Clinical Practice Guidelines in Cancer in Catalonia

# Lung cancer

# OncoGuia

## Update 2008

Generalitat de Catalunya
Departament de Salut

Clinical Practice Guidelines in Cancer in Catalonia

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## Update 2008

Agència d'Avaluació de Tecnologia i Recerca Mèdiques

Pla director d'oncologia

CatSalut Servei Català de la Salut

The Catalan Cancer Plan (CCP) is based on a comprehensive approach to cancer care, integrating the whole health care system and trying to meet all the health care and psychosocial needs of cancer patients. In this way, the development and continuous updating of the *OncoGuies*, as a key element to use scientific evidence for clinical decision-making, is one of the strategies used by the CCP in order to promote both therapeutic equity and the best quality of cancer care.

The updating of this *OncoGuia* has been developed through an agreement with The Health Department of Catalonia and in collaboration with the Catalan Agency for Health Technology Assessment and Research (CAHTA), within the framework of the *Plan de Calidad para el Sistema Nacional de Salud*.

# EXPERTS

## Lung cancer experts

- **Dr. Rafael Aguiló**
  Thoracic Surgery Department, Hospital del Mar
- **Dra. Maria Alejo**
  Pathology Department, Hospital de Vic
- **Dra. M. Mar Arnaiz**
  Radiation Therapy Department, ICO Hospital Duran i Reynals
- **Dr. Julio Astudillo**
  Thoracic Surgery Department, Hospital Universitari Germans Trias i Pujol
- **Dra. Remei Blanco**
  Oncology Department, Consorci Sanitari de Terrassa
- **Dr. Emili Canalís**
  Chest Surgery Department, Hospital Clínic i Provincial de Barcelona
- **Dr. Felip Cardenal**
  Oncology Department, ICO Hospital Duran i Reynals
- **Dr. Víctor Curull**
  Respiratory diseases Department, Hospital del Mar
- **Dra. Enriqueta Felip**
  Oncology Department, Hospital Universitari de la Vall d'Hebron
- **Dr. Rafael Fuentes**
  Radiation Oncology Department, Hospital Universitari de Girona Dr. Josep Trueta
- **Dr. Àngel Gayete**
  Radiodiagnostic Department, Hospital del Mar
- **Dra. Ana M. Giménez**
  Radiodiagnostic Department, Hospital de la Santa Creu i Sant Pau
- **Dr. Josep Jové**
  Radiation Oncology Department, Hospital Universitari Germans Trias i Pujol
- **Dra. Carmen Lainez**
  Radiation Therapy Department, Clínica Platón
- **Dr. Josep Lloreta**
  Pathology Department, Hospital del Mar
- **Dr. Ramon Marrades**
  Respiratory diseases Department, Hospital Clínic i Provincial de Barcelona
- **Dr. José Ignacio Martínez**
  Respiratory diseases Department, ICO Hospital Duran i Reynals
- **Dra. Xesca Martínez**
  Radiology Department, Hospital de Bellvitge
- **Dra. M. Ángeles Montero**
  Pathology Department, Hospital Universitari de la Vall d'Hebron
- **Dra. Cinta Pallarès**
  Oncology Department, Hospital de la Santa Creu i Sant Pau
- **Dr. Ramón Palmero**
  Oncology Department, ICO Hospital Duran i Reynals
- **Dr. Josep Ramírez**
  Pathology Department, Hospital Clínic i Provincial de Barcelona
- **Dra. Núria Rodríguez**
  Radiation Therapy Department, Hospital de l'Esperança
- **Dr. Antoni Rosell**
  Respiratory diseases Department, Hospital Universitari Germans Trias i Pujol
- **Dr. Josep Saumench**
  Thoracic Surgery Department, ICO Hospital Duran i Reynals
- **Dra. Núria Viñolas**
  Oncology Department, Hospital Clínic i Provincial de Barcelona
- **Dr. Àngel Olazábal**
  Radiodiagnostic Department, ICO Hospital Universitari Germans Trias i Pujol

## Coordinating clinical guideline team of the Catalan Cancer Plan (CCP)

- Dra. Paula Manchon
- Dr. Josep M. Borràs
- Sra. Tàrsila Ferro
- Dr. Josep Alfons Espinàs
- Sra. Meritxell Nomen *(Edition)*

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# PART I. CLINICAL PRACTICE GUIDELINES IN CANCER: PROCESS AND METHODOLOGY

## PROCESS

### General aims

The Department of Health of Catalonia has implemented the CCP in order to reduce the impact of cancer in Catalonia. The CCP states the promotion, planning, coordination as well as the evaluation of strategies and actions that have to be developed for different cancer areas. In this framework, the CCP develops measures for improvement of cancer care based on the best scientific evidence.

The *OncoGuies* are the key element used by the Catalan Cancer Plan (CCP) in order to promote equity of therapeutic access and quality cancer care. On the other hand, The Catalan Agency of Health Technology Assessment and Research (CAHTA), which is also a public institution of the Catalan Health Service *(CatSalut),* aimed to generate evidence based cancer care in order to ensure that those responsible for clinical decision-making can do so through the Catalan Health system. In this way, the CAHTA has a wide experience in the development and assessment of clinical practice guidelines.

These aims and goals were developed through an agreement to launch a joint program –the Clinical Practice Guidelines Program *(OncoGuies)*– defined by the basic attributes of quality, efficiency and transparency.

### Contributors and users

The *OncoGuies* are intended to promote that patients with cancer receive treatments recommended by scientific studies and experts worldwide. To achieve this goal, it was decided that although *CatSalut* and the CCP would coordinate the *OncoGuies* project, health care professionals would be responsible for their content.

Participants in the project are selected as follows: representatives of tumor boards and medical oncology, hematology, radiotherapy and surgery specialists; medical specialists in respiratory diseases and digestive diseases, endoscopy, gynecology, plastic surgery, and thoracic surgery fields; and specialists from centralized services and pathology, radiology and nuclear medicine departments belonging to the network of subsidized hospitals for public utilization *(Xarxa Hospitalària d'Utilització Pública).* Participants contribute with clinical experience embodied in existing protocols for the main tumor types, and, in the *OncoGuia* development process, discuss and review the design of the clinical algorithms and the content of the guidelines until a consensus is reached in the final document. This part of the process is fundamental to establishing the interactive participation and consensus that ensures that the final document is the outcome of all the participants' inputs and that ownership is as much of the experts as of the institutions in charge of developing the project.

The *OncoGuies,* which are shaped and adapted to the Catalan health care context, are based on state-of-the-art scientific knowledge, reviews of international expertise, and the contributions of experts. They guarantee to the patients the best available treatment, irrespective of where they live; noteworthy in this regard, is the innovative aspect of standardized treatment. The *OncoGuia* reflect the values of equity of access to the best health care, protection of the best interest of the patient, and expert consensus.

**Potential users** of this *OncoGuia* are health care professionals –operating at all levels– who provide care to patients with suspected or diagnosed lung cancer. The profiles of these target users correspond broadly to those of the professionals who participate in drawing up and updating the *OncoGuies.*

## Contents

The Lung Cancer *OncoGuia*, which covers clinical aspects of diagnosis, treatment, and follow-up, is for use with patients with suspected or diagnosed lung cancer.

The updated *OncoGuia* provides information as follows:

- Information on the *OncoGuia* organising and methodology committee and participating experts
- Table of contents
- Diagnostic, treatment, and follow-up care algorithms
- Explanatory text
- Information for patients
- References
- Appendix

This document forms part of the Lung Cancer *OncoGuia*, which includes:

- A full version
- A quick guide

## Changes to the previous version

Changes in explanatory text content with respect to the version for 2003 are indicated by a gray background. Modifications to algorithms are indicated by a pale yellow background.

## Update

The general aim of this new Lung Cancer *OncoGuia* was to update the November 2003 version.

Specific aims were as follows:

- To update the recommendations of the November 2003 version of the Lung Cancer *OncoGuia*.
- To update evidence supporting recommendations and add quality ratings.
- To improve general layout and enable key recommendations to be easily identified.

None of the participants in the updating process have declared any conflict of interests, for both the period of involvement in drawing up the clinical practice guidelines and for the year prior to their declaration in this regard. The declarations were made by completing a standard form.

A committee of lung cancer experts has been appointed to oversee future updates to the Lung Cancer *OncoGuia* based on emerging scientific evidence. This committee will meet every 6 months, at the request of any of its members, or when necessary to discuss any relevant developments.

## Evaluation

Implementation of the recommendations will be assessed by:

- Evaluating adherence to hospital protocols.

# METHODOLOGY

## Linking recommendations to available scientific evidence

The *OncoGuia* algorithms describe a series of diagnostic, preventive, and therapeutic interventions for different kinds of tumors. In deciding on intervention recommendations, account was taken of existing protocols, current clinical practice in Catalan hospitals, and opinions and arguments expressed by members of working groups in a series of open, scheduled meetings forming part of a structured work plan. The basic working methodology was the preparation, for debate, of preliminary drafts that were not considered definitive until a consensus was reached by the group of experts. The members of each working group made amendments to their draft recommendations (at or after their meetings) and these changes were further discussed at scheduled meetings.

For certain recommendations selected as being particularly relevant, two additional tasks were performed by the working groups. Firstly, each working group evaluated consensus in regard to the recommendation and then rated this consensus. Secondly, each group assessed available scientific evidence supporting the intervention and assigned it a category reflecting its quality, as agreed on by 2 experts.

Thus, the selected recommendations include a code that indicates the degree of consensus within the working group and occasionally a callout to a summary of the evidence. Included also is the result of an independent evaluation of the quality of the evidence by the 2 experts who reached a consensus.

Described below are the categories for consensus and for the quality of the scientific evidence available.

The consensus categories were devised bearing in mind currently valid recommendations of the National Cancer Institute, the National Comprehensive Cancer Network, the Scottish Intercollegiate Guidelines Network, the Institute for Clinical Systems Improvement, and the Fédération Nationale des Centres de Lutte Contre le Cancer.

### Consensus categories

| | |
|---|---|
| Category S | Standard. When the entire working group agrees on recommending a particular intervention within the specific context of the algorithm. |
| Category CO | Consensus Option. When the majority (at least 90%) of the working group agrees on recommending a particular intervention within the specific context of the algorithm. |
| Category O | Option. When there are major discrepancies as to whether a particular intervention should be recommended or not and no majority consensus was reached by the working group. |

## Classification of available scientific evidence

Most of the classification systems currently in use rate quality of evidence according to potential sources of bias in any study that supports the efficacy of a proposed intervention. In broad terms, the strongest evidence is awarded to studies in which patients have been randomly assigned to different groups (typically, randomized controlled trials or meta-analyses of such trials), whereas the weakest evidence is awarded to studies reporting expert opinions but no hard evidence. Intermediate levels of evidence are assigned to analytical observational epidemiologic studies that include a control group (for example, cohort and case control studies), and observational studies without a control group (for example, case series).

Given the many scales available for grading existing evidence and the absence of unanimity in terms of establishing any one particular scale as a gold standard, we opted for the widely used guidelines manuals drawn up by the National Institute for Health and Clinical Excellence.[1] The instruments used were the Scottish Intercollegiate Guidelines Network (SIGN) scale to evaluate therapeutic intervention studies and the Centre for Evidence-Based Medicine (CEBM-OXFORD) scale to evaluate diagnostic intervention studies.

Occasionally the working groups were unable to identify evidence supporting important clinical aspects that are considered to be good practice point (GPP).

### Classification of available scientific evidence

#### SIGN scale for intervention studies

| | |
|---|---|
| 1++ | High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias |
| 1+ | Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias |
| 1- | Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias |
| 2++ | High-quality systematic review of case control or cohort studies.<br>High-quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is casual |
| 2+ | Well-conducted case control or cohort studies with a low risk of bias and with a moderate probability that the relationship is causal |
| 2- | Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal |
| 3 | Nonanalytic studies, e.g., case reports, case series |
| 4 | Expert opinion |

#### CEBM-OXFORD scale for diagnostic studies

| | |
|---|---|
| Ia | Systematic review of level 1 studies |
| Ib | Level 1 studies |
| II | Level 2 studies and systematic reviews of level 2 studies |
| III | Level 3 studies and systematic reviews of level 3 studies |
| IV | Expert opinion |
| Level 1 | Blind comparison of the test with a validated reference standard<br>In a suitably sized sample of patients |
| Level 2 | One of the following criteria is fulfilled:<br>The population is not representative<br>The reference standard is unsuitable<br>Unblinded comparison of the test with the reference standard<br>Case control study |
| Level 3 | Two or more of the above criteria are fulfilled |

## OncoGuia review

The final draft of the *OncoGuia* was reviewed externally by the private cancer foundation ONCOLLIGA *(Fundació Privada Lliga Catalana d'Ajuda Oncològica)* whose suggestions and contributions were taken into account in the definitive version.

The CAHTA realized an external quality review of the *OncoGuia* using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument. Nonetheless, their agreement with the final content which, ultimately, is the responsibility of the authors, was not necessarily implied.

## Limitations of the methodology

*Consensus classification*

Generally speaking, no formal voting took place in the working groups; rather, the degree of consensus was assessed by the group coordinator, who noted the consensus for each intervention in turn. These provisional consensus categories were endorsed –or modified as appropriate– in subsequent meetings of the working group.

No specific method for interpreting the classification of available scientific evidence in terms of an actual recommendation for each intervention was defined, and no explicit criteria were defined for considering issues such as, for example, the extent of the benefit, iatrogenic risk, etc. Some of these issues were, nonetheless, discussed by the working groups on the basis of occasionally contradictory evidence and this had a bearing on the final consensus. In the future, an appraisal will be made in regard to whether there is a need to modify the method for classifying available evidence in terms of recommendations and for classifying the degree of consensus.

*Classification of available evidence*

Susceptibility to bias was the main factor evaluated when rating the quality of a study supporting a particular intervention. The focus was on efficacy, but magnitude of benefit or doubts regarding the reliability of the system used to evaluate efficacy (measurement accuracy) were not formally taken into account. Nor was a formal evaluation of the iatrogenic or toxicity risk associated with the intervention considered. Many of these issues, nonetheless, were raised in working group discussions and had a greater or lesser bearing on the final consensus in regard to recommendations for particular interventions. An appraisal will be made at some point in the future in regard to formally taking into account any or all of these issues in terms of classifying evidence or adjusting the strength of recommendations.

Another limitation of the methodology was that no explicit criteria were defined for identifying and selecting the scientific evidence supporting each intervention. For each intervention, members of the group of experts drew up a summary of scientific evidence supported by references, for discussion –and modification if appropriate– by the group. In some cases, scientific evidence compiled in other published clinical practice recommendations or guidelines was taken into account; in other cases, a systematic search of the literature was made.

## SOURCES OF INFORMATION

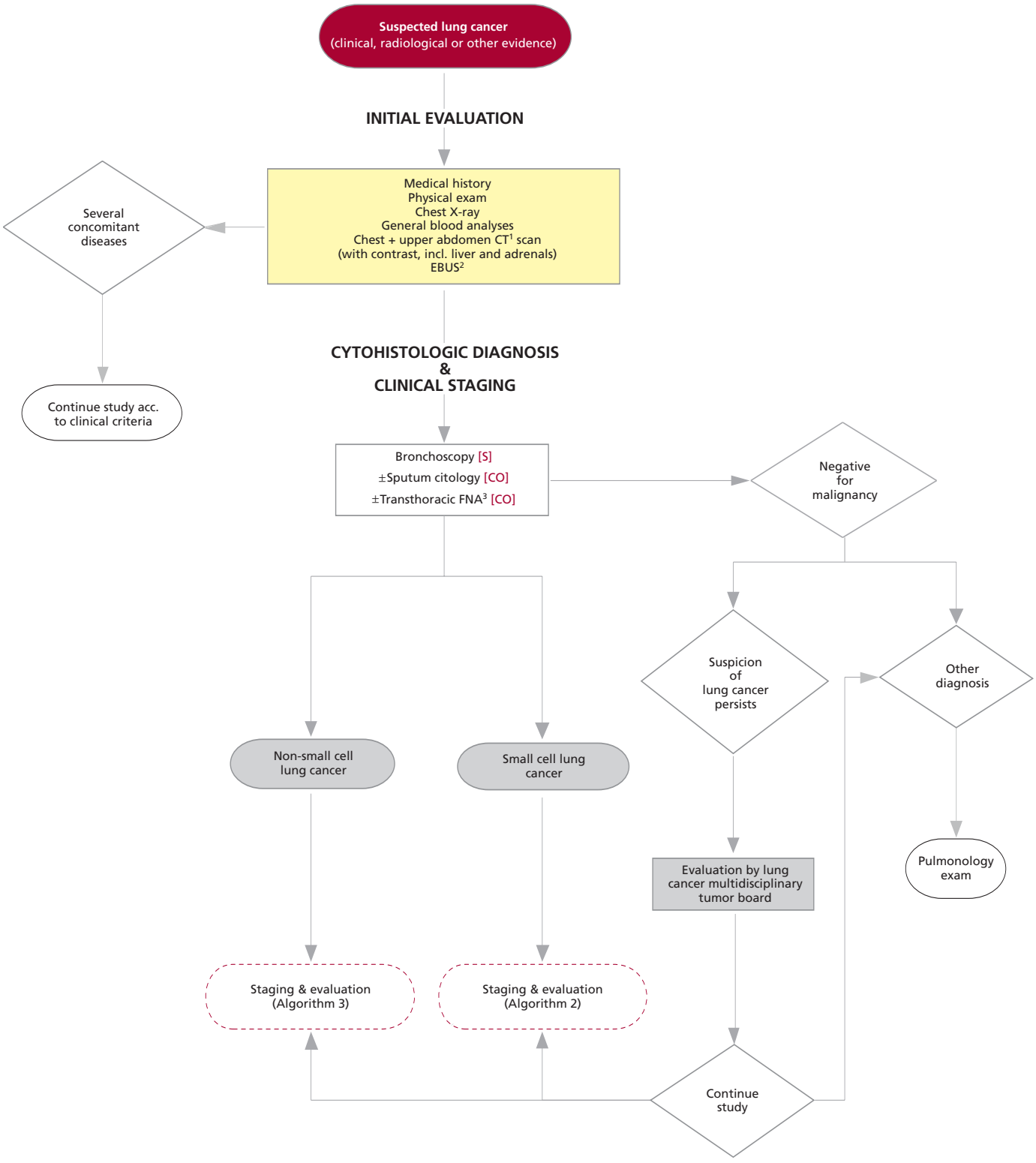
- Fédération Nationale des Centres de Lutte Contre le Cancer (www.fnclcc.fr) **[FNCLCC]**
- Institute for Clinical Systems Improvement, ICSI (www.icsi.org/) **[ICSI]**
- National Cancer Institute (www.cancer.gov/cancerinfo/pdq) **[NCI]**
- National Comprehensive Cancer Network (www.nccn.org/) **[NCCN]**
- Scottish Intercollegiate Guidelines Network (www.show.scot.nhs.uk/sign/guidelines) **[SIGN]**
- National Institute for Health and Clinical Excellence (www.nice.org.uk/) **[NICE]**
- European Society for Medical Oncology (www.esmo.org/) **[ESMO]**
- American Society of Clinical Oncology (www.asco.org/) **[ASCO]**
- American College of Chest Physicians (www.chestnet.org/) **[ACCP]**

- Sociedad Española de Neumología y de Cirugía Torácica (www.separ.es/publicaciones/normativas_y_procedimientos.html) **[SEPAR]**
- European Respiratory Society-American Thoracic Society Task Force (www.ers-education.org/pages/default.aspx?id=725) **[ERS-ATS]**
- American Brachytherapy Society (formerly the American Endocurietherapy Society) (http://www.americanbrachytherapy.org/) **[AES]**

PART II. LUNG CANCER ONCOGUIA

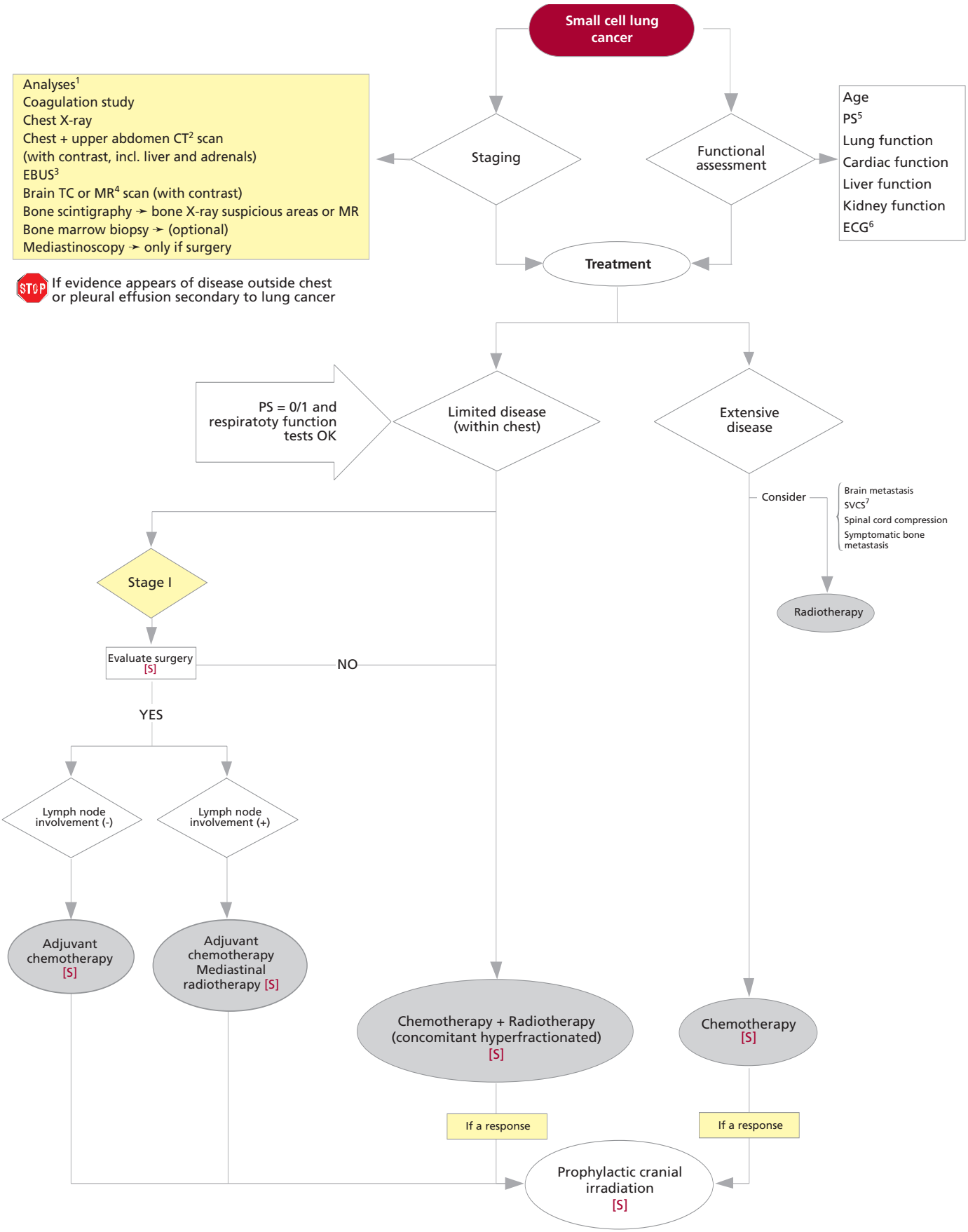
## ALGORITHMS

### ALGORITHM 1. Lung cancer diagnosis



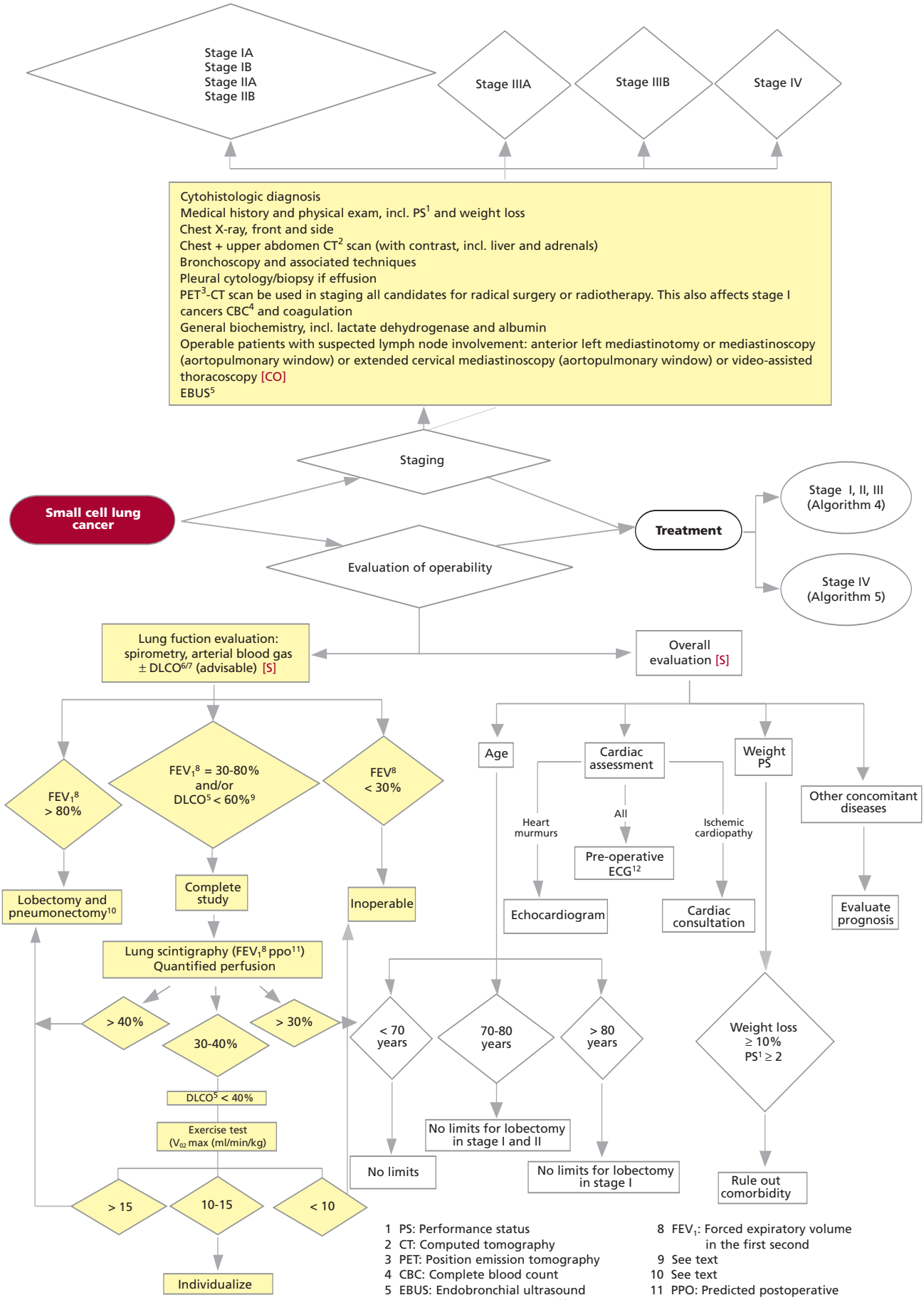

1 CT: Computed tomography
2 EBUS: Endobronchial ultrasound
3 FNA: Fine-needle aspiration
S Standard; CO: consensus option

# ALGORITHM 2. Small cell lung cancer diagnosis and treatment



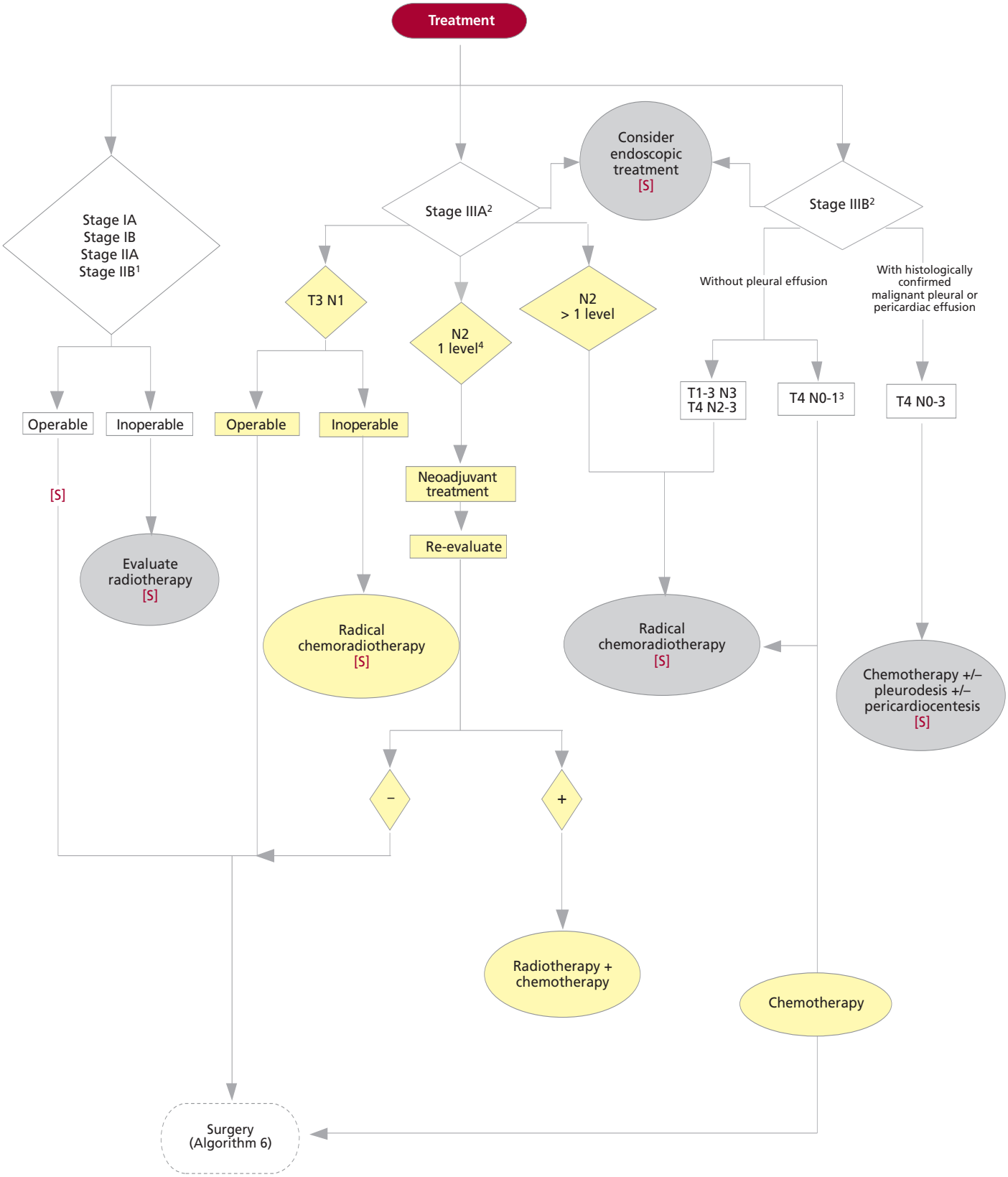

1 Complete blood count (CBC), creatinine, urea, sodium, potasium, calcium, lactate dehydrogenase, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase
2 CT: Computed tomography
3 EBUS: Endobronchial ultrasound
4 MR: Magnetic resonance
5 PS: Performance status
6 ECG: Electrocardiogram
7 SVCS: Superior vena cava syndrome

# ALGORITHM 3. Non-small cell lung cancer staging and evaluation



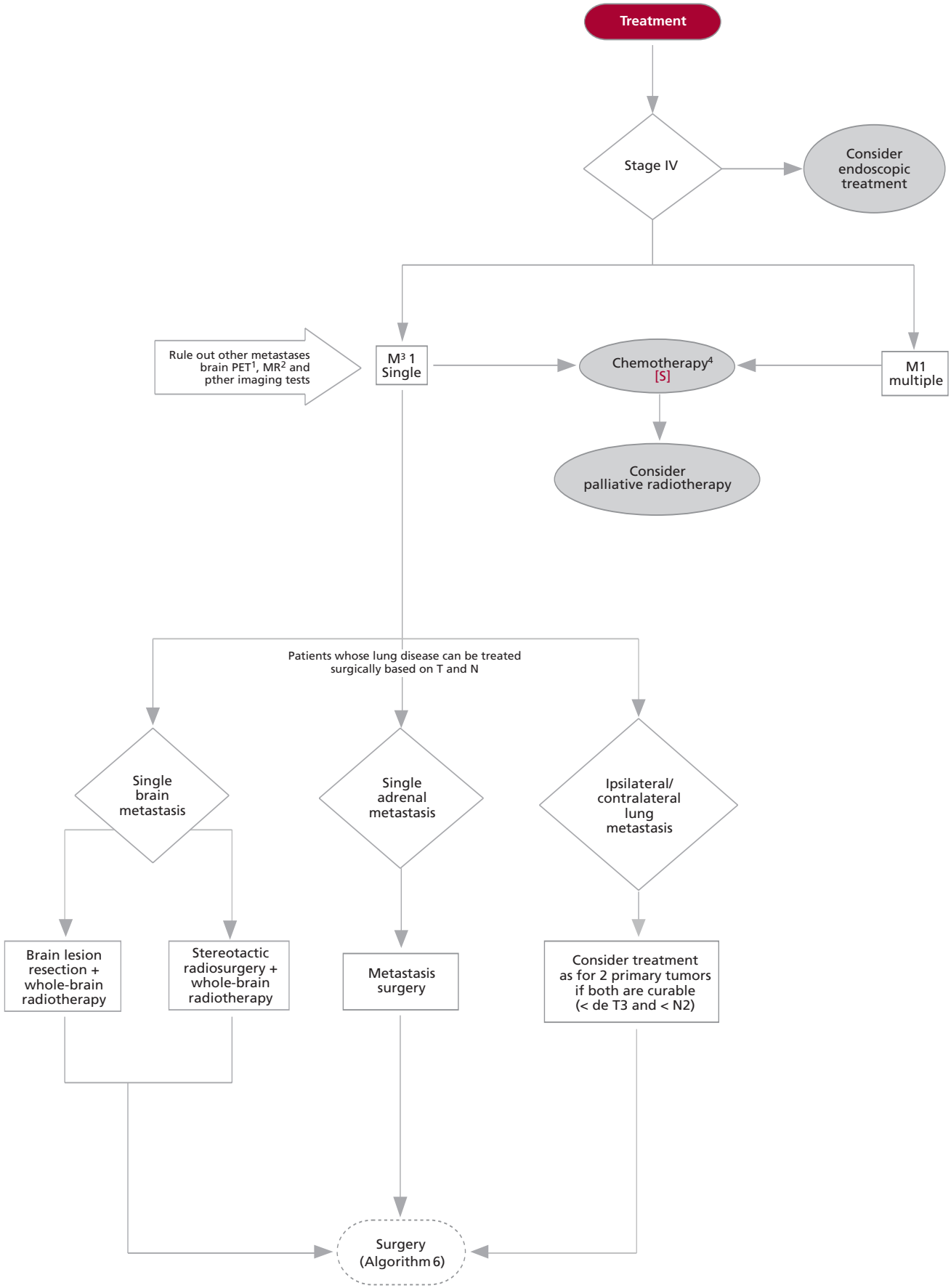

1 PS: Performance status
2 CT: Computed tomography
3 PET: Position emission tomography
4 CBC: Complete blood count
5 EBUS: Endobronchial ultrasound
6 DLCO: Carbon monoxide diffusing
7 Recommended
8 $FEV_1$: Forced expiratory volume in the first second
9 See text
10 See text
11 PPO: Predicted postoperative
12 ECG: Electrocardiogram

## ALGORITHM 4. Non-small cell lung cancer treatment



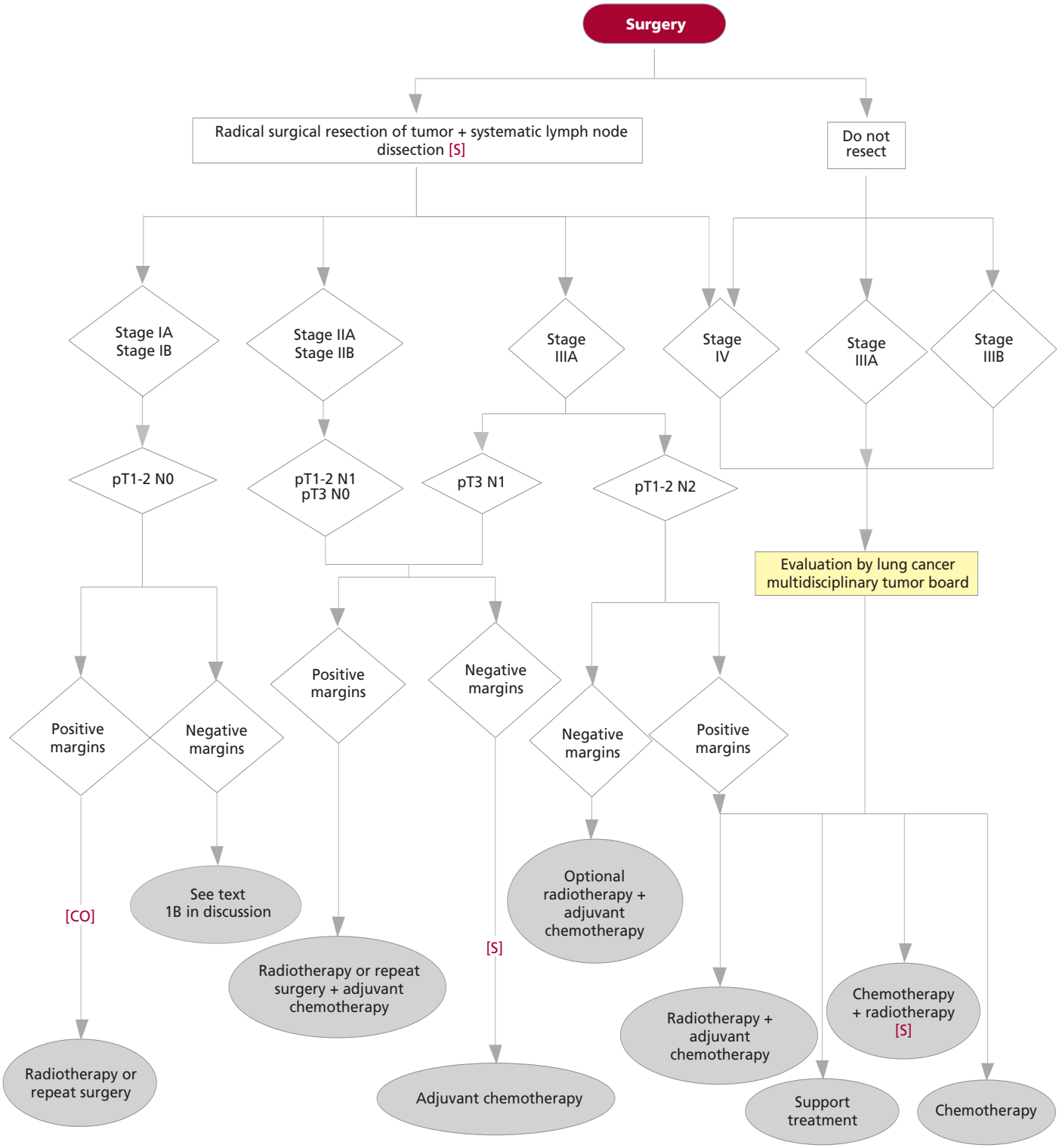

1 Pancoast tumor: neoadjuvant chemoradiotherapy or preoperative radiotherapy
2 Cytohistologic confirmation strongly recommended for patients with radiologic criteria and mediastinal lymph node involvement
3 Includes T4 on account of a satellite nodule in the same lobe
4 Less than T3 and proposed surgery less than a pneumonectomy

## ALGORITHM 5. Non-small cell lung cancer treatment




1 PET: Positron emission tomography
2 MR: Magnetic resonance
3 M: Metastasis
4 Consider radiosurgery for suitable cases. See text

## ALGORITHM 6. Non-small cell lung cancer postoperative treatment



## BACKGROUND AND EPIDEMIOLOGY

Lung cancer, also known as bronchogenic carcinoma, is considered to be any malignant neoplasm originating in the bronchopulmonary region. Since over 95% of lung cancers are carcinomas arising in the epithelial cells, in clinical practice the terms lung cancer and lung carcinoma are considered to be synonymous, and so are used interchangeably in cancer literature worldwide. However, in this *OncoGuia* the term lung cancer will be used to refer to lung carcinomas, as other malignant tumors of the lung are not covered given their low prevalence.

In broad terms, lung cancer refers to the most common carcinomas of the lungs and the bronchi. For study and treatment purposes, lung cancer is divided into two main groups:

- Small cell lung cancer (SCLC).
- Non-small cell lung cancer (NSCLC), which includes squamous cell lung cancer, adenocarcinoma, large cell lung cancer, and mixed carcinoma, each with different degrees of differentiation.

Other tumors, such as, for example, sarcomas, are excluded from this generic lung cancer classification. Also excluded are more unusual carcinomas and carcinomas with a different behavior, such as carcinoid tumors, mucoepidermoid carcinoma, and adenoid cystic carcinoma. The reason for excluding these tumors, apart from their low prevalence, is that they do not behave like the typical lung cancers and so are studied and treated differently. Furthermore, since survival rates for these tumors are generally better, their inclusion with general lung cancers would severely distort data on response to treatment and survival.

In Catalonia, the annual adjusted lung cancer incidence rates per 100 000 population are 52.91 and 4.69 for men and women, respectively. Lung cancer is the second most common cancer in men. The incidence of lung cancer in women has been steadily increasing worldwide; in Catalonia, for example, it increased by 2.68% between 1985 and 2004.[2]

The prognosis for lung cancer is poor, with an overall 5-year survival rate in Catalonia of 14% for men and 20% for women. This poor prognosis is largely due to the nature of the disease, which is often detected after it has rapidly begun to spread. However, poor prognosis is also due to the fact that patients with lung cancer typically have concomitant diseases associated with smoking (especially chronic obstructive pulmonary disease and cardiovascular disorders). Treatment is therefore complicated and morbidity and mortality rates are high.

## DIAGNOSIS

The suspicion of lung cancer usually emerges in one of the following situations:

- A chest X-ray obtained to investigate specific symptoms or for other reasons raises a suspicion of cancer.
- A patient consults for a symptom that would possibly point to lung cancer, for example, a smoker with hemoptysis.

As of this moment, the examinations required will be conducted as follows to:

- Firstly, confirm or rule out a diagnosis of lung cancer.
- Secondly, if lung cancer is confirmed, stage the tumor.
- Thirdly, evaluate the functional condition of the patient with a view to plan the most suitable treatment.

Although these examinations may overlap, studies of patients should be conducted in a way that avoids unnecessary tests.[3, 4] **[ESMO]**[5]

## Diagnosis of lung cancer [ACCP],[6] [SEPAR][7]

A diagnosis of lung cancer must be based on cytologic or histologic samples that confirm malignancy. [S]

Imaging studies may suggest a diagnosis but should never be considered conclusive.

Samples for diagnostic purposes must be obtained using at least one of the following techniques: sputum cytology, bronchoscopy, transthoracic fine-needle aspiration (FNA), or image-guided transthoracic needle biopsy. [S]

If a suspicion of cancer persists despite not being confirmed cytohistologically by the examinations listed above (which can be repeated if necessary), a more invasive examination should be considered, whether for exclusively diagnostic purposes-e.g., mediastinoscopy-or for both diagnostic and treatment purposes-e.g., thoracotomy (Table 1). [S]

The lack of a pretreatment diagnosis should not delay treatment for patients suitable for curative treatment. [S]

Table 1. Lung cancer diagnostic methods

| First phase |
|---|
| Sputum cytology |
| Bronchoscopy with its different techniques |
| Transthoracic fine-needle aspiration |
| Image-guided transthoracic biopsy with needle |
| **Second phase** |
| Mediastinoscopy |
| Mediastinotomy |
| Thoracoscopy |
| Thoracotomy |

First phase of the diagnosis

### ¬ Sputum cytology

Sputum studies should be conducted by a cytologist with experience of lung cancer so as to minimize the likelihood of false positives (FP).[8, 9]

This technique is used as a first examination for patients unwilling to undergo bronchoscopy or FNA or when a conservative approach is dictated by the patient's condition or the presence of comorbidities.

The diagnostic performance of sputum cytology –which can be as high as 85%– depends on the number and quality of the samples (3 samples of morning expectoration are recommended), and also on the size and location of the tumor. Sensitivity and specificity for sputum cytology are, respectively, 69% and 96%. Cytohistologic correlation for different types of carcinoma is high, reaching a maximum of 96.5% for SCLC, 95.3% for squamous cell cancer, 87.8% for adenocarcinoma, and 81.4% for large cell carcinomas.[10]

Note that the most important histologic difference –because it is crucial for treatment purposes– nis that between SCLC and NSCLC.

## ¬ Bronchoscopy

Flexible bronchoscopy has the dual advantage of enabling lung cancer to be both diagnosed and staged. Bronchoscopic techniques (Table 2) include obtaining samples of visible endobronchial and peripheral lesions using an imaging technique for guidance, or of mediastinal lesions using either conventional transbronchial FNA (blind) or endobronchial ultrasound (EBUS). Examination of the digestive tract using endoscopic ultrasound (EUS) with FNA provides access to masses bordering the oesophagus.

A computed tomography (CT) scan of the chest is recommended prior to performing the bronchoscopy. [S]

NICE recommends conducting a CT scan of the chest prior to bronchoscopy because it significantly increases the probability of obtaining a diagnosis. **[III] [NICE]**[11]

Table 2. Bronchoscopy techniques

| Flexible bronchoscopy |
|---|
| Bronchial aspiration |
| Brush cytology |
| Bronchoalveolar wash |
| Bronchial biopsy |
| Transbronchial lung biopsy |
| Conventional transtracheal or transbronchial fine-needle aspiration or endobronchial ultrasound |
| Rigid bronchoscopy |

Exceptionally, rigid bronchoscopy is used as a diagnostic method for highly necrotic or bleeding tumors, or whenever a first therapeutic intervention has to be undertaken.

For central lesions, a diagnostic performance of up to 95% is obtained for combinations of histologic and cytologic specimens, whereas the corresponding figure is 60% for peripheral lesions with a diameter of more than 2 cm. The performance for EBUS with FNA ranges between 79% and 95% for a sample of masses and lymph node stations in contact with the airway.[12, 13]

## ¬ Transthoracic fine-needle aspiration

This is preferably used for peripheral lesions, particularly if a bronchoscopy fails to reveal a tumor. Sensitivity to a malignancy diagnosis is 95% to 100%, even in nodules measuring 10-15 mm. The most typical approach is to perform a CT-guided aspiration, as this ensures that the needle is located within the lesion when the material is aspirated. The main complications are pneumothorax –requiring drainage in some 15% of cases– and pulmonary hemorrhage, typically self-limiting.[14, 15]

## ¬ Transthoracic biopsy

The cytology procedure occasionally produces necrotic material that makes it impossible to arrive at a conclusive diagnosis of neoplasm. In such cases, an image-guided core needle biopsy (tru-cut or similar) can be performed on the outside part of the tumor.

Second phase of the diagnosis:

A second study phase using a different set of techniques is implemented when it is not advisable to base a diagnosis on repetition of the first phase techniques. These second phase techniques are generally used for fewer than 3% of patients.

If an indication of surgery persists –despite tests failing to confirm the neoplasm– it is important not to lose time repeating tests but to perform an immediate surgical biopsy. **[GPP]**

Table 3. TNM staging of malignant tumors (UICC, 1997)

| CATEGORY T (PRIMARY TUMOR) | |
|---|---|
| T0 | ¬ No evidence of primary tumor. |
| Tx | ¬ Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial aspiration but not visualized by imaging or bronchoscopy. |
| Tis | ¬ Carcinoma *in situ*. |
| T1 | ¬ Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus. |
| T2 | ¬ Tumor with any of the following features of size or extent:<br>• More than 3 cm in greatest dimension<br>• Involves main bronchus, 2 cm or more distal to the carina<br>• Invades visceral pleura<br>• Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung. |
| T3 | ¬ Tumor of any size, as follows:<br>• Directly invading any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium.<br>• Bronchoscopically invading the main bronchus at least 2 cm distal to the carina but without involvement of the carina<br>• With associated atelectasis or obstructive pneumonitis of the entire lung |
| T4 | ¬ Tumor of any size, as follows:<br>• Invading any of the following: mediastinum, heart, great vessels, trachea, oesophagus, vertebral body, carina. Separate tumor nodule(s) within the same lobe of the lung; tumor with malignant pleural or pericardial effusion.[a]<br>Vocal cord paralysis, superior vena cava obstruction, or extrinsic compression of the trachea or oesophagus classifies a tumor as T4. However, when the tumor is peripheral, the corresponding lymph node stage (N2 or N3) is considered.[a] |

| CATEGORY N (REGIONAL LYMPH NODES) | |
|---|---|
| N0 | ¬ No regional nodal metastasis. |
| Nx | ¬ Regional lymph nodes cannot be assessed. |
| N1 | ¬ Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and including nodes involved by direct extension of the primary tumor. |
| N2 | ¬ Metastasis in ipsilateral mediastinal and/or subcarinal lymph nodes. |
| N3 | ¬ Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes. |

| CATEGORY M (DISTANT METASTASIS) | |
|---|---|
| M0 | ¬ No distant metastasis. |
| Mx | ¬ Distant metastasis cannot be assessed. |
| M1 | ¬ Distant metastasis. Includes separate tumor nodule(s) in a different lobe (ipsilateral or contralateral). |

| STAGE GROUPING | |
|---|---|
| 0 | Carcinoma *in situ* |
| IA | T1 N0 M0 |
| IB | T2 N0 M0 |
| IIA | T1 N1 M0 |
| IIB | T2 N1 M0 T3 N0 M0 |
| IIIA | T3 N1 M0 T1 N2 M0 T2 N2 M0 T3 N2 M0 |
| IIIB | T4 N0 M0 T4 N1 M0 T4 N2 M0 T1 N3 M0 T2 N3 M0 T3 N3 M0 T4 N3 M0 |
| IV | Any T Any N M1 |

a Most pleural effusions with lung cancer are due to tumor. In a few patients, however, multiple cythopathological examinations of pleural fluid are negative for tumor, and the fluid is non-bloody and is not an exudates. When these elements and clinical judgment dictate that the effusion is unrelated to the tumor, the effusion should be excluded as a staging element and the patient should be classified as T1, T2, or T3.

## Lung cancer staging

The TNM staging system used is the latest classification agreed by the International Union Against Cancer (UICC) in 2002 (Table 3).[16] An update is expected to be published in 2009.[17]

For SCLC, the distinction between limited disease and extensive disease is of practical use for therapeutic purposes. When the tumor is confined to the thorax and can be radically irradiated the disease is limited, whereas bilateral mediastinal and ipsilateral supraclavicular node involvement and superior vena cava obstruction indicate extensive disease. Although the division into these two forms of cancer is crucial for treatment purposes, it is also advisable to TNM-stage the tumor for prognostic and results purposes; even if the disease is limited, a T1N0M0 is not the same as a T3N2, for example.[18-20]

Although TNM staging for NSCLC is undoubtedly useful in terms of deciding treatment, prognosis based exclusively on TNM staging is very variable, given that other factors independently affect prognosis, primarily, recent weight loss, a poor nutritional state, and a generally poor condition.

When issuing the report, it should be noted whether TNM staging is clinical (prior to surgery, i.e., cTNM), pathologic (when there is a pathology report for the resected specimen, i.e., pTNM), or post-neoadjuvant treatment (restaging of a patient who has received neoadjuvant treatment prior to surgery, i.e., yTNM).

## Diagnostic approach to TNM classification

### Table 4. TNM study phases

| |
|---|
| PHASE I |
| Medical history<br>Full physical examination<br>Chest X-ray<br>Chest computed tomography scan<br>Bronchoscopy<br>Laboratory workups |
| PHASE II |
| Magnetic resonance imaging |
| PHASE III |
| Brain computed tomography or magnetic resonance imaging<br>Magnetic resonance imaging<br>Other tests |

### Tumor staging (T)

Tumor study consists of 3 phases:

1. General and specific clinical history, a full physical examination, and posteroanterior and lateral chest X-ray.
2. Chest CT scan that includes the upper abdomen, the adrenal glands, and the liver.
3. Flexible bronchoscopy.

If the data obtained in the first 3 steps would indicate their advisability, other tests such as magnetic resonance imaging (MRI) or an oesophagogram can be performed.

Table 4 describes the TNM study phases, and Table 5 shows the certainty factors applied to TNM staging, depending on the tests performed in order to classify the tumor. TNM staging does not require a minimum of tests in order to classify a tumor

### Table 5. Certainty factors

| | |
|---|---|
| C1 | Evidence obtained by standard diagnosis means (e.g., inspection, X-ray, endoscopy). |
| C2 | Evidence obtained by special diagnosis means (e.g., computed tomography, positron emission tomography, magnetic resonance imaging, bronchial biopsy). |
| C3 | Evidence from surgical exploration, including biopsy and/or cytology. |
| C4 | Evidence of the extent of disease following definitive surgery and pathologic examination of the resected specimen. |
| C5 | Evidence from autopsy. |

## Difficulties in determining T

- Differentiation between T1 and T2 should be based on radiologic and endoscopic tests. Although radiologic classification of T1 and T2 tumors is prone to false negative (FN) and FP results (values of up to 18% and 47%, respectively), the significance of the possible error is minimal given that it does not affect the choice of treatment.

- A surgical examination is recommended for patients who are either cT3 or cT4 and possible candidates for surgery. [S]

Correct classification of T3 and of T4 if considered to be a surgical case is extremely important. CT scan accuracy in predicting T3 and T4 is poor, with average FN and FP values (for several studies) of 18% and 32%, respectively, both for peripheral involvement (chest wall) and central involvement (mediastinum). If the chest wall is affected, the most reliable indicators are chest pain, rib destruction, protrusion through the ribs, and contact extending over 3 cm or over more than half the tumor.

CT scan capacity to rule out mediastinal invasion in tumors protruding into the mediastinum is good (average FN value of 14% in several studies). On the other hand, its accuracy in predicting mediastinal invasion is poor (average FP value of 33% for all the cited studies). For a high proportion of patients, no radiologic test is capable of predicting whether a tumor is unresectable. **[Ib]**[21-23]

For patients for whom doubt remains between cT3 and cT4 cancers and who are possible candidates for surgery, a surgical examination will be necessary (even though the resectability rate is only 70%).

- For patients with Pancoast tumor, MRI with sagittal and coronal views is preferable to CT as it is better at predicting brachial plexus and subclavian vessel involvement (FN and FP values of 6% and 0%, respectively, for MRI, and FN and FP values of 19% and 19% for CT in a study of 31 patients). **[NICE]**[11, 24]

If there is chest wall involvement in a Pancoast tumor, an estimation error for T staging will greatly affect treatment, as it is not possible to entirely resect 30% to 50% of these patients.

- Patients with extensive mediastinal involvement. Such patients have tumors around mediastinal structures (superior vena cava, pulmonary artery, trachea, and main bronchi) or tumors with massive mediastinal involvement –possibly adenopathic but indistinguishable from the main tumor because together they form a single block. Non-surgical treatment– with no need to confirm involvement of the mediastinum –is indicated for tumors that surround unresectable mediastinal structures.[25]

- Patients with poor functional performance status (PS) for whom pneumonectomy but not lobectomy is contraindicated. In a retrospective study of 26 patients with tumors central or adjacent to the sulcus, CT scan evidence of invasion of a main bronchus or crossover to the sulcus was a good predictor of the need for a pneumonectomy (zero FP value for both cases); radiologic evidence of invasion of the pulmonary artery, on the other hand, was a poor predictor (FP of 67%).

## Lymph node staging (N)

- The presence of enlarged lymph nodes must be determined by physical exploration in the case of supraclavicular adenopathies and by CT for mediastinal adenopathies. Diagnostic certainty of malignancy is obtained by aspiration or biopsy (see Table 1).

- A short-axis diameter of 1 cm has been widely adopted by radiologists as the threshold for differentiating normal from abnormal nodes. Mediastinal lymph nodes with a short-axis diameter of 1.5 cm or more are considered to be pathological. They are associated with tumors in 70% to 80% of cases and are reactive in the remaining cases. Lymph nodes with a short-axis diameter of between 1 cm and 1.5 cm are regarded as indeterminate and may be affected in up to 50% of cases.

- CT has a high negative predictive value (0.82 to 0.84) according to different studies cited in the SEPAR[7] manual; nonetheless, FN values are 16% to 18%. The positive predictive value is both lower and more variable (0.51 to 0.78), which means that histological confirmation of the presence of tumorous lymph nodes will be necessary prior to ruling out surgery.

As a general rule, a pathology report is necessary to confirm mediastinal lymph node involvement detected by CT scan and/or combined positron emission tomography and CT scan (PET-CT). [S]

The method used for a confirmation study (mediastinoscopy, mediastinotomy, respiratory and/or digestive echoendoscopy, or video-assisted thoracoscopy) will depend on the expertise and equipment available in each hospital. As a general rule, preferred techniques are those that, for the same diagnostic performance, have lower morbidity and cost. **[Ia]**[26, 27]

- A radiologic suspicion of lymph node invasion (CT or PET-CT) for cases in which endoscopic cytology resulted negative should be confirmed by surgery. [S]

Very often CT scans are incapable of determining whether a hilar mass is an enlarged lymph node (N1) or part of the tumor. Although an N1 diagnosis is important for the prognosis of the disease, it does not affect tumor resectability. **[SEPAR]**

- Histological confirmation of enlarged mediastinal lymph nodes in patients with stage IIIA and IIIB cancers is recommended. [S]

Lymph node stations 2, 4, 7, 10 and 11 are accessible to FNA via flexible bronchoscopy. The conventional blind procedure obtains a diagnostic performance of between 15% and 83%, with a positive predictive value of 89% to 100%. With EBUS, performance increases to 90% (79% to 95%) for a specificity of 100%.[12, 13] Digestive EUS-FNA obtains samples from lymph node stations 4, 5, 7, 8 and 9, for an overall diagnostic performance of 84% (71% to 100%), and for an overall specificity of 99.5% (88% to 100%).[28, 29] The combination of EUS-FNA and EBUS achieves a sensitivity of 93% and a specificity of 97%, producing better results than the techniques used separately.

PET-CT scan is particularly indicated for staging patients suitable for radical treatment (surgery or radiotherapy), given its efficacy in predicting negative values. [S]

There is evidence to support PET-CT efficacy in predicting negative values, which is why this combination is particularly indicated for patients suitable for radical treatment. **[II]**[30-35]

- Mediastinoscopy is the gold standard for a pretherapeutic study of the mediastinum. Although the procedure is invasive, morbidity and mortality are low, at 2% and 0.08%, respectively. The paratracheal lymph nodes (stations 2R, 2L, 4R, and 4L), superior mediastinal lymph nodes *(1)* and anterior subcarinal lymph nodes *(7)* are accessible to mediastinoscopy. However, posterior subcarinal lymph nodes *(7)* and lower mediastinal lymph nodes *(8* and *9),* aortopulmonary window lymph nodes and anterior mediastinal lymph nodes *(5* and *6),* and prevascular and retrotracheal region lymph nodes *(3)* cannot be biopsied by mediastinoscopy. Ideally, examination of 5 nodular stations (2R, 4R, 7, 4L, and 2L) should be routine, by means of a biopsy of at least 1 lymph node in each station (except when no node is detectable). The FN value for mediastinoscopy is around 9%.

In patients with mediastinal abnormality but without extensive involvement (in other words, there is CT evidence of enlarged lymph nodes differentiated from the main tumor), confirmation should be obtained –given the high FP rate– by means of EUS-FNA or surgery (mediastinoscopy) before deciding treatment.

In patients with tumors in the left upper lobe, and provided the other lymph node stations are unaffected, the aortopulmonary window should be explored by means of EUS-FNA, extended mediastinoscopy, or left-side video-assisted thoracoscopy.

There is no universal agreement as to whether a mediastinoscopy should be performed in all operable patients with lung cancer. The FN rate can reach 10% (for example, for peripheral tumors with a radiologically normal mediastinum), in which case mediastinoscopy can be ruled out. For other groups of tumors for which no mediastinoscopy is performed, surgery can result in a clinical FN rate of over 20% (central tumors, cN1 with a diagnosis of adenocarcinoma, or large cell carcinoma). This FN rate is clearly unacceptable, making it necessary to perform systematic mediastinoscopies in this subgroup of patients, irrespective of CT scan findings.

### Metastasis staging (M)

Any anomalous data collected in the first part of the study should be taken into account in terms of deciding new tests for each patient.[36]

- When collecting data on medical history, the patient should be expressly questioned on the appearance of skin nodules, bone pain, headache, etc.
- Any recent skin nodule should be treated as suspicious, and an FNA should be performed.
- In NSCLC, if there is no bone pain, and if calcium and alkaline phosphatase levels are normal, the probability of finding metastasis in a bone scan is zero.[37]
- In early-stage NSCLC, a routine search for metastasis is pointless. The adrenal glands should be included in a chest CT given that adrenal metastasis is generally silent and the additional cost is negligible.
- It is important to take into account metastasis patterns (e.g., adenocarcinoma, SCLC, and cerebral metastasis). Staging should also be considered, since the probability of metastasis is logically related to tumor stage.

- When a PET-CT scan diagnoses metastasis to a single location in a patient suitable for radical treatment, the metastasis should whenever possible be confirmed using other techniques (e.g., histology). [S]

In such cases, 50% of the detected lesions will be either benign lesions or other neoplasms. [II][38]

- A multidisciplinary medical team should discuss cases of patients who are candidates for curative treatment, and a cranial CT-MRI should be performed as part of the extended study before treatment commences.

## PRETREATMENT EVALUATION

[ACCP][39], [SEPAR][40]

Age and comorbidity are among the criteria considered in the clinical practice guidelines for the physiologic evaluation of patients with lung cancer for surgery of the American College of Chest Physicians (ACCP), other than the performance status criteria. The ACCP recommendations, graded according to levels of evidence, are very similar to recommendations published recently by the Spanish Society of Pneumology and Thoracic Surgery (SEPAR). Our working group compared both guidelines and our recommendations are summarized below:

### Age

- For stage I and II cancers, age does not contraindicate surgery.
- For stage I cancer in patients aged 80 and over, lobectomy is not contraindicated.
- The need for a pneumonectomy is a limiting factor, as mortality is greater above the age of 70 years.

## Lung function

Lung function in all patients being considered for a lung resection should be evaluated by means of spirometry (forced expiratory tests) and arterial blood gas analysis. [S]

Measuring diffusion capacity of the lung for carbon monoxide (DLCO) is recommended for all patients, but is absolutely essential for patients with interstitial lung disease, undue dyspnea, or undergoing induction chemotherapy. [S]

Lung function should be evaluated when patients are clinically stable and maximally bronchodilated following a period of abstention from smoking.

If forced expiratory volume in the first second ($FEV_1$) of > 80% is predicted, other tests are not necessary. In all other cases, predicted postoperative $FEV_1$ (ppo-$FEV_1$) should be calculated in accordance with the proposed resection. Postoperative lung function should also be evaluated if DLCO < 60%.

Lung perfusion scintigraphy with $^{99}$Tc-labeling is recommended for evaluating postoperative lung function.

Surgery is not recommended if ppo-$FEV_1$ is < 30%.

If ppo-$FEV_1$ is 30% to 40% and/or DLCO < 40% of the corresponding theoretical values, an incremental exercise test to measure oxygen uptake ($VO_2$) is indicated:

- $VO_{2max}$> 15 mL/min/kg. Patient is operable but has an enhanced risk.
- $VO_{2max}$ 10-15 mL/min/kg. Patient has a much enhanced risk, and each case should be considered individually.
- $VO_{2max}$< 10 mL/min/kg. Patient for whom lung resection is contraindicated.

The surgical risk is assumable if ppo-$FEV_1$ of > 40% is predicted, and so the patient can be rated as operable.

## Cardiac assessment

The risk of postoperative myocardial infarct, which is 0.07% in the general population, increases to 37% in patients who undergo surgery in the 3 months after a heart attack, but falls to 16% if surgery is performed 3 to 6 months after the attack, and to 6% if surgery is performed after 6 months.

- All patients should undergo a preoperative electrocardiogram (ECG).
- An echocardiogram should be performed in any patient with a heart murmur.
- No surgery should be performed in the 6 weeks after a heart attack.
- A cardiologist should be consulted in the 6-month period following a heart attack.

## Weight loss, nutritional status, and general clinical status

- Patients who have experienced weight loss of 10% or more and/or who have a WHO performance status (PS) score of 2 or less are highly likely to have advanced disease so must be accurately staged and assessed for possible comorbidities.
- Preoperative evaluation should include nutritional status measurements, such as body mass index and serum albumin levels, as low values imply an enhanced risk of postoperative complications.

# SURGICAL TREATMENT OF LUNG CANCER

## Diagnosis and staging [SEPAR][7]

- All surgery candidates should undergo a routine chest X-ray and a chest CT scan including liver and adrenal glands. [S]

- For patients with very low surgery risk, FNA confirmation of recently developed peripheral lesions is not necessary before surgery.

## Operability and adjuvant treatment

- The proportion of patients found to be inoperable during intervention should not be more than 5% to 10%.
- Generally, patients with stage IIIB cancer with lymph node involvement and patients with stage IV cancer should be regarded as inoperable.

## Types of surgery

- For stages I, II and IIIA , the work group recommends surgery as the standard treatment. [S]

- The standard surgical treatment is the lobectomy. [S]

- The lobectomy is the minimum resection considered to be a treatment for cancer. [SEPAR][41]
- Sublobar resection is a useful alternative in patients with a compromised lung function. However, the likelihood of local relapse is greater than for a lobectomy and long-term survival is reduced by 5% to 10%.
- Postoperative mortality should not be more than 4% for lobectomy and 8% for pneumonectomy.

- At least 3 lymph node stations and/or at least 6 lymph nodes should be biopsied or extirpated to be able to assert that a cancer is pNO. [S]

To ensure accurate cancer staging, either a systematic nodular dissection or a sampling of all regions during surgery should be performed. The choice of stations to biopsy will depend on the lung and lobe where the tumor is located. The therapeutic value of radical lymphadenectomy is uncertain. [SEPAR][7]

## Locally advanced disease

- Well-screened patients with vertebral involvement or with superior sulcus tumors may be candidates for radical surgery combined with other treatments. Surgery is not indicated if there is mediastinal node involvement.
- Surgery is not contraindicated if there is involvement of a main bronchus or of the extrapericardial mediastinal part of the right or left pulmonary artery, whereas it is contraindicated if there is involvement of the pulmonary trunk, trachea, oesophagus, or heart. Patients with invasion of the carina, the superior vena cava, or the vertebral body may, in exceptional cases, be considered for surgery.

Surgery should not be ruled out as long as there remains the slightest possibility of treating the patient in this way. [S]

## COMPLEMENTARY TREATMENTS

### NSCLC stages I and II

Stage I: Treatment with radical radiotherapy must be considered for inoperable patients[42] **[NICE]**,[11] **[NCCN]**.[43]

Stage II: Adjuvant treatment with cisplatin-based chemotherapy must be considered for all patients with a satisfactory PS. [S]

This treatment has been demonstrated to improve overall survival of patients with stage II and IIIA cancers following complete resection. **[1++]**[44, 45]

### NSCLC stages III and IV

For patients with stage IIIA, none of the optimal sequence of treatments, the specific drugs to use and the chemotherapy duration has been defined.[46]

**Stage IIIA.** *Resectable in operable patients:*

Neoadjuvant chemotherapy or chemoradiotherapy is recommended for operable patients with resectable stage IIIA cancer and with cytohistologically confirmed N2 disease, provided the proposed surgery is inferior to a pneumonectomy. It is indicated for patients as follows: with a tumor staged as T3 or less, with an acceptable lung function, with no significant comorbidity, and who are not elderly. [S]

There is evidence that neoadjuvant chemotherapy or chemoradiotherapy significantly improves survival in such patients. **[1+]**[47-49]

Since the benefit of surgical treatment appears to be restricted to patients in whom neoadjuvant treatment has reduced tumor extension from cN2 to ypN0,[50, 51] it is recommended to confirm postinduction staging with a lymph node biopsy performed using (as available) transtracheal needle aspiration, transesophageal needle aspiration, mediastinoscopy, or repeat mediastinoscopy.

If this cytohistologic examination is positive, the patient should not undergo surgery.

**Stage IIIB.** *Resectable in operable patients:* Neoadjuvant chemotherapy and chemoradiotherapy with subsequent assessment for surgery are accepted.

**Stages IIIA and IIIB.** *Unresectable or inoperable patients:*

Pacients with stages IIIA and IIIB who are medically inoperable or having unresectable cancer, should be offered combined chemotherapy and radical radiotherapy as a standart treatment. [S]

RCTs have demonstrated that concomitant chemotherapy and radical radiotherapy improves survival for such patients. **[1+]**[52-58] **[ACCP]**[59]

Initial endoscopic treatment should be considered when there is obstruction of the trachea or main bronchi with accompanying symptoms, or when there is severe persistent hemoptysis.

**Stage IV.** Chemotherapy is recommended for patients with stage IV cancer and a PS of 0 or 1. [S]

Chemotherapy is preferable to support care for patients with stage IV cancer with a PS of 0 or 1. **[1++]**[60, 61]

Although benefit is moderate, it is consistent, for which reason the clinical trial option should always be considered. Chemotherapy should be based on cisplatin (or carboplatin as a second choice), combined with another active drug such as vinorelbine, gemcitabine, paclitaxel or docetaxel. **[1++]**[62, 63]

The ideal number of cycles has not been determined, although prolonged regimens do not seem to improve survival. Response should be assessed every 2 to 3 cycles. Cisplatin-based

chemotherapy is not regarded as indicated for a PS of 2. Monotherapy or drug combinations that exclude cisplatin may be considered. Treatment with chemotherapy is not indicated if PS is 3 or 4.[64-66]

Second-line treatment should be considered, above all, for patients who have responded well to first-line treatment and who are in good general condition. Patients previously treated with platinum can be treated with docetaxel, pemetrexed[67] or erlotinib.[68]

## SCLC

The treatment of choice for limited disease recommended by the working group is concomitant chemoradiotherapy. [S]

There is evidence that concomitant chemoradiotherapy is the most effective treatment for limited disease. **[1+]**[69, 70]

The working group recommends palliative chemotherapy for extensive disease as a consensus option. **[CO]**

Suggested drug combinations are cisplatin or carboplatin with etoposide.[71] Even though it is difficult to evaluate response for an irradiated area, patients who do respond can be offered prophylactic cranial radiotherapy.[72] Treatment with carboplatin and etoposide or carboplatin alone may be considered for patients with comorbidities or whose general state of health is poor. Although the prognosis is uniformly poor for relapsed patients, if their condition permits it they may be treated again with chemotherapy.

# ENDOSCOPIC TREATMENT [ERS-ATS][73-75]

Endoscopic treatment is recommended for resolution of symptomatic main airway obstruction, control of persistent hemoptysis, and occlusion of a tracheoesophageal fistula. [S]

## Resolving main airway obstruction

- Indications. To resolve symptomatic obstruction of the main airway at initial presentation and throughout the course of the disease. The effects are evident in an improvement in dyspnea and in the patient's general condition.
- Exclusions. Terminal patients, patients with NSCLC who are candidates for surgery, and patients with SCLC whose breathing is unimpaired and who might benefit from chemotherapy.
- Methods. There are 3 groups of techniques which can be used in combination. The recommended approach is to combine rigid and flexible bronchoscopy.

*Thermal procedures:* These techniques, which are indicated to treat growing endoluminal tumors, involve applying extreme heat or cold. They include electrocautery, argon plasma coagulation, laser therapy, and cryotherapy. The effect is immediate for all the treatments except cryotherapy.

*Brachytherapy (endoluminal irradiation).* This technique is used for mixed lesions of less than 2 cm (endoluminal and with extrinsic compression). The effect is delayed (10 to 20 days), the technique is compatible with external irradiation, and rigid bronchoscopy is not essential.[76]

*Tracheobronchial stents.* Made in a range of materials (silicone, other polymers, or metal), these stents are implanted when there is extrinsic compression and to avoid relapse when an extensive tumor bed remains after resection. Their effect is immediate.

## Persistent hemoptysis

- Indications. Life-threatening or persistent hemoptysis that does not respond to the usual treatments.
- Exclusions. Terminally ill patients.
- Methods. Effective treatments for hemoptysis associated with a peripheral tumor are wedging, vasoconstrictor instillation, and cellulose mesh tamponade therapy.[77] Treatments of choice for central tumors are laser photocoagulation, electrocautery, and argon plasma coagulation.[78]

## Tracheoesophageal fistula

Tracheoesophageal fistula is an unusual complication of lung cancer. No controlled studies exist that compare single tracheal or esophageal stenting with double tracheal-esophageal stenting. If the double alternative is chosen, it is recommended to commence with tracheal stenting to avoid compressing the airway. Stents should always be covered.

Exclusions: Terminal patients and tracheostomy patients.

# RADIOTHERAPY

## SCLC

### Thoracic radiotherapy

The tumor and any involved lymph regions should be irradiated along with safety margins in the three axes. Prophylactic mediastinal irradiation is optional. In treatments concomitant with chemotherapy, doses of 50-55 Gy should be administered conventionally fractionated into 1.8-2 Gy daily or doses up to 45 Gy in hyperfractionated regimen, administered in fractions of 1.5 Gy twice daily, separated by a minimal interval of 6 hours. For postchemotherapy treatments, a conventionally fractionated dose of 50-60 Gy should be administered. Megavoltage equipment, International Commission on Radiation Units and Measurements 50 (ICRU-50) reference point prescription dose, and 3D planning techniques are recommended.[70, 79, 80]

### Prophylactic cranial radiotherapy

Brain irradiation is recommended for patients with both limited disease and disseminated disease. The treatment should be administered as a total dose of 36-40 Gy in daily fractions of 2 Gy, or as a total dose of 24-30 Gy in daily fractions of 3 Gy.[72, 81, 82]

## NSCLC

### Radical radiotherapy (stages I and II)

Radical radiotherapy is recommended for inoperable patients, patients unwilling to undergo surgery, and elderly patients. [S]

Radical radiotherapy is considered to be a viable alternative treatment for inoperable patients with stages I or II, for patients unwilling to go surgery, and for elderly patients.

Conventionally fractionated doses of over 60 Gy are recommended to the macroscopic tumor volume (lung tumor and affected lymph nodes) with safety margins in the three axes. Megavoltage equipment, ICRU-50 reference point prescription dose, and 3D planning techniques are recommended. Prophylactic mediastinal irradiation does not appear to be indicated. [ACCP][83-86]

### Complementary postoperative radiotherapy

This treatment is not indicated for patients with stages I or II who have had a complete resection. It is indicated, however, for stage III cancers which have been fully resected, and, optionally, for certain N1 patients or when adverse factors exist (doubts regarding radicality, narrow margins, etc).

Conventionally fractionated doses of 50 Gy or more –or of 60 Gy or more if there are positive margins– are recommended for the surgery bed and/or the mediastinum with safety margins in the three axes. Megavoltage equipment, ICRU-50 reference point prescription dose, and 3D planning techniques are recommended.[87]

### Chemoradiotherapy (stage III)

Conventionally fractionated doses of 60 Gy or more to the macroscopic tumor volume (lung tumor and affected lymph nodes) with safety margins in the three axes are recommended. Megavoltage equipment, ICRU-50 reference point prescription dose, and 3D planning techniques are recommended. Prophylactic mediastinal irradiation does not appear to be indicated.[59, 88, 89]

### Palliative radiotherapy

Doses should be administered according to location and the symptoms to be controlled. Recommended are high doses per fraction, megavoltage equipment, ICRU-50 reference point prescription dose, and the simplest possible planning techniques adapted to location and to objective.

## RADIOSURGERY FOR INTRACRANIAL METASTASES[90-92]

Conformal stereotactic intracranial radiotherapy enables small lesions to be treated directly with high doses of radiation while sparing surrounding healthy tissue. A stereotactic system, guided by coordinates in the 3 dimensions of the stereotactic space, is used to immobilize the head and to locate and treat the target volume.

Administration should be considered for patients with brain metastases with more favorable prognoses (recursive partitioning analysis (RPA) classes I and II of the Radiation Therapy Oncology Group (RTOG), or a Karnofsky PS of 70 or more, but without progressive extracranial disease). Furthermore, patients should have no more than 3 metastases, and 40 mm should be the maximum diameter of the largest lesion.

Stereotactic radiotherapy can be administered either sequentially with prophylactic cranial radiotherapy to deliver very high doses to the macroscopic tumor lesions, or as salvage treatment for patients who have previously been irradiated.

While awaiting results that confirm or otherwise the need for immediate prophylactic cranial radiotherapy, stereotactic radiotherapy alone can be considered for selected cases (patients with single or very small lesions, patients with lesions whose histologies make then insensitive to low radiation doses, and patients at risk of developing neurocognitive damage). Prophylactic cranial radiotherapy can, if necessary, be delayed to the point when progression becomes evident.

The treatment can be administered in a single session (radiosurgery) or in more than one session (fractionated stereotactic radiotherapy). The latter technique is particularly suitable for large lesions or lesions located adjacent to organs at risk (such as the brainstem or optic nerve), and also in patients who, for whatever reason, may poorly tolerate single-dose stereotactic radiotherapy.

### Technique

- Multiple static or dynamic isocentric and non-coplanar beam arrangement (arc therapy), contoured with circular or microleaf collimators.
- ICRU-50 reference point prescription dose (100% of the dose to the target volume center, i.e., the planning tumor volume) or reference isodose of 70% to 80%.
- Doses, which should be administered in a single session, are 16-20 Gy prescribed to the 80% isodose line (the typically prescribed maximum, minimum and mean dose to the target volume). Dose should be adapted to each patient depending on factors such as lesion volume and previous radiation doses. Fractionated stereotactic radiotherapy should be administered in a hypofractionated regimen of radiobiologically equivalent doses

## HIGH DOSE RATE BRACHYTHERAPY FOR TRACHEAL AND BRONCHIAL NEOPLASMS [AES]

Tracheobronchial tree tumors are irradiated using a temporary endoluminal brachytherapy technique in several sessions separated by days, at a high dose rate (maximum biological effective dose (BED) 12 < 120 $Gy_{12}$) and either after external beam radiotherapy or as monotherapy.[76, 93, 94]

### 1. Curative intent indication

- Exclusive brachytherapy. Patients who are inoperable, who cannot be irradiated using external beam radiotherapy because of serious concomitant conditions, and exclusively with intrabronchial tumors (primary tumor, relapse or metastasis).
  Recommended dose. 6 sessions x 5 Gy/session x I session/week over 6 consecutive weeks.
- High dose brachytherapy. As a complement to external beam radiotherapy.
  Recommended dose. Equivalent to 70-80 Gy (external beam radiotherapy + brachytherapy).
- Salvage brachytherapy. For local recurrence in patients previously treated with external beam radiotherapy but with a good curative profile, as a way of minimizing radiation to organs at risk. Recommended dose. 4 sessions x 5 Gy/session x I session/week over 4 consecutive weeks.

### 2. Palliative intent indication

Patients with endobronchial metastasis of other primary tumors, relapsed radiotherapy patients who cannot be radically irradiated, and patients with symptomatic airway obstruction are not regarded as candidates for curative treatments. Recommended dose. 2 to 3 sessions x 7-8 Gy/session x I session/week over 2 to 3 consecutive weeks.

### 3. Contraindications

- Tumors with a major post-external beam radiotherapy extrabronchial component
- Significantly enlarged post-external beam radiotherapy lymph nodes
- Extrinsic bronchial compression
- Lesions affecting or in contact with great vessels
- Endoscopically visible ulcerous lesions or necrosis of the bronchial wall
- Lesions which cannot be accessed by a central venous access device
- All bronchoscopy contraindications.

## FOLLOW-UP AFTER CURATIVE INTENT TREATMENT [NCCN][43]

- ¬ Six-monthly (the first 2 years) then annual monitoring is recommended depending on medical history, physical examinations, and chest X-ray or CT scan. [S]

- ¬ Patients should be counseled with regard to both recognizing the symptoms of relapse or of a new tumor and contacting their doctor if any worrisome symptoms appear. **[GPP]**

- ¬ Smokers should be strongly urged to stop smoking. [S]

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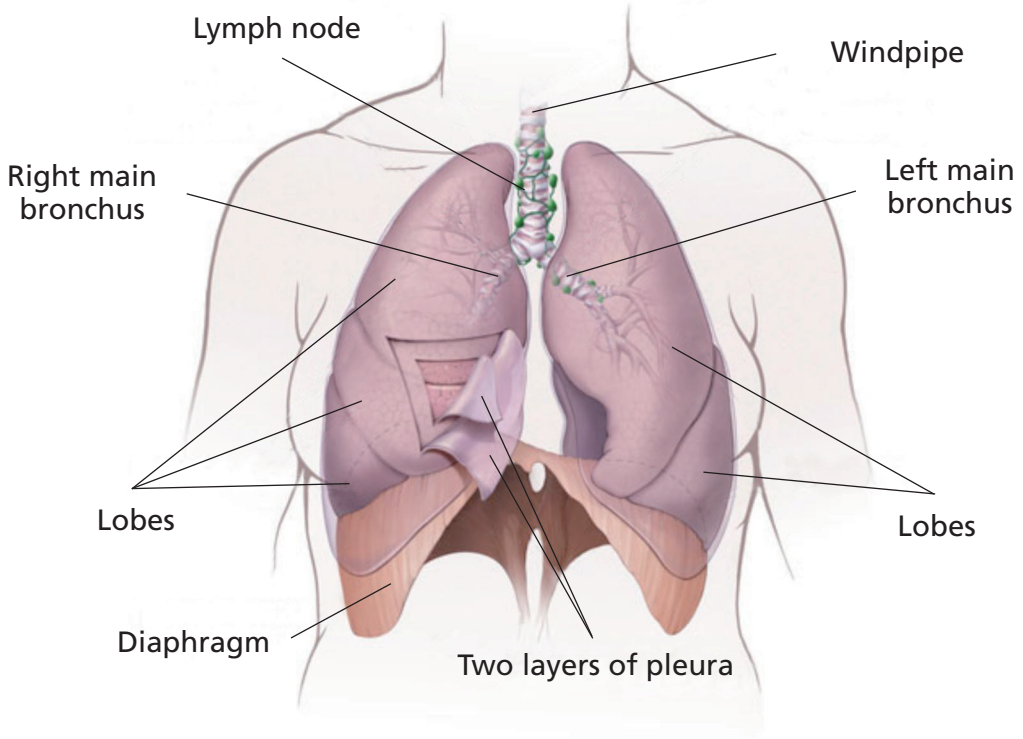
PART III. INFORMATION FOR PATIENTS WITH LUNG CANCER

## DEFINITION

Lung cancer is a tumor that develops in lung tissue.

### The lungs




The lungs are two similar, elongated organs, located in the chest and forming part of the respiratory system. When you breathe in through the nose and the mouth, air passes through the windpipe (trachea) and the bronchi into the lungs, which expand (inflate). The lungs absorb the oxygen in the air and send it to the blood, which distributes the oxygen throughout the body.

As the body's cells use the oxygen, they release carbon dioxide, which is sent back to the lungs via the blood system. When you breathe out, the body eliminates this carbon dioxide from the body.

The lungs also have lymph vessels and nodes in which a transparent liquid called lymph –containing immune (defense) system cells– circulates, trapping foreign particles. Lymph nodes are located mainly around the bronchi and the mediastinum.

The right lung, which is slightly larger than the left lung, has 3 lobes, and the left lung has 2 lobes.

The lungs are surrounded by a tissue called pleura. There are 2 layers in the pleura, between which a small amount of liquid called pleural fluid circulates. The main function of the pleural fluid is to protect the lungs and lubricate respiratory movements.

### Lung cancer

The cells in our body are constantly growing, dividing to form new cells, dying, and being replaced by new cells. This cycle, however, can occasionally be altered, and when this happens, old cells do not die but continue to create new cells, leading to an excess of unnecessary cells that can form a mass of tissue known as a tumor.

Tumors can be benign or malignant:

**Benign tumors.** These are not cancerous and their cells do not invade other parts of the body. Once they are removed they do not recur.

**Malignant tumors.** Cancerous cells from malignant tumors can invade tissues and spread to other parts of the body through the blood or lymphatic system. The spread of cancer in the body is known as metastasis.

Lung cancer originates in lung tissue cells and can spread through the blood or lymph vessels.

From a treatment perspective, there are 2 main lung cancer groups:

- **Small cell lung cancer.** This type of cancer, which tends to spread rapidly, is less frequent.
- **Non-small cell lung cancer.** This cancer spreads more slowly than small cell cancer and is also more common.

## CAUSES

The exact causes of lung cancer are unknown. Research has shown that people with certain risk factors have a greater risk of developing lung cancer than those without these factors. Smoking is a major risk factor, with 90% to 95% of lung cancers occurring in smokers.

A risk factor is any characteristic or variable that increases a person's risk of developing a disease, in this case, cancer. Most risk factors, however, are not the direct cause of cancer. Certain risk factors such as smoking can be controlled, whereas others, such as age or hereditary factors, are beyond our control.

Risk factors for lung cancer are as follows:

**Smoking.** Most lung cancers occur in smokers. Cigarette smoke damages lung cells and causes abnormal growth. The risk of developing cancer among smokers increases in people who smoke a lot and/or over a long period.

Regular exposure of nonsmokers to cigarette, cigar or tobacco smoke –what is referred to as passive smoking– increases the risk of developing lung cancer.

**Asbestos and other substances.** People who are exposed to substances such as asbestos, arsenic, chrome, nickel, etc in the workplace are at a greater risk of developing lung cancer. The risk increases with years of continuous exposure and is enhanced in smokers. Using protective breathing equipment reduces this risk.

**Radon.** Radon is a radioactive substance that cannot be seen or smelled. It is found in nature in certain kinds of soils and rocks. People who work in mines may be exposed to radon. Complying with safety recommendations helps reduce this risk, which is enhanced in smokers.

**Environmental pollution.** Environmental pollution may slightly increase the risk of developing lung cancer. Again, this risk is enhanced in smokers.

**Family history of lung cancer.** People whose parents, brothers or sisters have had lung cancer may also run a slightly higher risk of developing lung cancer, especially smokers.

**Personal history of lung cancer.** People who have already had lung cancer have a higher risk of developing a second tumor.

**Age.** The risk of developing lung cancer increases with age.

## SYMPTOMS

Lung cancer in its early stages produces no symptoms. When symptoms begin to occur, the most common ones are as follows:

- Cough
- Difficulty in breathing
- Chest pain
- Bloody sputum
- Hoarseness
- Frequent lung infections
- Fatigue
- Weight loss for no apparent reason.

These symptoms may be caused by other health problems. If any of these symptoms appear, a doctor should be contacted for a diagnosis as soon as possible.

## DIAGNOSIS

A number of different tests are used to diagnose cancer and to determine if it has metastasized to other organs. Not all tests are done on all patients, and the choice of which tests to do depends on factors such as age, state of health, type of cancer, severity of symptoms, and the results of previous tests.

Diagnostic tests are described as follows:

**Medical history and physical examination.** The patient is asked about current symptoms and past medical history and that of family members. An initial physical examination is also performed.

**Chest x-ray.** This enables any tumors or abnormalities in the lungs to be identified.

**Computed tomography.** This test, commonly called a CT scan, uses x-rays to obtain a 3D view of the internal structures of the body. A special dye called contrast is sometimes injected into the veins to help view structures in more detail. This test may confirm a tumor, abnormal fluid, or inflammation of the lymph nodes.

**Identifying lung tumor cells.** A definitive diagnosis is based on direct analysis of cell or tissue samples taken from the body. This analysis enables the type of tumor and its characteristics to be determined. Samples are obtained using one or several of the following techniques:

- **Sputum cytology.** A sample of sputum –which is mucus coughed up from the lungs– is analyzed.
- **Thoracentesis.** A small quantity of pleural fluid is collected from the lungs in a syringe attached to a thin needle inserted into the chest.
- **Bronchoscopy.** A thin, flexible tube inserted into the lung through the nose or mouth enables the airways to be viewed and tissue samples to be extracted. Sometimes water is introduced to wash the area so as to collect cells for analysis.
- **Fine-needle aspiration.** This technique is used to extract tissue or fluid from the lung or from a lymph node. Sometime a CT image is used to guide the insertion of the needle into the lung or the lymph node.
- **Thoracoscopy.** This technique enables the lungs and nearby tissues to be directly viewed. A small incision is made in the chest and a narrow tube with a light is introduced into the chest cavity. Samples of any abnormal tissues are collected for analysis.
- **Thoracotomy.** This surgical technique involves making an incision in the middle part of the chest so as to be able to remove tissues or lymph nodes for analysis.
- **Mediastinoscopy.** This technique allows the mediastinum to be examined. A narrow tube with a light is introduced and, if necessary, a sample of lymph nodes is collected.

**Magnetic resonance imaging.** MRI is a scanning technique that produces images of the inside of the body. It uses magnetic fields rather than x-rays and is useful for viewing specific bone marrow, brain and spinal cord tissues. It is used in lung cancer to check whether the cancer has metastasized to the brain or spinal cord.

**Bone scintigraphy.** This technique is used to find out whether lung cancer has spread to the bones. A radioactive substance (radioisotope) is injected into the veins, and once this has been absorbed by the bone, a special device called a gamma camera records the radioactivity in the tissue, then reflects it as images showing healthy and diseased parts of the bone.

**Positron emission tomography.** In this test, commonly called a PET scan, the vein is injected with a glucose containing radioactive material that attracts tumor cells. The PET machine produces images of this metabolic activity in the cells. Malignant cells are revealed by images showing high metabolic activity. PET scans are used to complement information from other tests.

**Blood testing.** Cancer that has metastasized to the bone or liver may be revealed by abnormalities in the blood.

### Disease stages

Once a diagnosis of lung cancer has been made, the doctor determines the extent –or stage– of the disease so as to choose the most appropriate treatment.

**Small cell lung cancer.** There are 2 main stages, as follows:

- **Limited stage.** The tumor is located in a lung and in lymph nodes on the same side of the chest.
- **Extensive stage.** The cancer affects both lungs or has spread to other parts of the body.

**Non-small cell lung cancer.** Staging is based on the size of the tumor and on whether the cancer has spread to the lymph nodes or other organs. Staging is as follows:

- Occult stage

  Cancer cells are found in the sputum or in other samples but no tumor can be found in the lung.

- Stage 0 (carcinoma *in situ*)

  The tumor is limited to the internal layer of the lung tissue.

- Stage IA

  The tumor, a maximum of 3 cm in diameter, has grown through the lung lining into deeper layers of lung tissue. However, the tissue surrounding the tumor is healthy, the bronchi are unaffected, and the cancer has not spread to the lymph nodes.

- Stage IB

  The tumor has become more embedded in the lung tissue but has not spread to nearby lymph nodes. It has at least one of the following features:

  - It is larger than 3 cm in diameter
  - It involves the main bronchus
  - It invades the pleura

- Stage IIA

  The tumor is no bigger than 3 cm in diameter and has spread to the nearby lymph nodes.

- Stage IIB

  The tumor has at least one of the following features:

  - Tumorous cells have not affected the lymph nodes but have invaded the chest wall, diaphragm, pleura, a main bronchus, or tissues surrounding the heart.
  - Tumorous cells have invaded the lymph nodes and the tumor has at least one of the following features:
    - It is larger than 3 cm in diamet
    - It involves the main bronchus
    - It invades the pleura.

- Stage IIIA

  Cells from the tumor, which can be any size, have invaded lymph nodes close to the lungs and the bronchi, and also lymph nodes close to the midpoint between the lungs but on the side of the lung with the tumor.

- Stage IIIB

  Cells from the tumor, which can be any size, have spread from the primary site to the other side of the chest, endangering nearby organs in the mediastinum, such as the heart, esophagus, or trachea. More than 1 tumor nodule may have developed in the same lobe, and tumorous cells may also be identified in the pleural fluid.

- Stage IV

  The cancer has spread to another lobe in the same or the other lung, and tumor cells may be identified in other parts of the body such as the brain, the bones, the liver, or the adrenal glands (located over the kidneys and responsible for regulating certain hormones).

## TREATMENT

Treatment options depend on the type of lung cancer, the cancer stage, and the general state of health of the patient. The different treatments for lung cancer –surgery, chemotherapy, biological therapy, and radiation therapy– can be used alone or in combination.

### 1. TREATMENT TYPES

#### 1.1. Surgery

Depending on the stage of the cancer, surgery may be used to remove the tumor, part of the healthy tissue surrounding it, and some of the nearby lymph nodes. It may require removal of part or all of a lung.

**Lobectomy** is when the lobe containing the tumor is removed.

**Pneumonectomy** is when the entire lung with the cancer is removed.

Both these procedures require admission to hospital for the surgery, and daily respiratory exercises in the postoperative period.

#### 1.2. Chemotherapy

Chemotherapy involves the use of special drugs designed to destroy cancer cells. This type of treatment is called systemic treatment because the drugs are delivered throughout the body by the blood. Chemotherapy may, therefore, also affect healthy cells and produce side effects. These effects vary according to drug type and dose, treatment duration, and the individual characteristics of each patient.

Chemotherapy is used as the main treatment for lung cancer or is combined with other treatments such as surgery or radiation therapy.

Chemotherapy to treat lung cancer is generally based on combining different types of drugs which are administered in an outpatient setting, mostly intravenously (through the veins), but also orally.

Chemotherapy is administered in cycles composed of a treatment cycle followed by a rest period before commencing a new cycle. Cycles generally last 21 to 28 days, and the number of cycles is usually between 4 and 6, depending on the type of medication.

### 1.3. Radiation therapy

Radiation therapy (also called radiotherapy) eliminates cancer cells using high-energy rays. The treatment consists of either external beam radiotherapy, which is administered by a machine outside the body, or internal radiotherapy (or brachytherapy), in which radioactive material is placed inside the tumor. External beam radiotherapy is the most typical kind of radiation therapy for lung cancer.

Since radiation targeting a tumor could also affect nearby healthy tissue, it is not used to treat large areas of the lung.

This treatment can be administered before surgery (neoadjuvant radiotherapy) or after surgery (adjuvant radiotherapy), and can also be combined with chemotherapy.

The health care team assesses radiotherapy options, depending on the circumstances of each patient.

### 1.4. Biological therapy

Biological therapy, also known as immunotherapy, works through the body's immune (defense) system by targeting mostly malignant cells rather than healthy cells. It therefore causes fewer and more tolerable side effects than other treatments.

Monoclonal antibodies, which attach to the cancer cells to stop them from growing and spreading, are used in some cases of disseminated non-small cell lung cancer.

There are 2 types of biological treatment for lung cancer, one administered intravenously in combination with chemotherapy, and the other administered orally without chemotherapy.

### 1.5. Combined treatments

Lung cancer is frequently treated by combining different therapies, such as surgery with chemotherapy, or surgery with radiotherapy, or chemotherapy and radiotherapy in combination (chemoradiotherapy), and either before or after surgery.

Chemotherapy and radiotherapy can be combined in different ways:

- Chemotherapy at the same time as radiotherapy.
- Chemoradiotherapy followed up by chemotherapy alone
- Chemotherapy and radiotherapy in turn, with chemotherapy, generally but not always, delivered before radiotherapy.

Treatment is decided on the basis of the type and stage of the tumor.

## 2. SIDE EFFECTS

Both lung cancer and its treatment can cause side effects. Whether or not a patient develops side effects depends on many factors such as the type of surgery, the type of chemotherapy or radiation therapy administered, dose levels and treatment duration, and the characteristics of the patient. Many side effects are temporary and can be easily controlled, whereas others require more specific treatment. Regular checks are made throughout the treatment period to prevent side effects wherever possible and to treat unavoidable side effects. Talk to your health care team about whatever side effects you experience.

## 2.1. Surgery

The length of time it takes to recover from an operation depends on the kind of surgery and varies from person to person. It is normal to experience discomfort and to feel tired and weak in the first few days after surgery. This is all part of the recovery process and these symptoms will disappear once the surgery wound has healed internally and externally.

**Chest drainage.** A flexible tube put in place during lung surgery and connected to a bag or container drains fluid and/or air remaining in the lung in the first few days after the surgery so as to remove excess matter and help the lung to function properly. The tube is easily removed later.

**Pain.** As with any surgery you are likely to feel pain or discomfort. In lung surgery, the chest has to be opened to obtain access to the lungs. This procedure affects the ribs and is likely to cause postoperative pain. A choice of painkillers for controlling the pain will be available to you.

**Respiratory physiotherapy.** Physiotherapy is very important to recovering lung function. A physiotherapist or nurse (possibly even before the surgery) describes and explains how to do specific daily exercises after surgery. Physiotherapy exercises are an important aspect of postoperative healing.

Once out of hospital, it will take some time before you will be able to live your life as normal again.

## 2.2. Radiation therapy

The side effects of radiation therapy vary depending on the type of therapy, the doses given, and the part of the body that is treated. The most common side effects in patients with lung cancer are described below.

**Local skin alterations.** Radiation therapy often causes the skin around the area treated to become more sensitive, dry, and even a little red. These alterations will all disappear with time.

*Recommendations*

- Wear cotton clothing.
- Wear loose clothing that will allow air to circulate and that will not rub against irritated areas.
- Look after your skin. Check with your health care team before using any soaps, body milks, or antiseptic products, as certain products can interfere with radiation treatment or make your skin condition worse.
- Use mild soap and prevent anything from rubbing against your skin.
- Do not scratch your skin. If it is itchy, apply cold chamomile or ice wrapped in cotton to the affected area.

**Fatigue or tiredness.** Radiation therapy can cause you to feel tired, especially in the last few weeks of treatment. This feeling can persist for some weeks after treatment ends.

*Recommendations*

- Do regular exercise but adapt the level to your habits, your capacity, and to how you are feeling. A daily walk is an excellent way to exercise. People who do exercise feel stronger and have a better appetite, more regular bowel movements, and a better body image.
- Maintain your energy levels and adjust activities to how you are feeling. You will feel more or less energetic at different times of the day. Make the most of the moments when you feel most energetic to do activities that require greater effort.
- Monitor any other side effects or problems that might increase your feelings of fatigue, such as difficulty in sleeping. Check with your health care team if you have any doubts.

The area irradiated through the chest may include nearby organs and tissues, and this may produce side effects, such as difficulty in swallowing if the esophagus is affected, or cough resulting from irritated lung tissue. The same recommendations as those for chemotherapy should be followed. Consult your health care team if any worrying changes take place.

## 2.3. Chemotherapy

Because chemotherapy targets cells that divide quickly, it affects healthy cells as well as cancer cells. This is why you may experience side effects, which will vary in type and severity depending on the drug used, the dose, and the duration of treatment. The possible side effects of chemotherapy are related to the location of rapidly dividing cells.

- *Blood cells.* When chemotherapy affects healthy blood cells, you have an increased risk of developing infections and of bruising or bleeding more easily. You are also likely to feel weaker or more tired than usual.
- *Hair root cells.* Certain chemotherapy drugs may cause hair loss or change hair color or texture.
- *Digestive tract cells.* When chemotherapy affects these cells –found in the mouth, stomach, and other parts of the digestive system– possible side effects are loss of appetite, nausea, vomiting, diarrhea, difficulty in swallowing, and mouth and lip sores.

The most common side effects in patients with lung cancer are described below.

### Loss of appetite

This is quite common and can cause weight loss. To ensure a well-balanced diet, it is important to consume sufficient proteins and calories and to avoid significant swings in weight.

*Recommendations*

- Spread your meals throughout the day.
- Use small plates so that it seems as if you are eating small quantities.
- Eat cold or warm food rather than hot food.
- Eat foods with a pleasant texture that are easily chewed and swallowed.
- Eat meals that are appealing to the eye and in pleasant surroundings.
- Use plastic cutlery.
- Avoid food with strong odors and, if possible, do not prepare meals yourself.
- Drink fluids such as water, juices, and shakes outside of mealtimes to avoid filling up during meals.
- Add nutritionally rich ingredients to your dishes to ensure that are meeting your daily nutrition needs. For example:
  - Use full-fat milk, cream, cheese, and ground nuts to increase the consistency of dishes served with sauces or broths.
  - Include cooked egg whites to increase the intake of proteins without increasing the size of the dishes.
  - Eat desserts made with milk: ice-cream, shakes, etc.
- If possible, eat a snack before going to bed as the sensation of fullness will help you fall asleep, yet will not affect your appetite for your next meal.
- Always carry around small snacks such as shakes, nuts, etc in case you feel hungry outside mealtimes.

If you continue to lose weight, tell your health care team.

### Alterations of the mouth mucosa

- *Dry mouth (xerostomia).* Dry mouth occurs when the saliva glands do not produce enough saliva. This is a temporary side effect that disappears once the glands begin producing saliva again.
- *Mouth sores (mucositis).* Mucositis is an inflammation of the mucosa inside the mouth. Prevention is the best cure. If sores do appear, they should be treated as early as possible to minimize discomfort.

Mouth sores can make it difficult to chew, swallow, talk, and appreciate flavors.

*Recommendations*

- Maintain good oral hygiene. Brush your teeth 3 to 4 times a day with a soft brush. Wetting the brush first in warm water will make it softer.
- Rinse your mouth 4 to 6 times a day –for example, after meals– with a non-alcoholic mouthwash or a cold infusion of chamomile or thyme.
- Sip small amounts of water throughout the day and use artificial saliva to keep your mouth moist.
- Eat sugar-free chewing gum or sweets to stimulate the production of saliva.
- Eat soft foods that are cold or warm rather than hot. Use sauces and broths to make your meals juicier.
- Avoid rough-textured foods.
- Avoid very acidic or spicy foods.
- Avoid irritants such as coffee, tobacco, and alcohol.
- Avoid sweet, sticky food.
- If you have a metallic taste in your mouth, use plastic cutlery.

## Nausea and vomiting

Nausea and vomiting can occur during different phases of treatment, as follows:

- Acute nausea and vomiting generally occurs within several hours of treatment
- Delayed nausea and vomiting occurs within 1 to 5 days of treatment
- Anticipatory vomiting occurs before treatment as a consequence of prior treatments. In this case, nausea and vomiting can be triggered by smells or even just by thinking about treatment.

Mild nausea and vomiting that are treated rapidly can cause discomfort but are not serious. When persistent, however, they can cause dehydration, electrolytic disturbance, weight loss, and even the desire to abandon treatment. Highly effective drugs are available to control nausea and vomiting.

*Recommendations*

- Eat small amounts of food 5 or 6 times a day.
- Chew slowly, taking all the time you need.
- If you feel nauseous, wait some time before eating.
- Avoid food with strong odors and,
- avoid tight clothes, belts, etc.
- Sip small amounts of cold liquids throughout the day.
- Drink small amounts of liquid during mealtimes to make you feel fuller.
- Rest after each meal but do not lie down in the first hour.

Some people feel better when they do activities such as concentration, relaxation, or positive visualization exercises. These exercises help to reduce anxiety levels and thoughts about nausea and vomiting.

## Diarrhea

Diarrhea is characterized by an increased frequency of watery stools. Consult your health care team if the diarrhea lasts for more than 24 hours as it may cause electrolytic disturbances and dehydration.

*Recommendations*

- Avoid caffeine, alcohol, fat, excessive amounts of fiber, orange and prune juices, and very spicy foods.
- Do not use laxatives unless told to do so by your doctor.
- Eat smaller amounts at more frequent intervals throughout the day.

- Drink plenty of liquid such as water, infusions, juice, and broth to avoid dehydration. Patients with severe diarrhea may need intravenous fluids to compensate for fluid and electrolyte losses.
- In certain circumstances, you might be prescribed anti-diarrhea drugs. Your doctor might also change treatment dosage if he/she considers this necessary.

### Constipation

Chemotherapy can sometimes cause constipation but there are other contributory factors such as a reduction in normal activity levels and changes in diet. Consult your health care team if you are still constipated after 2 days. Under no circumstances take laxatives or other such products without first finding out if this is advisable.

*Recommendations*

- Do some exercise every day, for example, walking.
- Drink 1.5 to 2 liters of fluids (water, infusions, broth) a day and start the day with an infusion or a glass of warm water.
- Eat high-fiber foods such as fruit and vegetables.
- Try to establish regular bowel habits.

### Fatigue or tiredness

Loss of energy and feelings of tiredness are among the most common side effects of chemotherapy and potentially have a major impact on daily life. Tiredness can start during treatment –especially towards the end– and last for several days afterwards.

Follow the same recommendations as indicated for radiation therapy.

### Weakening of natural defenses

Infections develop when invading bacteria, viruses, or fungi are not rapidly destroyed by the body's immune (defense) system. This defense system is made up of the skin, the spleen, lymph nodes, bone marrow in long bones, and leukocytes (white blood cells). Neutrophils are a subset of white blood cells that destroy harmful bacteria. A fall in the number of neutrophils that weakens your defenses is called neutropenia.

When a person has neutropenia, there is a risk of a minor infection becoming serious. Symptoms of serious infection are as follows:

- A high temperature
- Shivering
- Inflammation of the throat or mouth
- Abdominal pain
- Pain or a burning sensation when urinating and increased urination frequency
- Diarrhea and/or irritation of the perianal area
- Reddening or inflammation around wounds or small cuts
- Abnormal vaginal discharge or itching.

Treatment options include antibiotics or antifungals (to fight fungi) and drugs that help to build up your body's defenses. Patients with serious infection may need to be admitted to hospital for intravenous treatment.

*Recommendations*

- Consult your health care team if you have a temperature of 38 °C or higher.
- Eat a balanced diet and make sure you get enough rest.
- Avoid crowds and people who are ill.
- Check with your doctor before a vaccination. Some vaccines (such as the flu vaccine) contain weakened viruses and can cause severe infections.
- For the same reason, avoid people, including children, who have been recently vaccinated with live weakened viruses (polio, flu, measles, etc).

- Do not share personal items such as eating and drinking utensils or toothbrushes.
- Do not eat raw food such as meat, shellfish, or eggs. Wash fresh fruit and vegetables well before eating them.
- Wash your hands frequently throughout the day, particularly before mealtimes and after going to the toilet.
- Take a daily shower or bath and apply moisturizing creams or lotions to prevent dry, cracked skin.
- Take care when using sharp objects such as knives and scissors.
- If you have a pet, do not clean their eating or drinking utensils or pick up their poop, even with a plastic bag.
- When doing housework or gardening, use gloves to protect yourself from cuts or burns.
- Clean your teeth and gums with a very soft brush.
- Take care not to cut your cuticles when trimming your finger and toe nails.

### Reduced red blood cell count

People who produce too few red blood cells, otherwise known as erythrocytes, develop anemia. These cells are responsible for transporting oxygen from the lungs to the rest of the body. As there may be no symptoms, routine tests are conducted during treatment to detect possible decreases. The condition is easy to correct. Symptoms may appear if the red blood cell levels are particularly low. The most common symptoms are tiredness, weakness, difficulty breathing with minimal exertion, palpitations, dizziness, and pale skin.

*Recommendations*

- Rest as much as possible.
- Sleep enough hours to feel refreshed.
- Only do activities you feel capable of doing. Avoid activities that cause additional tiredness.
- Spread your meals throughout the day to avoid heavy digestion.

### Tingling or numbness in the fingers and toes

Some chemotherapy drugs can cause tingling or numbness in the fingers and toes (peripheral sensorial neuropathy), which is the consequence of nerves in your legs and arms becoming irritated. This can occur during or shortly after treatment and can last for 1 to 2 days (acute sensorial neuropathy) or become persistent during prolonged treatment (chronic sensorial neuropathy). Although it does not affect muscle strength, it does make the skin more sensitive and can cause some discomfort.

If you experience tingling or numbness, consult your doctor.

### Hair loss

Hair loss (alopecia) is quite a common side effect of chemotherapy. Hair loss may not occur at all, or it may be partial or complete, depending on the type of treatment. By knowing what treatment you are going to receive, you can prepare as suits you best. Some suggestions are as follows:

- *Hair and scalp care:*
  - Use a mild shampoo such as a baby shampoo.
  - If the treatment you are going to receive causes complete hair loss, cut your hair very short before it begins to fall out. This helps to reduce the distress caused by seeing your hair fall out gradually.
  - Moisturize your scalp regularly.
  - Use a hat or scarf to protect your head from the sun and to retain body heat in winter.
  - Do not blow dry your hair with hot air.
  - Do not use chemical products such as hair dyes and straighteners (even if semi-permanent).

- *Hair pieces and wigs:*
  - By choosing a hair piece or wig before your hair begins to fall out, you will be able to choose one that is similar to the color and style of your own hair.
  - Go to a shop that is experienced in dealing with patients with cancer. Choose a good-quality wig to prevent irritation of the scalp.

- *New hair:*

  Your hair will start to grow back after treatment and will normally take about 12 months to return to normal. At the beginning, you might find that your hair is thinner, more fragile, and perhaps even a slightly different color. Follow the recommendations below while your hair is growing back:

  - Wash your hair twice a week.
  - Massage your scalp to remove dry skin and flakes.
  - Brush your hair gently and as little as possible. Do not blow dry your hair with hot air.
  - Use a soft hairbrush for new hair growth.
  - Do not use any type of hair dye for at least 3 months after treatment ends.

### 2.4. Biological therapy

The side effects of biological therapy are similar to cold and flu symptoms: high temperature, shivering, weakness, and nausea. These symptoms tend to diminish after the first treatment.

## DAILY LIFE

Your daily routine will probably be affected during treatment. During this time, take good care of yourself, deal with needs as they arise, and adjust your daily routine to your new circumstances.

Each person adapts differently, depending on their capacities, priorities, and experiences. It is a time to think about how you can continue your daily routine without feeling overwhelmed and without allowing your illness to become the center of your life.

Taking care of yourself involves many aspects, but following a healthy diet and keeping active are key to ensuring a sensation of well-being.

Make sure that your daily intake of calories and proteins is sufficient to avoid weight loss and to keep you strong. Eating well will help you to feel better and more energetic. Occasionally, however, and particularly when receiving treatment, you will lose your appetite and certain side effects will make you feel less like eating. Your health care team will be able to help you with special recommendations for a suitable diet.

Moderate regular exercise also helps. Be aware of feelings of fatigue, and adapt activities accordingly. There are many activities to choose from, for example, walking, swimming, and yoga. Keeping active will help you to feel stronger, more energetic, and less stressed.

Talk to your health care team about what type of exercise is best for you.

## REFERENCES

The National Comprehensive Cancer Network Patient Guidelines.
http://www.nccn.org/patients/patient_gls.asp

National Cancer Institute.
http://www.cancer.gov/cancertopics/types/lung

Cancer Net.
http://www.asco.org/patient/Cancer+Types/Lung+Cancer

## APPENDIX

# LUNG AND PLEURAL CANCER PATHOLOGY REPORT GUIDELINE

The guideline below is aimed at standardizing descriptions of diagnoses in lung and pleural cancer pathology reports so that it is fully comparable regardless of the pathologist who issues the diagnosis.

Bearing in mind that biopsy is limited, an example description of radical pulmonary resection is provided, with annotations for lesser biopsies.

Given the general consensus regarding the differences in lung carcinomas, definitive diagnosis of histologic type and grade should be based on the resection specimen. Small cell carcinoma is a special case, however, as treatment and prognosis are determined by histologic grade, regardless of whether there is another associated component.

Cytology is not discussed, as the diagnosis referred to here only covers tumor type. Cytology should confirm whether a tumor is epithelial and whether the cancer is small cell or non-small cell cancer, although confirmation may depend on the technique used (sputum cytology, bronchial aspiration, transbronchial/transTumoral aspiration, transbronchial/nodular aspiration, or percutaneous aspiration).

## Diagnosing the resection specimen

¬ Resection site (lung, lobe or segment, right or left)

- Resection type (pneumonectomy, lobectomy, segmentectomy, tumorectomy)
  - Histologic grade (according to the WHO staging table, reproduced below)
  - Histologic differentiation (well/moderately/poorly differentiated)
  - Tumor size (maximum diameter)
  - Tumor site (lobe)
  - Infiltration:
    - bronchial surgical margin (disease-free margin)
    - pleura (disease-free margin)
    - if wall tissue is included, indicate if a tumor is present and its margins
  - Specimen lymph nodes (N1):
    - hilar
    - other (interbronchial, subpleural, intrapulmonary)
  - Other lymph nodes: specify the site for surgery (see N staging)
  - Disorders secondary to the tumor:
    - obstructive pneumonitis (indicate extension/size)
    - other (bronchial dilatation, airway inflammation, acute parenchymatous inflammation)
  - Tumor-associated disorders (bronchial metaplasia, dysplasia, or extension *in situ)*

¬ Condition not associated with the neoplasm (*):

- Chronic obstructive pulmonary disease, residual lesions, granulomatous lesions, pneumoconiosis, etc.

* All postoperative lung resection patients continue to function with the remainder of the lung. Any information on preexisting, diffuse, or bilateral diseases may be useful for the patient's prognosis.

EXAMPLE: LUNG, RIGHT PNEUMONECTOMY

*WELL DIFFERENTIATED ADENOCARCINOMA*

- *Tumor size: 3.5 cm*
- *Location: upper lobe*
- *Infiltration of lymphatic vessels*
- *Metastasis in 1 of the 4 identified hilar nodes*

*DISTAL BRONCHIAL DILATATION WITH ORGANIZING AREAS*

## Bronchial / pulmonary biopsy cancer diagnosis

¬ Biopsy site (side and/or lobe)

- Specimen type (bronchial, transbronchial, or pulmonary)
  - Histologic grade (according to the WHO staging table, reproduced below)
  - Vascular infiltration
  - Tumor-associated disorders (bronchial metaplasia, dysplasia, or extension *in situ)*

EXAMPLE: RIGHT UPPER LOBAR BRONCHUS, BRONCHIAL BIOPSY
*WELL-DIFFERENTIATED ADENOCARCINOMA*
*- Infiltration of lymphatic vessels*

### LUNG AND PLEURAL CANCER CLASSIFICATION AND CODING WHO 2004. MALIGNANT PULMONARY AND PLEURAL EPITHELIAL TUMORS

### MALIGNANT EPITHELIAL PULMONARY TUMORS

| | |
|---|---|
| **SQUAMOUS CELL CARCINOMA** | **M80703** |
| Papillary squamous cell carcinoma | M80523 |
| Clear cell squamous cell carcinoma | M80843 |
| Small cell squamous cell carcinoma | M80733 |
| Basaloid squamous cell carcinoma | M80833 |
| **SMALL CELL CARCINOMA** | **M80413** |
| Combined small cell carcinoma (with another type of cancer) | M80453 |
| **ADENOCARCINOMA** | **M81403** |
| Acinar adenocarcinoma | M85503 |
| Papillary adenocarcinoma | M82603 |
| **Bronchioloalveolar carcinoma** | **M82503** |
| Nonmucinous bronchioloalveolar carcinoma | M82523 |
| Mucinous bronchioloalveolar carcinoma | M82533 |
| Mixed nonmucinous and mucinous bronchioloalveolar carcinoma or indeterminate | M82543 |
| Solid adenocarcinoma with mucin production | M82303 |
| Adenocarcinoma, mixed subtype | M82553 |
| Adenocarcinoma variants | |
| Fetal adenocarcinoma, well differentiated | M83333 |
| Mucinous (colloid) adenocarcinoma | M84803 |
| Mucinous cystadenocarcinoma | M84703 |
| Signet ring adenocarcinoma | M84903 |
| Clear cell adenocarcinoma | M83103 |
| **LARGE CELL CARCINOMA** | **M80123** |
| Large cell neuroendocrine carcinoma | M80133 |
| Combined large cell neuroendocrine carcinoma | M80133 |
| Basaloid carcinoma | M81233 |
| Lymphoepithelioma-like carcinoma | M80823 |
| Clear cell carcinoma | M83103 |
| Large cell carcinoma with rhabdoid phenotype | M80143 |
| **ADENOSQUAMOUS CARCINOMA** | **M85603** |
| SARCOMATOID CARCINOMA | M80333 |

Continua a la pàgina següent

FALTA TRADUCIR

| | |
|---|---|
| Pleomorphic carcinoma | M80223 |
| Spindle cell carcinoma | M80323 |
| Giant cell carcinoma | M80313 |
| Carcinosarcoma | M89803 |
| Pulmonary blastoma | M89723 |
| Other | |
| **CARCINOID tumor** | |
| **Typical carcinoid tumor** | **M82403** |
| Atypical carcinoid tumor | M82493 |
| **SALIVARY GLAND CANCER** | |
| Mucoepidermoid carcinoma | M84303 |
| Adenoid cystic carcinoma | M82003 |
| Epithelial-myoepithelial carcinoma | M85623 |
| **MALIGNANT PLEURAL MESOTHELIOMAS** | |
| **DIFFUSE MALIGNANT MESOTHELIOMA** | **M90503** |
| Epithelioid mesothelioma | M90523 |
| Sarcomatoid mesothelioma | M90513 |
| Desmoplastic mesothelioma | M90513 |
| Biphasic mesothelioma | M90533 |
| **LOCALIZED MALIGNANT MESOTHELIOMA** | **M90503** |
| **OTHER LOCALIZED tumorS** | |
| Papillary mesothelioma, well differentiated | M90521 |
| Adenomatoid tumore | M90540 |

### Comments on the classification:

The classification codes are those of the WHO Blue Book for 2004.

Highlighted in the list are the most frequent diagnoses.

### Staging of pulmonary carcinoma

WHO staging is used, based on the initial TNM and, following initial surgery, on pTNM.

**T:** important details to be provided by the pathologist after surgical resection:

**Tis:** carcinoma *in situ*.

**T1:** tumor of 3 cm or less surrounded by noninfiltrated pleura and without main bronchus involvement (> 2 cm distal to the carina).

**T2:** tumor of more than 3 cm and/or invasion of visceral pleura and/or main bronchus involvement (< 2 cm distal to the carina) and/or obstructive pneumonitis not affecting the whole lung.

**T3:** T2 criteria, plus invasion of chest wall and/or diaphragm and/or mediastinal, parietal or pericardium pleura and/or obstructive pneumonitis of the entire lung.

**T4:** There is usually no surgical resection, due to unresectability. There is resection when there is a second carcinoma nodule in the same lobe. If the nodule is in another lobe, the stage will be M1.

**N:** Always indicate the total number of lymph nodes studied in each field, the number of affected lymph nodes, and whether there is intra/extracapsular invasion. Nodes will be named by the surgeon following international guidelines based on a number and R/L for right/left side.

**M:** Metastasis: Note that a second tumorous nodule in a different lobe is regarded as M1. If in the same lobe it is regarded as T4.

| LUNG CANCER STAGING TABLE | | | |
|---|---|---|---|
| Stage 0 | Tis | N0 | M0 |
| Stage IA | T1 | N0 | M0 |
| Stagei IB | T2 | N0 | M0 |
| Stage IIA | T1 | N1 | M0 |
| Stage IIB | T2 | N1 | M0 |
| | T3 | N0 | M0 |
| Stage IIIA | T1 | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N1/2 | M0 |
| Stage IIIB | T* | N3 | M0 |
| | T4 | N* | M0 |
| Stage IV | T* | N* | M1 |

** any number*

## Pleural mesothelioma diagnosis

Purely epithelial tumors should be differentiated from metastasis. Cell block material (cytology), biopsy or pleural decortication should be used for diagnostic purposes. A diagnosis based on pleural fluid cytology is not conclusive and so should not be regarded as definitive.

Mesothelioma diagnosis should be made according to WHO guidelines, Diagnosis should be reassessed or confirmed using basic immunohistochemistry. Morphology must at least be compatible and tests should be negative for CEA and another adenocarcinoma marker (CD15, BerEp4, or B72.3). It is regarded as a good idea to enhance the study with mesothelioma markers (e.g., calretinin or thrombomodulin) or other adenocarcinoma markers (eg, thyroid transcription factor 1). Note that WHO recommends the use of mesothelioma markers, and this is the minimum recommended.

Pleural mesothelioma staging

**T:** Important details should be provided by the pathologist:

**T1:** Involvement of visceral/parietal pleura.

**T2:** Invasion of the lung and/or diaphragm and/or pericardium and/or endothoracic fascia.

**T3:** Invasion of thoracic wall muscle and/or rib and/or mediastinal organs

**T4:** Contralateral and/or abdominal and/or cervical infiltration.

**N:** Indicate the number of nodes involved of the total studied. Intra/extracapsular infiltration.

**M:** Distant metastasis.

| MALIGNANT PLEURAL MESOTHELIOMA STAGING TABLE | | | |
|---|---|---|---|
| Stage I | T1 | N0 | M0 |
| | T2 | N0 | M0 |
| Stage II | T1 | N1 | M0 |
| | T2 | N1 | M0 |
| Stage II | T1 | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N* | M0 |
| Stage IV | T* | N3 | M0 |
| | T4 | N* | M0 |
| | T* | N* | M1 |

** any number*

## REFERENCES

World Health Organization Classification of Tumors. Pathology and Genetics of Tumors of the Lung, Pleura, Thymus and Heart. IARC Press: Lyon 2004.

www.gencat.cat/salut