node status:	Not involved Peribronchial 0/6 Mediastinal 0/1
Non-neoplastic lung:	Emphysema

ANCILLARY STUDIES — Not performed

Reported by Dr Samuel Wilks

Authorised 4/3/2013

Appendix 4 World Health Organization classification of lung neoplasms[11]

- 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

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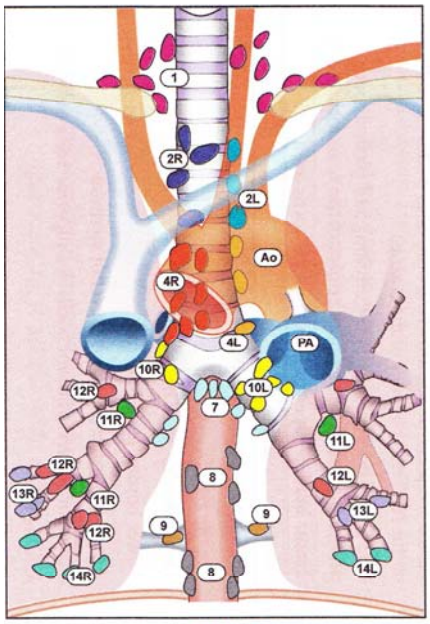
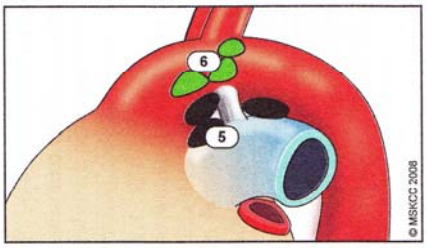
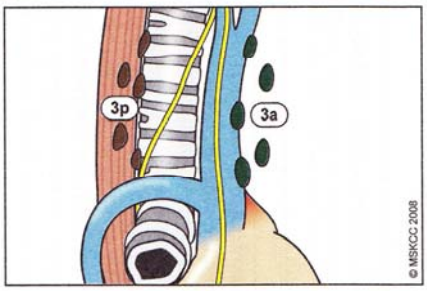
Appendix 5 The IASLC/ATS/ERS Classification of Lung Adenocarcinoma in Resection Specimens

- 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

Appendix 6 IASLC Lymph node map







Supraclavicular zone

- **1** Low cervical, supraclavicular, and sternal notch nodes

Superior Mediastinal Nodes

Upper zone

- **2R** Upper Paratracheal (right)
- **2L** Upper Paratracheal (left)
- **3a** Pre-vascular
- **3p** Retrotracheal
- **4R** Lower Paratracheal (right)
- **4L** Lower Paratracheal (left)

Aortic Nodes

AP zone

- **5** Subaortic
- **6** Para-aortic (ascending aorta or phrenic)

Inferior Mediastinal Nodes

Subcarinal zone

- **7** Subcarinal

Lower zone

- **8** Paraesophageal (below carina)
- **9** Pulmonary ligament

N_1 Nodes

Hilar/Interlobar zone

- **10** Hilar
- **11** Interlobar

Peripheral zone

- **12** Lobar
- **13** Segmental
- **14** Subsegmental

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Appendix 7 Staging of lung cancer

7th edition of the TNM classification for lung cancer, 2010

The seventh edition of the TNM classification of lung cancer was published and implemented at the beginning of 2010.[34,118] The classification is based on the sixth edition published in 2002[13] but with significant changes to the T and M components[21].

The full staging descriptors for the 7th edition TNM classification for lung cancer 2010 are included in tables A7.01 and A7.02 below.[21 ,34,118]

Table A7.01 **Definitions for T, N, M descriptors.** Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springerlink.com.

Descriptors	Definitions
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)	
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.

Table A7.02 **TNM elements included in stage groups.** Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springerlink.com.

Stage group	T	N	M
Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b

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