Suggestions, Opinions and Recommendations for the Diagnosis, Management, Treatment and Surveillance of Lung Cancer
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In addition, these guidelines describe evaluations and administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that such clinical studies are designed to test innovative management strategies in a disease for which better treatment is sorely needed. However, by reviewing and synthesizing the latest literature, this practice guideline serves to identify questions for further research and the settings in which investigational therapy should be considered.
## Evidence Level and Recommendation Grade

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<th>Level of Evidence</th>
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<tr>
<td>I</td>
<td>Evidence from at least one large randomized control trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted RCTs without heterogeneity</td>
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<td>II</td>
<td>Small RCTs or large RCTs with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity</td>
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<td>III</td>
<td>Prospective cohort studies</td>
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<td>IV</td>
<td>Retrospective cohort studies or case-control studies</td>
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<td>V</td>
<td>Studies without control group, case reports, experts opinions</td>
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<td>Strong evidence for efficacy with a substantial clinical benefit, strongly recommended</td>
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<td>B</td>
<td>Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended</td>
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<td>C</td>
<td>Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,…) optional</td>
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<td>D</td>
<td>Moderate evidence against efficacy or for adverse outcome, generally not recommended</td>
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<tr>
<td>E</td>
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</tbody>
</table>
Contents

LEGAL DISCLAIMER .................................................................................................................. 1
Evidence Level and Recommendation Grade .............................................................................. 2
1 LUNG CANCER SCREENING AND STAGING ........................................................................ 6
  1.1 LUNG CANCER SCREENING ....................................................................................... 6
  1.2 NEW TNM STAGING SYSTEM OF NON-SMALL CELL LUNG CANCER ....................... 11
2 LUNG CANCER INITIAL EVALUATION .............................................................................. 23
  2.1 IMAGING ..................................................................................................................... 23
    2.1.1 FDG-PET ............................................................................................................. 23
    2.1.2 Magnetic Resonance Imaging (MRI) .................................................................... 25
  2.2 NON-INVASIVE STAGING ......................................................................................... 30
    2.2.1 Diagnosis of Early Lung Cancer and pre-invasive lesions .................................. 30
    2.2.2 Diagnosis of Symptomatic Lung Cancer .......................................................... 34
  2.3 INVASIVE MEDIASTENAL STAGING ......................................................................... 41
3 PATHOLOGIC CLASSIFICATION .......................................................................................... 47
  3.1 PATHOLOGIC CLASSIFICATION OF NSCLC .............................................................. 47
  3.2 CYTOPATHOLOGICAL CLASSIFICATION OF NSCLC ............................................. 60
4 EARLY STAGE NSCLC .......................................................................................................... 65
  4.1 SURGERY FOR STAGE I AND STAGE II ...................................................................... 65
  4.2 EARLY STAGE, MEDICALLY INOPERABLE NSCLC .................................................. 74
  4.3 ADJUVANT CHEMOTHERAPY IN NSCLC ................................................................. 75
  4.4 NEOADJUVANT CHEMOTHERAPY IN EARLY STAGE NSCLC .................................. 82
  4.5 FOLLOW-UP AND SURVEILLANCE OF THE LUNG CANCER PATIENT TREATED WITH CURATIVE INTENT ...................................................................................... 87
5 STAGE III NSCLC ................................................................................................................ 88
  5.1 THE ROLE OF POST-OPERATIVE RADIOTHERAPY .................................................. 88
  5.2 NEO-ADJUVANT CHEMOTHERAPY, CHEMORADIOTHERAPY ................................... 89
    5.2.1 Neoadjuvant chemotherapy versus surgery alone .............................................. 89
    5.2.2 Neoadjuvant versus perioperative chemotherapy ............................................ 90
    5.2.3 Induction chemotherapy followed by surgical resection or definitive radiotherapy .................................................................................................................. 90
    5.2.4 Induction chemo-radiotherapy followed by surgical resection or radiotherapy .................................................................................................................. 91
    5.2.5 Induction chemotherapy followed by chemo-radiotherapy versus chemoradiotherapy followed by consolidation chemotherapy ......................................... 92
  5.3 THE ROLE OF SURGERY ............................................................................................ 97
  5.4 MEDIASTINAL STAGING AFTER INDUCTION THERAPY ....................................... 108
  5.5 AKTINΟΘΕΡΑΠΕΙΑ ΤΟΥ ΠΝΕΥΜΟΝΑ ........................................................................ 112
    5.5.1 Γενικά .................................................................................................................. 112
    5.5.2 Γενικές αρχές ακτινοθεραπείας .............................................................................. 113
  5.6 ΡΙΖΙΚΗ ΑΚΤΙΝΟΘΕΡΑΠΕΙΑ ΤΟΥ ΠΝΕΥΜΟΝΑ ................................................................. 116
    5.6.1 Επιδημιολογικά στοιχεία .................................................................................. 116
    5.6.2 Κύριοι παθολογοανατομικοί τύποι ..................................................................... 117
    5.6.3 Διαγνωστική προσέγγιση πριν από την ακτινοθεραπεία ................................. 117
    5.6.4 Ριζική ακτινοθεραπεία .................................................................................. 118
    5.6.5 Ριζική χημειο-ακτινοθεραπεία στάδιου III ΜΜΚΠ ............................................. 118
6 STAGE IV NSCLC ................................................................................................................ 124
6.1 MOLECULAR ANALYSIS OF NSCLC ............................................. 124
6.2 FIRST-LINE THERAPY .................................................................... 147
6.3 MAINTENANCE THERAPY ............................................................. 159
6.4 SECOND-LINE THERAPY IN NSCLC ............................................. 161
  6.4.1 Cytotoxic chemotherapy ........................................................... 161
  6.4.2 Pemetrexed .............................................................................. 162
  6.4.3 Combination chemotherapy ..................................................... 163
  6.4.4 Epidermal growth factor receptor inhibitors .............................. 163
  6.4.5 ALK inhibition ........................................................................... 164
6.5 THIRD-LINE THERAPY .................................................................... 167
6.6 NSCLC IN THE ELDERLY ................................................................ 171
  6.6.1 Introduction .............................................................................. 171
  6.6.2 Surgical treatment .................................................................... 172
  6.6.3 Radical radiotherapy for potentially resectable tumors ............. 173
  6.6.4 Adjuvant chemotherapy after surgical resection ....................... 173
  6.6.5 Adjuvant RT after surgical resection ........................................ 174
  Locally advanced disease ............................................................ 174
6.7 TREATMENT OF NSCLC PATIENTS WITH PS2 .................... 182
6.8 SURGICAL TREATMENT OF OLIGO-METASTATIC NON-SMALL
  CELL LUNG CANCER ........................................................................ 191
  6.8.1 Brain metastases ..................................................................... 191
  6.8.2 Adrenal metastases .................................................................. 192
  6.8.3 Lung metastases ..................................................................... 193
  6.8.4 Other extrathoracic metastases ............................................... 194
6.9 MALIGNANT PLEURA MESOTHELIOMA .................................... 200
  6.9.1 Epidemiology ............................................................................ 200
  6.9.2 Methods to evaluate asbestos exposure .................................. 200
  6.9.3 MPM Diagnosis ....................................................................... 201
  6.9.4 Classification ............................................................................ 202
  6.9.5 Staging System ........................................................................ 203
  6.9.6 Management ............................................................................ 203
6.10 MESOTHELIOMA ............................................................................ 211
7 ADVANCED LUNG CANCER DISEASE .............................................. 212
  7.1 LUNG CANCER AND MALIGNANT PLEURAL EFFUSION ............ 212
    7.1.2 Thoracentesis ......................................................................... 212
    7.1.3 Chest tube drainage ............................................................... 213
    7.1.4 Selecting a sclerosing agent .................................................. 213
    7.1.5 Thoracoscopy and malignant pleural effusion ....................... 213
    7.1.6 Long term indwelling pleural catheter drainage ...................... 214
    7.1.7 Pleuroperitoneal shunting ...................................................... 214
    7.1.8 Pleurectomy ............................................................................ 214
  7.2 LUNG CANCER AND MALIGNANT PERICARDIAL EFFUSION ....... 214
  7.3 LUNG CANCER AND CENTRAL AIRWAY OBSTRUCTION .......... 215
  7.4 LUNG CANCER AND MASSIVE HEMOPTYSIS ............................. 216
  7.5 LUNG CANCER AND TRACHEOESOPHAGEAL FISTULA ............. 217
    7.5.1 Supportive therapy ............................................................... 217
    7.5.2 Endoscopic interventions ...................................................... 217
    7.5.3 Surgery .................................................................................. 217
7.6 LUNG CANCER AND SUPERIOR VENA CAVA SYNDROME ..........218
1 LUNG CANCER SCREENING AND STAGING

1.1.1 LUNG CANCER SCREENING

Angelidou M.

The concept of cancer screening

The goal of screening for lung cancer is to identify asymptomatic patients with early stage unrecognized disease and patients at increased risk for developing the disease (e.g. smoking, occupational exposure).

Usual clinical practice identifies only ~20% of lung cancer in stage I. CT screening series report that 58-93% of prevalence cancers and 25-100% of incidence cancers identified were stage I (1-3).

The ideal screening tool should be accurate, safe, widely applicable, of low cost and, most importantly, it should reduce the disease specific mortality. Although the potential of screening to detect early cancers may both increase the overall cure rate and allow a more limited surgical resection, whether screening will decrease mortality and morbidity remains uncertain.

Outcomes to be assessed

- Cancer detection rates;
- Stage at detection;
- Survival;
- Disease-specific mortality;
- Overall mortality.

Use of screening test introduces biases that are inherent in screening. The most significant of this include lead time, length time, and overdiagnosis.

- Screening does not change the natural history of the disease.
- Apparent survival of the disease is improved.
- Randomized controlled trials are needed.
Chest radiography and sputum cytology studies

Studies for lung cancer screening with chest x-ray and sputum cytology have failed to demonstrate that screening lowers lung cancer mortality rates (The Mayo Lung Project detected more cancers at an early stage in the screened cohort but no reduction was observed in late stage cancers and most importantly there was no reduction in mortality (4).

Screening with LDCT

Low dose CT scanning remains the most promising of lung cancer screening techniques. Results are available from one large randomized and several observational cohort studies; additional randomized trials are ongoing (5-8).

Available Evidence

Chest x-ray and CT screening frequently detect early stage asymptomatic lung cancers in screened individuals.

CT screening is significantly more sensitive than chest x-ray for identifying small asymptomatic lung cancers.

Chest x-ray and CT screening have high rates of “false positive” findings leading to additional testing, which usually includes serial imaging but may also include invasive procedures.

The National Lung Screening Trial (NLST) is a large randomized trial that enrolled 53,454 individuals at high risk for lung cancer at 33 U.S medical centers. Patients were assigned to undergo three annual screenings with either low–dose CT or single-view posteroanterior chest radiography. A lung cancer mortality benefit of 20% was demonstrated, with all-cause mortality reduced by 6.7 percent. A total of 96.4% of the positive screening results in the low–dose CT group and 94.5% in the radiography group were false positive results. Several limitations exist with NLST. The relatively low procedural complication rates in this trial may not be reproducible in other settings, and thus harms may be greater than reported. Second, the scanners currently used are more advanced than the ones used in the study. Third, the
NLST was conducted in a variety of institutions many of which are recognized for their expertise in radiology and the diagnosis and treatment of cancer. Further analysis, including cost effectiveness analysis, will determine a role for screening frequency, appropriate population target and the criteria for a “positive” finding. Thus, diagnostic follow up protocols remain to be addressed.

Expert screening groups have not yet incorporated the results from NLST in their recommendations.

**Other methods of screening**

Screening techniques include sputum analysis and screening the breath for volatile organic compounds and DNA alterations.

Proteomic analysis can be used to detect malignant changes in blood and tissue. A proteomic profile of tissue may also be used to screen for both invasive lung tumors and preinvasive lesions.

New bronchoscopic techniques such as autofluorescence bronchoscopy, narrow band imaging, and more recently bronchoscopic imaging using fibered confocal fluorescence microscopy have improved the detection of airway neoplasia by the bronchoscopist.

**Recommendations**

- We do not recommend that low-dose CT should be used to screen for lung cancer except in the context of a well-designed clinical trial.
- We recommend against the use of serial chest x-ray to screen for the presence of lung cancer.
- We recommend against the use of single or serial sputum cytologic evaluation to screen for the presence of lung cancer.
Questions

- What is the real cost of screening and what is the real target group?
  Based on the cost, is screening for lung cancer affordable?
- Is the survival benefit so insignificant when on the other hand we give chemotherapy to gain only 3 months of life extension?
- Where and who will perform the screening?

References


Suggestions, Opinions & Recommendations for the Diagnosis, Management, Treatment and Surveillance of Lung Cancer

Diagram:

- **Size**
  - Size at which cancer causes death
  - Size at which cancer causes symptoms

- **Time**
  - Fast
  - Slow
  - Very slow
  - Nonprogressive

- **Death from other causes**

**Diagnosis**

A) **Unscreened**
- Onset
- Early
- Usual
- Death

B) **Screened:** Early treatment not effective
- Onset
- Early
- Usual
- Death

C) **Screened:** Early treatment is effective
- Onset
- Early
- Usual
- Death

**Survival**

- Improved

1.1.2 LUNG CANCER SCREENING

Lung cancer mortality was reduced through the use of screening. Studies indicate that the use of low-dose helical Computed Tomography (CT) detects many tumors at early stages [1]. Individuals at high risk for lung cancer (history of cigarette smoking of at least 30 pack-years, and, if former smokers, had quit within the previous 15 years), should be participants in Lung Cancer Screening.

Individuals who had previously received a diagnosis of lung cancer, had undergone chest CT within 18 months before enrollment, had hemoptysis, cough, chest pain, or had an unexplained weight loss of more than 6.8 kg in the preceding year are excluded from Screening [1].

According to the National Lung Screening Trial (NLST-2011, NEJM) there was a lung cancer mortality reduction of 20%.

Chest Radiography

Although effective mass screening of high-risk groups could potentially be of benefit, randomized trials of screening with the use of chest radiography with or without cytologic analysis of sputum specimens have shown no reduction in lung-cancer mortality [2], [3].

Chest radiographs are obtained with the use of either screen-film radiography or digital equipment. Images are interpreted first in isolation and then in comparison with available historical images. The comparative interpretations are used to determine the outcome of the examination [4].

- Positive results are considered to be radiographic images that reveal any noncalcified nodule or mass. A screening test with chest radiography was considered to be positive if it revealed a nodule or mass of any size or other abnormalities suspicious for lung cancer.
• Other abnormalities, such as adenopathy or effusion, could be classified as a positive result as well.
• Abnormalities suggesting clinically significant conditions other than lung cancer also are noted as minor abnormalities.
• At the third round of screening, abnormalities suspicious for lung cancer that are stable across the three rounds could be classified as minor abnormalities rather than positive results.

Low dose helical Computed Tomography
According to the National Lung Screening Trial (NLST-2011, NEJM), there is a lung cancer mortality reduction of 20% using LDCT, fewer deaths from lung cancer than using chest radiography.

Participants were between 55 and 74 years of age with a history of heavy smoking. They were screened once a year for 3 years and were then followed for 3.5 additional years with no screening.

All low-dose CT scans are acquired with the use of multidetector scanners with a minimum of four channels. The acquisition variables were chosen to reduce exposure to an average effective dose of 1.5 mSv (100-120kVp & 40-60 mAs or less). The average effective dose with diagnostic chest CT varies widely but is approximately 8 mSv [4], [5], [6].

The percentage of all screening tests that identify a clinically significant abnormality other than an abnormality suspicious for lung cancer is more than three times as high with the use of low-dose CT as with the use of radiography (7.5% vs. 2.1%) [8], [9].

• Several observational studies have shown that low-dose helical CT of the lung detects more nodules and lung cancers, including early-stage cancers, than chest radiography does.
• A screening test with low-dose CT is considered to be positive if it reveals a nodule at least 4mm in any diameter or other abnormalities suspicious for lung cancer.
- A 20.0% decrease in mortality from lung cancer is observed with the use of low-dose CT as compared with the radiography use. [1]
- Low dose CT is more sensitive in detecting complications (major, intermediate, or minor) from invasive diagnostic evaluation procedures.

According to Harold C. Sox’s article in NEJM (August 2011) Better Evidence about Screening for Lung Cancer, policymakers should wait for cost-effectiveness analyses of the NLST data, further follow-up data to determine the amount of overdiagnosis in the NLST, and, perhaps, identification of biologic markers of cancers that do not progress.[11]

**Laboratory**

Other strategies for early detection of lung cancer — in particular, molecular markers in blood, sputum, and urine, — can help select persons who are best suited for low-dose CT screening.

**Further examinations**

Persons with positive low-dose CT screening tests should undergo more rigorous diagnostic evaluation [1], [10]:

- *FDG PET or FDG PET–CT*
- *Percutaneous cytologic examination or biopsy*
  - Transthoracic
  - Extrathoracic
- *Bronchoscopy*
  - With neither biopsy nor cytologic testing
  - With biopsy or cytologic testing
- *Surgical procedures*
  - Mediastinoscopy or mediastinotomy
  - Thoracoscopy
  - Thoracotomy
- *Other procedures*
Recommendations

- The advent of low dose helical computed tomography (CT) altered the landscape of lung-cancer screening, with studies indicating that low-dose CT detects many tumors at early stages.
- Several observational studies have shown that low-dose helical CT of the lung detects more nodules and lung cancers, including early-stage cancers, than chest radiography does.
- Reduction of mortality from lung cancer was achieved among high-risk persons.
- The potential effect of low-dose CT screening (quality-of-life effects, costs, and cost-effectiveness) is not yet detected.
References


1.2 NEW TNM STAGING SYSTEM OF NON-SMALL CELL LUNG CANCER

Giozos I, Angelidou M.

Non-small cell lung cancer stage classification system is correlated with the anatomical extent of the disease based on the characteristics of the primary tumor, the invasion of the regional lymph nodes and the presence of distant metastasis.

The *International Union against Cancer* and the *American Joint Committee on Cancer* approved the proposals of the *International Association for the Study of Lung Cancer* since January 2010.

The IASLC proposals were based on an international data base of 68.463 non-small cell lung cancer patients from 46 different medical centers in 19 countries, treated by all modalities of care, who were internally and externally validated.

The staging system is useful because of its strong prognostic value, the ability to evaluate the response to the treatment; it is a crucial parameter for the treatment strategy algorithm and is a common language between different medical specialists who are involved in the management of lung cancer patients or in an international clinical trial.

**Advantages of the New 7th Revision of TNM Classification System**

- International data base, 68.463 cases
- Multi-modality treatment algorithm
- Internal-External Validation of IASLC Project
- Based on CT’s versus Chest X-Ray
- Better prognostic value of the T descriptor size
- Widening of II_A stage
- Better prognostic value for separate tumor nodules in same lobe or ipsilateral lobe, pleural effusion, pleural nodules, pericardial effusion.
Limitations of the New 7th Revision of TNM Classification System

- Data base not specifically designed to study the TNM classification;
- Non global distribution (China, India, Russia, Africa, South America);
- Spread of treatment modalities does not reflect the practice in most institutions;
- Not evaluation of non-size-based T descriptors (small number of patients, inconsistent clinical and pathologic results, lack of validation);
- Not an internationally accepted regional lymph node map;
- Skip metastasis not mentioned;
- Lymphangitis carcinomatosis is not evaluated;
- PET/CT scan is a more accurate imaging-functional tool for preoperative lung cancer staging.

Approximately, 1 out of 6 lung cancer patients will be classified into a different stage category due to the changes implemented in the 7th edition of TNM Classification.

In principle, a change in stage does not automatically means a change in therapy, but each case of ‘stage shifters’ must be considered individually by the multidisciplinary team assessing all possible factors in addition to lung cancer stage, in order to plan the treatment strategy until the development of new clinical trials based on the 7th TNM Revision.

Recommendations

- We adopt the new TNM staging system (The 7th revised edition) for NSCLC.
- We particularly emphasize the need for a multidisciplinary approach in the management of “Stage shifters”.
References


THE NEW TNM STAGING SYSTEM ACCORDING TO IASLC RECOMMENDATIONS

The changes are related to the T and M descriptors only while the existing N descriptors were validated and no changes were proposed.

- **T (Primary Tumor)**

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

- **N (Regional Lymph Nodes)**
  - Nx  Regional lymph nodes cannot be assessed
  - N₀  No regional lymph node metastasis
  - N₁  Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
  - N₂  Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
  - N₃  Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

- **M (Distal Metastasis)**
  - M₀  No distant metastasis
  - M₁  Distant metastasis
  - M₁ₐ  Separate tumor nodule(s) in a contralateral lobe; tumor with malignant pleural nodules or malignant pleural (or pericardial) effusion
  - M₁ₚ  Distant metastasis
# Modifications in TNM Classifications and Stage Groupings from the 6th to the 7th Edition

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<td>T1b (&gt;2-3 cm)</td>
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<td>II A</td>
<td>II A</td>
<td>II A</td>
<td>IIIB</td>
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<td>II A</td>
<td>IIIB</td>
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<tr>
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<td>T2b (&gt;5-7 cm)</td>
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<td>IIIB</td>
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<tr>
<td></td>
<td>T3 (&gt;7 cm)</td>
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<td>II A (IB)</td>
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<tr>
<td>T3 invasion</td>
<td>T3</td>
<td>II B</td>
<td>II A</td>
<td>II A</td>
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<td>T4 (same lobe nodules)</td>
<td>T3</td>
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<td>II A (IB)</td>
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<tr>
<td>T4 (extension)</td>
<td>T4</td>
<td>III A (IB)</td>
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<td>IIIB</td>
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<tr>
<td>M1 (ipsilateral lung)</td>
<td>T4</td>
<td>III A (IV)</td>
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<td>II A (IV)</td>
<td>II B (IV)</td>
<td>IIIB (IV)</td>
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<tr>
<td>T4 (pleural effusion)</td>
<td>M1\text{a}</td>
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<tr>
<td>M1 (contralateral lung)</td>
<td>M1\text{a}</td>
<td>IV</td>
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<td>IV</td>
</tr>
<tr>
<td>M1 (distant)</td>
<td>M1\text{b}</td>
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* - Change in classification with 7th edition of TNM from 6th edition in ()
STAGE-BASED TREATMENT STRATEGY

Stage I\textsubscript{a} NSCLC \hspace{5cm} Surgery (LOE I, GOR A),
If Medically Inoperable Radical
Radiotherapy (LOE I, GOR A)

Stage I\textsubscript{b} NSCLC \hspace{5cm} Surgery (LOE I, GOR A),
If Medically Inoperable Radical
Radiotherapy (LOE I, GOR A)

Stage II\textsubscript{a} NSCLC \hspace{5cm} Surgery + Adjuvant
Chemotherapy
If Medically Inoperable Radical
Radiotherapy + Adjuvant
Chemotherapy (LOE I, GOR A)

Stage II\textsubscript{b} NSCLC \hspace{5cm} Surgery + Adjuvant
Chemotherapy
If Medically Inoperable Radical
Radiotherapy + Adjuvant
Chemotherapy (LOE I, GOR A)

Stage III\textsubscript{a} NSCLC \hspace{5cm} Consider Multimodality Treatment
(LOE I, GOR A)

Stage III\textsubscript{b} NSCLC \hspace{5cm} ChemoRadiation (LOE I, GOR A)

Stage IV NSCLC \hspace{5cm}Chemotherapy (LOE I, GOR A)
2 LUNG CANCER INITIAL EVALUATION

Thanos L.

2.1 IMAGING

Imaging studies are used for diagnosis and to determine the stage of the disease as well as to assess tumor response and, thus, guide further treatment of patients.

The treatment and prognosis of patients with NSCLC depend on disease staging. Radiologic imaging is directed at detecting non-resectable disease (T4 or N3 or M1) [1],[2],[3].

Diagnostic means for initial staging (before treatment):
Radiograph, CT scan

The accurate diagnosis of local tumor growth, intrathoracic metastases, extrathoracic metastases, TNM-stage and cell type is essential for defining the treatment strategy. Typically, the primary lesion is identified by a radiograph or a CT scan.

A chest radiograph and contrast-enhanced chest CT, which should include the liver and the adrenal glands, should be performed.

2.1.1 FDG-PET

A whole-body FDG-PET should be performed when there is no evidence of distant metastasis on CT scan [4], as FDG-PET imaging improves the detection of nodal and distant metastases and frequently alters patient management [5],[6],[7].

When there is a positive FDG-PET result, further diagnostic procedures should be done to avoid overstaging such as bronchoscopy with or without transbronchial needle aspiration (TBNA), endobronchial ultrasonography-guided transbronchial needle aspiration (EBUS-TBNA), transthoracic needle aspiration (TNB), video-assisted thoracoscopy, mediastinoscopy.
The high sensitivity and high negative predictive value of FDG-PET in most malignant tumors enables this technique to play an even greater role in tumor management at initial staging and follow-up [8].

➔ **Contrast enhanced CT scanning of the chest and abdomen is recommended in all patients with suspected lung cancer, regardless of chest X-ray results.**

➔ **Contrast-enhanced chest CT scanning should be performed prior to further diagnostic investigations, including bronchoscopy, and the results used to guide the investigation that is most likely to provide both a diagnosis and stage the disease to the highest level.**

➔ **A whole-body FDG-PET/CT should be performed whenever treatment with curative intent is planned.**

➔ **When there is a positive FDG-PET/CT result, further diagnostic procedures should be done.**

➔ **MRI is preferred for the evaluation of brain.**

➔ **MRI is superior to CT scan in the evaluation of superior sulcus tumors.**

➔ **MRI is preferred to assess involvement of major blood vessels, trachea, carina, or chest wall, and to look for cardiac and diaphragmatic invasion.**

➔ **MRI has no role in the routine staging of mediastinal lymphadenopathy.**
2.1.2 Magnetic Resonance Imaging (MRI)

Complementary to CT scan

It is mainly used to assess involvement of major blood vessels, trachea, carina, or chest wall, and to look for cardiac and diaphragmatic invasion and brain metastases.

MRI is superior to CT scan in the evaluation of brain tumors and superior sulcus tumors [9], [10], [11].

- MRI is preferred for the evaluation of brain tumors, for staging of distant metastases.
- MRI is superior to CT scan in the evaluation of superior sulcus tumors.
- MRI is preferred to assess involvement of major blood vessels, trachea, carina, or chest wall, and to look for cardiac and diaphragmatic invasion.
- MRI has no role in the routine staging of mediastinal lymphadenopathy.

Evaluation of pleural effusion

The majority of pleural effusions are due to involvement of the pleura by tumor (T4). Cytologic examination will detect approximately 65% of malignant effusions. Aspiration of the pleural effusion under imaging guidance may be needed, especially in cases of small or loculated effusions [12],[13],[14],[15]. Some patients may require VATS biopsy to confirm pleural malignancy as aspiration and closed biopsy alone may be insufficient [16].

➔ In case of pleural effusion, further diagnostic work up should be done to rule out malignancy.
➔ CT guided pleural biopsy/medical thoracoscopy/VATS is now considered a far more reliable diagnostic test compared to thoracentesis in an undiagnosed unilateral pleural effusion.
The presence of malignant cells is required to categorise the lesion as M1a.

Follow-up
Follow-up should include CT scan of the chest every 4-6 months for 2 years; after this period, CT scan of the chest should be done annually [1].

Questions to be discussed:
- Which is the examination of choice for NSCLC staging?
- If CT scan has no evidence of distant metastasis, what is the next choice?
- Is MRI useful in NSCLC evaluation?
- Is it important to evaluate pleural effusion?
- Are image guided interventional methods useful in NSCLC staging?

Recommendations

- **Stage I (A and B):** PET/CT scan, if available.
- **Stage IIA:** PET/CT scan, if available. Brain MRI for nonsquamous histology.
- **Stage IIB:** PET/CT scan, if available MRI brain, MRI spine and thoracic inlet for superior sulcus tumor abutting the spine or the suclavian vessels.
- **Stage IIIA:** PET/CT scan; if not available, bone scan. MRI brain MRI spine and thoracic inlet for superior sulcus tumors abutting the spine or the suclavian vessels.
- **Stage IIIB:** PET/CT scan; if not available, bone scan. Brain MRI, thoracentesis or pericardiocentesis. If two thoracentesis attempts are negative, perform thoracoscopy.
- **Stage IV with solitary metastasis:** PET/CT scan; if not available, bone scan. Brain MRI.
- **Stage IV with disseminated metastasis:** Workup as clinically indicated.
References


2.2 NON-INVASIVE STAGING

Zachariadis M., M.D., Stratakis G., M.D.

2.2.1 Diagnosis of Early Lung Cancer and pre-invasive lesions
The majority of lung cancer cases are diagnosed in a late stage, and fewer than 15% of patients with invasive lung cancer survive 5 years after treatment. Early detection and treatment of pre-invasive bronchial lesions (dysplasia and Ca in situ) as well as accurate staging and recognition of synchronous neoplastic lesions has an important impact in prognosis.

White light bronchoscopy (WLB) is unfortunately limited in its ability to detect small intraepithelial and microinvasive pre-invasive lesions. Bronchoscopic imaging techniques capable of detecting preinvasive lesions currently available in clinical practice include autofluorescence bronchoscopy (AFB), high magnification bronchovideoscope, and narrow band imaging (NBI). For a more precise evaluation of newly detected pre-invasive lesions to guide endobronchial treatment, endobronchial ultrasound (EBUS) can also be used.

AFB improves the sensitivity for detection of preinvasive lesions in the central airway [1,2] and increases the diagnostic accuracy for squamous dysplasia, CIS, and early lung carcinoma when used simultaneously with conventional white light bronchoscopy (WLB). Three multicenter and 2 randomized clinical trials have documented the usefulness of AFB as an adjunct to WLB for detecting intraepithelial neoplasia and CIS. [3-6] However, the specificity of AFB for diagnosing preinvasive lesions is low. Distinguishing between preinvasive lesions and other benign epithelial changes such as bronchitis is problematic.

NBI is an optical image technology that enhances vessels in the surface mucosa by using a specific wavelength, allowing the visualization of abnormal distribution and dilatation of blood vessels. There are only a few studies on NBI in the evaluation of the airway.
Recommendations

→ **AFB is a useful tool for the localization of microinvasive neoplasia.**
   
   *For patients with severe dysplasia, CIS, or carcinoma in sputum cytology but with negative chest imaging studies, combination of WLB and AFB or NBI is recommended. (LOE I, GOR B)*

→ **For patients being considered for curative endobronchial therapy to treat CIS in centers where it is available, AFB may be considered to guide therapy. (LOE II, GOR B)*

Longitudinal data using serial bronchoscopy and biopsy in patients with intraepithelial neoplasia detected by AFB have now been reported by a number of authors. Lam et al. reported the follow-up of 2,346 lesions detected in 566 subjects who had at least a 20 pack-year smoking history but no previous or current aerodigestive cancer. Reported progression rate of severe dysplasia to CIS/invasive carcinoma was 6%. Other studies have confirmed that low-grade epithelial lesions could be safely followed-up at 2 yr in patients without high-grade lesions at baseline, whereas severe dysplasia should be treated if they persist at 3 mo. Immediate treatment of carcinoma *in situ* appears warranted.

→ **For patients with known severe dysplasia or CIS in the central airways, standard WLB is recommended at periodic intervals (3 to 6 months) for follow-up. AFB should be used when available. (LOE II, GOR C)**

→ **For patients with SqCC who are not surgical candidates, PDT, electrocautery, cryotherapy, and brachytherapy are recommended as treatment options.**
Summary of Recommendations

1. **AFB is a useful tool for the localization of microinvasive neoplasia.** For patients with severe dysplasia, CIS, or carcinoma in sputum cytology but with negative chest imaging studies, combination of WLB and AFB is recommended. Use of NBI is recommended if available. (LOE I, GOR B)

2. **For patients being considered for curative endobronchial therapy to treat CIS in centers where it is available, AFB may be considered to guide therapy.** (LOE II, GOR B)

3. **For patients with known severe dysplasia or CIS in the central airways, standard WLB is recommended at periodic intervals (3 to 6 months) for follow-up. AFB should be used when available.** (LOE II, GOR C)

4. **For patients with SqCC who are not surgical candidates, PDT, electrocautery, cryotherapy, and brachytherapy are recommended as treatment options.** (LOE I, GOR C)
References


2.2.2 Diagnosis of Symptomatic Lung Cancer  

Definition of T stage

The decision about whether to pursue a diagnostic bronchoscopy for a lesion that is suspicious for lung cancer (1) and namely NSCLC, largely depends on the location of the lesion (central vs peripheral). Central lesions can present as an exophytic endobronchial mass, submucosal spread or a peribronchial tumor causing extrinsic compression. Thirty-five studies of a total of 4507 patients with central disease were identified. The overall sensitivity of FB was 0.88. Direct forceps biopsy of visible central lesions is the technique used most frequently, and sensitivity of this test by itself was 0.74. The sensitivity of washings and brushings is somewhat lower (0.48 and 0.59, respectively), but these tests are often combined with forceps biopsies. The addition of TBNA to obtain cytology or histology samples when there is submucosal tumor spread or peribronchial tumor causing extrinsic compression increases the sensitivity of bronchoscopy.

In patients suspected of having lung cancer who have a central lesion, bronchoscopy is recommended to confirm the diagnosis. However, it is recommended that further testing be performed if bronchoscopy results are nondiagnostic and suspicion of lung cancer remains. (LOE I, GOR C)

Peripheral lesions are defined in most studies as lesions that are not visible beyond the visual segmental bronchi; thus, it is not surprising that the sensitivity of FB in this instance is lower than for central lesions. Thirty-four studies reported on the sensitivity of FB for peripheral lesions. Transbronchial biopsies provided the highest sensitivity, followed by brush biopsy and BAL/washings. Although TBNA showed a high sensitivity (0.65; 7 studies), the data deserve caution in interpretation because of the limited number of studies and the differences in sample size. The overall sensitivity for all modalities in the diagnosis of peripheral disease was 0.78. Most studies used fluoroscopy routinely for peripheral lesions, which increases the reported sensitivity of bronchoscopy as it is higher also, if the CT scan shows a
bronchus extending to the peripheral lesion (0.60 vs 0.25 respectively). Ten studies were identified that reported on the sensitivity of bronchoscopy for peripheral lesions of <2cm or >2cm in diameter. Peripheral tumors with a diameter >2cm resulted in a sensitivity of 0.63. For lesions of <2cm in diameter the sensitivity was 0.34. Following the footsteps of gastroenterologists, pulmonologists have started using ultrasound (US) technology in the diagnosis and staging of bronchogenic carcinoma. Of the two kinds of ultrasonic probes (convex and radial), the radial probe is used to locate the peripheral lesions, which was previously thought to be inaccessible by conventional bronchoscopy. A flexible double-hinged curette or an electromagnetic device is used, if necessary, to maneuver an extended working channel to the area of interest, under fluoroscopic guidance.

- In expert hands, a radial probe EBUS device can increase the diagnostic yield of FB while dealing with peripheral lesions of <20mm in size. Its use can be considered prior to referring the patient for TTNA. (LOE II, GOR B)

NSCLC can present with extensive infiltration of the mediastinum, which is defined as a mass that infiltrates and encases the mediastinal structures where no discrete mediastinal lymph nodes are visible.

- In patients suspected of having lung cancer, who have extensive infiltration of the mediastinum based on radiographic studies, it is recommended that the diagnosis of lung cancer be established by the easiest and safest method (bronchoscopy with TBNA, EBUS-TBNA, EUS-FNA, TTNA, or mediastinoscopy). (LOE I, GOR C)
Definition of N stage
The treatment of non-small cell lung cancer (NSCLC) is determined by accurate definition of the stage. If there are no distant metastases, the status of the mediastinal lymph nodes is critical. Although imaging studies can provide some guidance, in many situations invasive staging is necessary. Many different complementary techniques are available.

In patients with extensive mediastinal infiltration, invasive staging is not needed. In patients with discrete node enlargement, staging by CT or positron emission tomography (PET) scanning is not sufficiently accurate. The sensitivity of various techniques is similar in this setting, although the false-negative (FN) rate of needle techniques is higher than that for mediastinoscopy.

In patients with a stage II or a central tumor, invasive staging of the mediastinal nodes is necessary. Mediastinoscopy is generally preferable because of the lower FN rates. Patients with a peripheral clinical stage I NSCLC do not usually need invasive confirmation of mediastinal nodes unless a PET scan finding is positive in the nodes. The staging of patients with left upper lobe tumors should include an assessment of the aortopulmonary window lymph nodes.

Several invasive procedures are available to stage (2) the mediastinum (mediastinoscopy, anterior mediastinotomy, thoracoscopy or VATS, transbronchial needle aspiration TBNA, EBUS-TBNA, esophageal endoscopic ultrasound EUS with needle aspiration). Among these, TBNA, EBUS-TBNA and EUS-NA are endoscopic techniques that can be performed with a negligible risk of infection or bleeding on an outpatient basis. The location of the suspected nodal involvement determines which test is performed as some nodal stations are easier accessible by one test and not by another. Experience of the endoscopist is very likely to affect the performance characteristics of a procedure. At any rate, it is best to view the different invasive staging procedures as complementary and not competitive. In many situations an invasive test can provide both confirmation of the diagnosis and stage at the same time.
**EUS-NA** of mediastinal lymph nodes is particularly useful for stations 9, 8, 7 and 5. Sixteen studies with 973 evaluable lung cancer patients found overall specificity 99.5%, and overall false positive rate 0.4%. However, in the only study which truly allowed the evaluation of these performance characteristics further investigating positive results, specificity and FP rate were much worse (97% and 7% respectively). False positive results can be eliminated by avoiding puncture in sites where there is evidence of mucosal invasion. It is clear that nodes <1cm can be sampled using this technique as it is for using EBUS-TBNA. Emerging data suggest that the combination of EUS-NA and EBUS-TBNA may allow complementary and nearly complete access to all mediastinal lymph node stations (3). EUS is also capable of detecting metastatic disease to subdiaphragmatic sites such as the left adrenal gland and also of evaluating the presence of direct invasion into the mediastinum especially within a blood vessel or the esophagus with the limitation of the high FP rate.

**TBNA** is used most frequently to assess enlarged subcarinal and lower paratracheal lymph nodes (7, 4R and 4L stations). The high false negative rate for small (<1-1.5 cm) lymph nodes makes this test less useful for staging of the mediastinum in patients with normal-sized lymph nodes. Positive TBNA results are fairly reliable, negative results, however, cannot exclude nodal involvement sufficiently.

**EBUS-TBNA** is performed through the dedicated EBUS-TBNA scope, which allows for real time US guided TBNA and can be used to sample the highest mediastinal, upper and lower paratracheal and subcarinal as well as hilar lymph node, under direct observation. The use of real time EBUS imaging and the immediate proximity of nodes to the airway greatly increase diagnostic accuracy for small nodes (4). Studies comparing directly EBUS-TBNA with mediastinoscopy have shown similar results in terms of sensitivity, specificity and negative predictive value (5). However, it is still suggested that negative EBUS-TBNA biopsy results should be confirmed by further assessment with mediastinoscopy.
→ For patients with discrete mediastinal lymph node enlargement (and no distant metastases), a nonmalignant result from a needle technique should be further confirmed with mediastinoscopy regardless of whether the findings of a PET scan of the nodes are positive or negative. (LOE I, GOR C)

→ For patients with a radiographically normal (by CT scan) mediastinum and a central tumor or N1 lymph nodes enlargement (and no distant metastases), invasive staging is recommended. In general, mediastinoscopy is suggested but EBUS-TBNA or EUS-NA may be a reasonable alternative if non-diagnostic results are followed by mediastinoscopy. (LOE II, GOR C)

→ For patients with a peripheral clinical stage I tumor in whom a PET scan shows uptake in the mediastinum (and no distant metastases), invasive staging is recommended. EBUS-TBNA or EUS-NA is a reasonable alternative to mediastinoscopy. If non-diagnostic results occur, should be confirmed by mediastinoscopy. (LOE I, GOR C)

→ For patients with peripheral clinical stage I tumor, invasive confirmation of the mediastinal nodes is not needed if the findings of a PET scan of the mediastinum are negative. (LOE I, GOR C)
Summary of Recommendations

1. In patients suspected of having lung cancer who have a central lesion, bronchoscopy is recommended to confirm the diagnosis. Every effort should be undertaken to obtain histologic material. However, it is recommended that further testing be performed if bronchoscopy results are nondiagnostic and suspicion of lung cancer remains. (LOE I, GOR C)

2. In expert hands, a radial probe EBUS device can increase the diagnostic yield of FB while dealing with peripheral lesions of <20mm in size. Its use can be considered prior to referring the patient for TTNA. (LOE II, GOR B)

3. In patients suspected of having lung cancer, who have possible infiltration of the mediastinum based on radiographic studies, it is recommended that the diagnosis of lung cancer be established by the easiest and safest method (bronchoscopy with TBNA, EBUS-TBNA, EUS-FNA, TTNA, or mediastinoscopy). (LOE I, GOR C)

4. For patients with discrete mediastinal lymph node enlargement (and no distant metastases), a non-malignant result from a needle technique should be further confirmed with mediastinoscopy regardless of whether the findings of a PET scan of the nodes are positive or negative. (LOE I, GOR C)

5. For patients with radiographically normal (by CT scan or PET/CT) mediastinum and a centrally located tumor or N1 lymph nodes enlargement (and no distant metastases), invasive staging is recommended. In general, mediastinoscopy is suggested but EBUS-TBNA or EUS-NA may be a reasonable alternative if non-diagnostic results are followed by mediastinoscopy. (LOE II, GOR C)

6. For patients with a peripheral clinical stage I tumor in whom a PET scan shows uptake in the mediastinum (and no distant metastases), invasive staging is recommended. EBUS-TBNA or EUS-NA is a reasonable alternative to mediastinoscopy. If non-diagnostic results occur, should be confirmed by mediastinoscopy. (LOE I, GOR C)
7. For patients with peripheral clinical stage I tumor, invasive confirmation of the mediastinal nodes is not needed if the findings of a PET/CT scan of the mediastinum are negative. (LOE I, GOR C)

References


3. Wallace M. Pascual JM .Complete medical mediastinoscopy under conscious sedation. Gastrointest Endoscopy 2006;63;AB96


2.3 INVASIVE MEDIASTENAL STAGING

Iliadis K, Barbetakis N.

The treatment of non-small cell lung cancer (NSCLC) is determined by accurate definition of the stage. If the presence of distant metastatic disease has been ruled out, the status of the mediastinum becomes the crucial factor in selecting the optimal treatment strategy. Non-invasive imaging tests can provide only a suspicion that involvement of the mediastinal nodes is present or absent, and in many clinical situations confirmation of the status of these nodes by an invasive test is necessary.

Surgical invasive tests include mediastinoscopy, extended cervical mediastinoscopy (ECM), anterior mediastinotomy (Chamberlain procedure) and video-assisted thoracic surgery (VATS). All these procedures are needed to more accurately confirm the presumptive mediastinal stage but they are also sometimes used to confirm the diagnosis.

In patients with extensive mediastinal infiltration, the radiographic evidence of mediastinal involvement is quite universally considered adequate.

**Recommendation:** *For patients with extensive mediastinal infiltration of tumor and no distant metastases, radiographic (CT scan) assessment of the mediastinal stage is usually sufficient without invasive confirmation. (LOE II, GOR C)*

Many patients present with a CT scan demonstrating the enlargement of discrete mediastinal lymph nodes (N2, N3). Detterbeck et al. reported that enlargement seen on CT scan alone carries a false positive rate of 40%.\(^1\) The false positive rate for PET scanning in the mediastinum has been widely shown to be 15-20%\(^2\).
Recommendations

➔ For patients with discrete mediastinal lymph node enlargement and no distant metastases, invasive confirmation of the radiographic stage is recommended (regardless of whether a PET scan finding is positive or negative in the mediastinal nodes). (LOE I, GOR B)

➔ For patients with discrete mediastinal lymph node enlargement and no distant metastases, many invasive techniques for the confirmation of the N2, 3 node status are suggested as reasonable approaches given the appropriate experience and skill (regardless of whether a PET scan finding is positive or negative in the mediastinal nodes). (LOE I, GOR B)

➔ For patients with discrete mediastinal lymph node enlargement and no distant metastases, a nonmalignant result from a needle technique (EUS-NA, EBUS-NA, TBNA, TTNA) should be further confirmed by mediastinoscopy (regardless of whether a PET scan finding is positive or negative in the mediastinal nodes). (LOE I, GOR C)

Patients with no evidence of mediastinal node enlargement but with a central tumor or N1 node involvement represent another distinct group. There is enough data indicating that the false negative rate of a CT scan with respect to mediastinal nodes is 20-25% and more limited data demonstrate that the false negative rate of PET scan in this situation is similarly high (24-83%) \(^3,4\).

Recommendation

➔ For patients with a radiographically normal mediastinum (by CT scan) and a central tumor or N1 lymph node enlargement (and no distant metastases), invasive confirmation of the radiographic stage is recommended (regardless of whether a PET scan finding is positive or negative in the mediastinal nodes). (LOE I, GOR C)
In patients with peripheral tumors in whom there is no enlargement of N1 or N2, 3 nodes seen on CT scans, the false negative rate of this radiographic assessment is approximately 10%\(^1\). A negative PET scan finding in the mediastinum carries a false negative rate of approximately 5%\(^5,6\). A positive PET scan finding suggests definitely surgical staging.

**Recommendations**

- For patients with a peripheral clinical stage I tumor in whom a PET scan shows uptake in mediastinal nodes (and no distant metastases), invasive staging is recommended. Video-mediastinoscopy is suggested but EUS-NA or EBUS-NA may be a reasonable alternative. (LOE I, GOR C)

- For patients with a peripheral clinical stage I tumor, invasive confirmation of the mediastinal nodes is not needed if the findings of a PET scan of the mediastinum are negative. (LOE I, GOR C)

Patients with tumors in the left upper lobe deserve special mention because the aortic arch raises technical issues of access to the mediastinal nodes in the aorto-pulmonary window (node zone 5). A full assessment of potentially involved mediastinal lymph node zones in the case of a left upper lobe tumor requires investigation of the paratracheal and subcarinal nodes, as well as a separate procedure to access the aorto-pulmonary window area.

If the usual mediastinal node zones (2R, 4R, 2L, 4L, 7) are found to be negative, it is controversial whether a separate procedure to assess the zone 5 area is needed. However, with the availability of techniques of assessing the aorto-pulmonary window area, the guidelines committee favors pursuing an invasive assessment.
Recommendation

→ For patients with a left upper lobe tumor in whom invasive mediastinal staging is indicated, it is suggested that invasive mediastinal staging include assessment of the aorto-pulmonary window nodes (via extended cervical mediastinoscopy, anterior mediastinotomy, VATS) if other mediastinal node zones are found to be uninvolved. (LOE II, GOR C)

Conclusions

Accurate mediastinal staging is crucial to the selection of the optimal therapy for patients without distant metastases. Imaging studies are not sufficiently reliable. Many different invasive staging tests, which should be viewed as complementary to one another, are available. Extent of mediastinal involvement by CT scan is very important for the choice of the appropriate technique. Needle techniques are useful in patients with enlarged mediastinal lymph nodes, while mediastinoscopy remains the gold standard in patients with normal-sized nodes.

Summary of Recommendations

1. For patients with extensive mediastinal infiltration of tumor and no distant metastases, radiographic (CT scan) assessment of the mediastinal stage is usually sufficient without invasive confirmation. (LOE II, GOR C)

2. For patients with discrete mediastinal lymph node enlargement and no distant metastases, invasive confirmation of the radiographic stage is recommended (regardless of whether a PET scan finding is positive or negative in the mediastinal nodes). (LOE I, GOR B)

3. For patients with discrete mediastinal lymph node enlargement and no distant metastases, many invasive techniques for the confirmation of the N2, 3 node status are suggested as reasonable approaches given the appropriate experience and skill (regardless of whether a PET scan finding is positive or negative in the mediastinal nodes). (LOE I, GOR B)
4. **For patients with discrete mediastinal lymph node enlargement and no distant metastases, a nonmalignant result from a needle technique (EUS-NA, EBUS-NA, TBNA, TTNA) should be further confirmed by mediastinoscopy (regardless of whether a PET scan finding is positive or negative in the mediastinal nodes).** (LOE I, GOR C)

5. **For patients with a radiographically normal mediastinum (by CT scan) and a central tumor or N1 lymph node enlargement (and no distant metastases), invasive confirmation of the radiographic stage is recommended (regardless of whether a PET scan finding is positive or negative in the mediastinal nodes).** (LOE I, GOR C)

6. **For patients with a peripheral clinical stage I tumor in whom a PET scan shows uptake in mediastinal nodes (and no distant metastases), invasive staging is recommended. Video-mediastinoscopy is suggested but EUS-NA or EBUS-NA may be a reasonable alternative.** (LOE I, GOR C)

7. **For patients with a peripheral clinical stage I tumor, invasive confirmation of the mediastinal nodes is not needed if the findings of a PET scan of the mediastinum are negative.** (LOE I, GOR C)

8. **For patients with an LUL tumor in whom invasive mediastinal staging is indicated, it is suggested that invasive mediastinal staging include assessment of the aorto-pulmonary window nodes (via extended cervical mediastinoscopy, anterior mediastinotomy, VATS) if other mediastinal node zones are found to be uninvolved.** (LOE II, GOR C)
References


Non-small cell lung carcinoma (NSCLC) is subdivided pathologically in distinct types, each subject to different treatment modalities. The 2004 WHO classification of lung tumors [1] includes the following major tumor types: squamous cell carcinoma (SCC), adenocarcinoma (ADC), large cell carcinoma (LCC), adenosquamous carcinoma, and sarcomatoid carcinoma (Table 1). ADC is, at present, the most frequent type of NSCLC and is often heterogeneous in morphology [2]. The recently proposed classification of lung ADC [3], after multidisciplinary approach, reflects the need for more accurate and specific diagnosis, especially on small biopsies. This classification emphasized the importance of recording the ADC heterogeneity and classifying ADC based on the predominant morphologic architectural pattern. The distinct ADC patterns provide important information for diagnosis, prognosis and prediction of response to specific targeted treatment modalities. The new ADC classification is applied primarily on resection specimens (Table 2), although a diagnostic algorithm (Figure 1) and recommendations are also provided for the diagnosis and classification of small biopsies and cytological specimens (Table 3). The proposed classification addressed several important issues and made significant recommendations, although as already discussed by its authors, there are points that merit further investigation.
Table 1. WHO classification of NSCLC [1].

**Malignant epithelial tumors**

**Squamous cell carcinoma**
- Papillary
- Clear cell
- Small cell
- Basaloid

**Adenocarcinoma**
- Adenocarcinoma, mixed subtype
- Acinar adenocarcinoma
- Papillary adenocarcinoma
- Bronchioloalveolar carcinoma
  - Nonmucinous
  - Mucinous
  - Mixed nonmucinous and mucinous, or indeterminate
- Solid adenocarcinoma with mucin production
- Fetal adenocarcinoma
- Mucinous (“colloid”) carcinoma
- Mucinous cystadenocarcinoma
- Signet ring adenocarcinoma
- Clear cell adenocarcinoma

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

**Adenosquamous carcinoma**

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

**Salivary gland tumours**
- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Epithelial-myoepithelial carcinoma
Table 2. IASLC/ATS/ERS Classification of Lung Adenocarcinoma in Resection Specimens [3].

<table>
<thead>
<tr>
<th>Adenocarcinoma</th>
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<tbody>
<tr>
<td><strong>Preinvasive lesions</strong></td>
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<tr>
<td>Atypical adenomatous hyperplasia</td>
</tr>
<tr>
<td>Adenocarcinoma in situ (≤3cm formerly BAC)</td>
</tr>
<tr>
<td>Nonmucinous</td>
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<tr>
<td>Mucinous</td>
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<tr>
<td>Mixed mucinous/nonmucinous</td>
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**Minimally invasive adenocarcinoma (≤3cm lepidic predominant tumor with ≤5mm invasion)**

| Nonmucinous                         |
| Mucinous                            |
| Mixed mucinous/nonmucinous          |

**Invasive adenocarcinoma**

| Lepidic predominant (formerly nonmucinous BAC pattern, with >5 mm invasion) |
| Acinar predominant                  |
| Papillary predominant               |
| Micropapillary predominant          |
| Solid predominant with mucin production |

**Variants of invasive adenocarcinoma**

| Invasive mucinous adenocarcinoma (formerly mucinous BAC) |
| Colloid                                              |
| Fetal (low and high grade)                          |
| Enteric                                              |
Figure 1. Algorithm for adenocarcinoma diagnosis in small biopsies and/or cytology [3].
Table 3. IASLC/ATS/ERS Classification of Lung Adenocarcinoma in small biopsies and cytology [3].

<table>
<thead>
<tr>
<th>2004 WHO Classification</th>
<th>SMALL BIOPSY/CYTOLOGY: IASLC/ATS/ERS</th>
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<tr>
<td>ADENOCARCINOMA</td>
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<td>Bronchioloalveolar</td>
<td>Adenocarcinoma with lepidic pattern</td>
</tr>
<tr>
<td>carcinoma (nonmucinous)</td>
<td>(if pure, add note: an invasive</td>
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<tr>
<td></td>
<td>component cannot be excluded)</td>
</tr>
<tr>
<td>Bronchioloalveolar</td>
<td>Mucinous adenocarcinoma (describe</td>
</tr>
<tr>
<td>carcinoma (mucinous)</td>
<td>patterns present)</td>
</tr>
<tr>
<td>Fetal</td>
<td>Adenocarcinoma with fetal pattern</td>
</tr>
<tr>
<td>Mucinous (colloid)</td>
<td>Adenocarcinoma with colloid pattern</td>
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<tr>
<td>Signet ring</td>
<td>Adenocarcinoma with (describe</td>
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<td>patterns present) and signet ring</td>
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<tr>
<td>Clear cell</td>
<td>features</td>
</tr>
<tr>
<td>No 2004 WHO counterpart</td>
<td>Morphologic adenocarcinoma patterns</td>
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<tr>
<td>– most will be solid</td>
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<tr>
<td>adenocarcinomas</td>
<td>stains):</td>
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<td></td>
<td>Non-small cell carcinoma, favor</td>
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<tr>
<td></td>
<td>adenocarcinoma</td>
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<tr>
<td>SQUAMOUS CELL CARCINOMA</td>
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<td>Papillary</td>
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<td>Clear cell</td>
<td>clearly present:</td>
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<tr>
<td>Small cell</td>
<td>Squamous cell carcinoma</td>
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<tr>
<td>Basaloid</td>
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<td>No 2004 WHO counterpart</td>
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<td>SMALL-CELL CARCINOMA</td>
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<td>Large cell neuroendocrine</td>
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<td></td>
<td>Non-small cell carcinoma with</td>
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<td>neuroendocrine(NE) morphology</td>
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<td>(positive NE markers), possib LCNEC</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>Non-small cell carcinoma with NE</td>
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<tr>
<td>with NE morphology</td>
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<td>(LCNEM)</td>
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<td>carcinoma where LCNEC is</td>
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<td>suspected, but stains failed to</td>
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<td>ADENOSQUAMOUS CARCINOMA</td>
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<td>squamous cell and adenocarcinoma</td>
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<td>patterns</td>
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<td>adenossquamous carcinoma.</td>
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<td>No counterpart in 2004</td>
<td>Morphologic squamous cell or</td>
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<td>but immunostain favor separate</td>
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<td>and adenocarcinoma components</td>
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<td>stains and the interpretation)</td>
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<td>Comment: this could represent</td>
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<td>adenossquamous carcinoma.</td>
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</table>
One of the major changes introduced in the new classification of ADC is the withdrawal of the term “bronchioloalveolar carcinoma” (BAC). Tumors with lepidic pattern are categorized according to the classification-specified criteria as ADC in situ, minimally invasive ADC, invasive ADC, lepidic predominant (formerly nonmucinous BAC) [4-9], invasive mucinous ADC (formerly mucinous BAC) [10-13], or lepidic pattern may comprise a minor component of invasive ADC of other type. Based on this classification, a more accurate prognostic stratification and prediction of molecular alterations can be achieved.

→ **We recommend the use of the WHO classification for all tumors, with the exception of ADC, for which we suggest the use of the recently proposed IASLC/ATS/ERS classification (Table 2).**

→ **We recommend the discontinuation of the term “BAC”.**

→ **For small (≤3cm), solitary adenocarcinomas with pure lepidic growth, we recommend the term “Adenocarcinoma in situ”, which defines patients who should have 100% disease specific survival if the lesion is completely resected.**

→ **For small (≤3cm), solitary, adenocarcinomas with predominant lepidic growth and small foci of invasion measuring ≤0.5cm, we recommend the new concept of “Minimally invasive adenocarcinoma” to define patients who have near 100%, disease-specific survival if completely resected.**

→ **For nonmucinous adenocarcinomas previously classified as mixed subtype where the predominant subtype consists of the former nonmucinous BAC, we recommend use of the term LPA and discontinuation of the term “mixed subtype”.**

→ **For adenocarcinomas formerly classified as mucinous BAC, we recommend they be separated from the adenocarcinomas formerly classified as nonmucinous BAC and, depending on the extent of lepidic versus invasive growth, that they be classified as mucinous AIS, mucinous MIA, or for overtly invasive tumors, “invasive mucinous adenocarcinoma”**.
Several recent studies classified lung ADC according to the predominant histologic type allowing for correlations with molecular and clinical characteristics of the tumors and for differentiation between multiple lung primary NSCLC from metastases [4, 14, 15]. Moreover, architectural subtypes such as micropapillary or solid are associated with adverse prognosis [4, 16-18] and solid carcinoma with signet ring cell features is related to the EML4-ALK fusion gene [19].

- For invasive adenocarcinomas, we suggest comprehensive histologic subtyping be used to assess histologic patterns semiquantitatively in 5% increments, choosing a single predominant pattern. Individual tumors are then classified according to the predominant pattern, and the percentages of the subtypes are also reported.

- In patients with multiple lung adenocarcinomas, we suggest comprehensive histologic subtyping may facilitate in the comparison of the complex, heterogeneous mixtures of histologic patterns to determine whether the tumors are metastases, or separate synchronous, or metachronous primaries.

- In patients with early-stage adenocarcinoma, we recommend the addition of “micropapillary predominant adenocarcinoma”, when applicable, as a major histologic subtype due to its association with poor prognosis.

Approximately 70% of lung carcinomas are diagnosed on biopsy material only [3]. The diagnosis of NSCLC should be minimized and replaced by diagnoses of more specific subtypes whenever possible, because of the differences in the molecular profile and treatment modalities applied in the subtypes of NSCLC. The tissue should be carefully managed. The least amount of tissue should be used to perform the necessary diagnostic stains for discrimination between the types of NSCLC and adequate tissue should be preserved for molecular tests. Differentiating between ADC and SCC can be often achieved with the use of mucin stains (presence of 5 PAS-diastase positive cells in
each of two high power fields of the tumor [1, 3]) and a panel of two antibodies (p63/TTF-1) with the possible addition of CK5/6 if necessary [20]. Patients with adenocarcinoma should be tested for EGFR mutations because patients with EGFR mutation-positive tumors may be eligible for first-line TKI therapy [21-23]. EGFR gene copy number determined by FISH has shown controversial results. In certain studies it has been related to response to EGFR TKIs [24, 25] while in others, mutation analysis is the most relevant method [26, 27]. Immunohistochemistry is not recommended for routine clinical use as a predictive marker for EGFR TKIs. Recent publications using EGFR-mutation specific antibodies raise the issue of immunohistochemical testing with these antibodies instead of mutation analysis for L858r and del19 [28, 29].

→ **For small biopsies and cytology, we recommend that NSCLC be further classified into a more specific histologic type, such as adenocarcinoma or squamous cell carcinoma, whenever possible.**

→ **We recommend that the term NSCLC-NOS be used as little as possible, and we recommend it be applied only when a more specific diagnosis is not possible by morphology and/or special stains.**

**Questions to be discussed**

- Which is the adequate tissue sample for molecular testing?
- Criteria for MIA are based on limited published data and require further validation. Persistent questions include what is the optimal method for measuring the size of the invasive component? Is 0.5 cm the best size cut off? Should criteria for MIA be different for mucinous versus non-mucinous tumors?
- The level of reproducibility for identifying predominant histologic patterns is untested. In particular, how should the lepidic pattern be distinguished from other invasive patterns such as acinar and papillary?
• Do tumors that meet criteria for MIA have 100% disease-free survival if the invasive component is predominantly solid, micropapillary or if they show giant cell and spindle cell components that fail to qualify for a diagnosis pleomorphic carcinoma?

• Does the micropapillary pattern have a similar poor prognostic significance in advanced stage and early stage or in relatively small amounts?

• Is immunohistochemical testing using EGFR mutation-specific antibodies a reliable method for predicting the presence of an EGFR mutation?

Pathology Recommendations

1. We recommend the use of the WHO classification for all tumors, with the exception of ADC, for which we fully adopt the use of the recently proposed IASLC/ATS/ERS classification (LOE IV, GOR A)

2. In order to minimize the diagnosis of NSCLC–NOS, immunohistochemical stains for TTF-1 and p63 are highly recommended. (LOE IV, GOR A)

3. Tissue samples should be evaluated on site to ascertain its quality. Management of tissue should be strategic both for diagnosis and molecular testing. (LOE IV, GOR A)

4. EGFR immunohistochemistry or FISH analysis are not currently recommended.

5. FISH and immunohistochemistry for EML4-ALK fusion gene should be performed in appropriate clinical settings.

6. The histologic material from pathology laboratories should be available upon request for further testing (molecular profile).
References


pathological marker to subclassify tumours with a significantly poor prognosis within small peripheral lung adenocarcinoma (≤20mm) with mixed bronchioloalveolar and invasive subtypes (Noguchi’s type C tumours). Histopathology 2005, 46(6):677-684.


3.2 CYTOPATHOLOGICAL CLASSIFICATION OF NSCLC  
Valeri R-M, Destouni Ch.

Many NSCLCs present at diagnosis in advanced stage and diagnosis is often obtained by cytology, either exfoliative or fine needle aspiration (FNA) (1,2,3). Also, in metastatic disease (serous cavity fluids, lymph nodes, liver, adrenals, etc.), cytologic examination is often the only one available.

The cytologic subtyping of NSCLC has recently become more important because of the emerging differences in medical treatment (personalized/target therapy) between squamous and nonsquamous cancer. It is therefore suggested that NSCLCs should be subgrouped into adenocarcinoma (ADC), squamous cell carcinoma (SCC), and NSCLC–not otherwise specified (NSCLC–NOS) (2,3).

Difficulties arise in a small number of cases because of a) poor differentiation, b) scant cellularity and c) tumors with mixed histology, but the adenosquamous carcinomas are rare (2-3%), (2,3,4).

In doubtful and unclassifiable cases, ancillary techniques, such as immunocytochemistry (ICC), should be applied.(1,2,3,4). ICC is more useful in Liquid Based Cytology (LBC) smears because of its reproducibility. (5,6).

- **Cytological material is usually the only material available for diagnosis of NSCLC.**
- **It can be a reliable tool for pulmonary carcinoma classification as ADC or SCC.**
- **In tumors with no clear-cut differentiation, immunocytochemistry could serve; otherwise, an NSCLC–NOS should be reported.**
Immunocytochemistry stains in the characterization of NSCLC subtypes

Most of the work has been concentrated on the expression of 4 markers: CK7, TTF-1, p63 and CK 5/6. Also, DPAS or Alcian Blue/PAS for ADC differentiation is suggested (2,3,7,8). Other recently described antibodies as napsin A (for ADC) and desmocollin-3 (for SCC) need more prospective investigation. (3).

It is recommended that undifferentiated NSCLCs are still reported as NSCLC with the qualification of “favour SCC/ADC” or “probably SCC/ADC” if the immunocytochemistry profile suggests a particular line of differentiation. (2)

The expression of miRNA in SCC is still controversial and needs to be further evaluated and validated. (3).

- A panel of antibodies can increase diagnostic accuracy (TTF-1-/p63+ and CK 5/6+ favour SCC, while CK7 +/ TTF-1 + favour ADC).
- Undifferentiated NSCLCs are still reported as ‘NSCLC favour SCC or ADC’ if molecular markers show appropriate positivity.
- MiRNA expression in SCC needs further investigation.

Molecular testing

Molecular testing for EGFR and KRAS mutations is of increasing clinical importance and cytologic material from FNAs and effusions (in LBC smears + cell blocks) can serve this purpose. It is considered suitable when >40% of the aspirated cells are tumor cells. (3,9,10,11)

Discrepancy in mutation status between primary tumors and corresponding metastases may exist (11). ALK-gene rearrangement can also be evaluated in cytologic material (3).

- Cytologic specimens (smears + cell blocks) are adequate for EGFR/KRAS mutations or ALK-gene rearrangement testing.
- EGFR and KRAS mutation status must be evaluated also in metastatic sites.
PROBLEMS/GREY ZONE

- Should the term “Large cell carcinoma” be rendered on cytology because it requires a surgically resected specimen for the final diagnosis?
- Also, Bronchoalveolar carcinoma (suggested as ADC in situ) should only be suspected on cytologic specimen?

Cytological diagnosis of large cell carcinoma and bronchoalveolar carcinoma could be implicated when smears are cellular with appropriate morphology and positive immunocytochemistry.

MESOTHELIOMA

Mesothelioma can be reliably diagnosed in serous effusions when appropriate morphology is present, two or more immunocytochemical markers for mesothelioma (calretinin, CK 5/6, N-cadherin, HBME-1, WT-1, and the newly described podoplanin) are positive and two or more immunocytochemical markers for adenocarcinoma (TTF-1, MOC 31,BG-8, CEA, CD 15, BER EP4, B72,3) are negative.

Recommendations

- Cytologic diagnosis, when performed by long experienced cytologists, is reliable both for identifying lung malignancy and for NSCLC subtyping (ADC/SCC). (LOE IV, GOR A)
- Cytologic results are considered acceptable for treatment planning mainly in cases when more invasive approaches are impracticable. (LOE IV, GOR A)
- In poorly differentiated and doubtful cases, the use of ancillary techniques, such as immunocytochemistry (CK7, TTF-1, p63, CK5/6), in LBC smears may be required to improve the diagnostic yield. (LOE IV, GOR B)
When specific diagnosis even after application of molecular markers is not feasible, then the diagnosis of NSCLC-NOS must be considered instead of large-cell carcinoma. (LOE IV, GOR B)

Effort should be made in order to obtain sufficient cytologic material for ancillary techniques and molecular procedures. (LOE IV, GOR A)

EGFR/KRAS mutations can be assessed in cytology material both in primary and metastatic site. (LOE IV, GOR B)

Molecular profiling in cytology material in experienced centers is feasible and could be considered as adequate although a tissue specimen is preferable. (LOE IV, GOR B)

References


4 EARLY STAGE NSCLC
4.1 SURGERY FOR STAGE I AND STAGE II

Dahabreh J, Barbetakis N.

Lung cancer remains the leading cause of death, worldwide, regardless of the achieved progress in surgery and chemo-radiotherapy. Patients who have early stage NSCLC (Stage I and II) without any mediastinal lymph node involvement are treated primarily with surgery and they represent the 25% to 30% of all lung cancer patients (1). The aim of surgery is to achieve complete resection of the visible or suspected disease. An incomplete resection, leaving visible tumor behind (R2), impairs the patient’s quality of life and confers no therapeutic advantage.

Stage I NSCLC, according to the last revised TNM Staging System for lung cancer (7th edition), proposed by the International Association for the Study of Lung Cancer (IASLC), includes T1aN0M0, T1bN0M0, T2aN0M0, while stage II includes patients with T1aN1M0, T1bN1M0, T2bN0M0, T2aN1M0, T2bN1M0, T3N0M0 (2).

T1 tumors are surrounded by lung parenchyma or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus). T1 tumor <2cm in greatest dimension belongs to T1a, tumor >2cm, but ≤3cm belongs to T1b).

T2 tumor ranges from 3cm to ≤7cm, in greatest dimension, may invade the main bronchus more than 2cm distant to the main carina, invades the visceral pleura, causes atelectasis or destructive pneumonitis in less than the entire lung (T2a tumor >3cm - ≤5cm. T2b is a tumor >5cm - ≤7cm in greatest dimension).

T3 tumor is that with greatest dimension more than 7cm or any T that invades chest wall (Pancoast tumors included), diaphragm, phrenic nerve, mediastinal
pleura, pericardium, or tumor of the main bronchus <2cm distal to the main carina without carinal involvement, or separate tumor nodule(s) in the same lobe.

T4 tumor is a tumor of any size that invades mediastinum, heart, esophagus, superior Vena Cava, aorta, recurrent laryngeal nerve, and vertebral body or that with tumor nodule(s) in a different ipsilateral lobe.

Regarding N lymph node involvement, there was no modification from the previous TNM staging system, while the M1 was separated in M1a, which is a tumor with tumor nodules in the contralateral lung or pleural dissemination and M1b are tumors with distant metastasis (3).

There are no randomized clinical trials comparing surgery alone to chemotherapy or radiotherapy alone in the treatment of patients with stage I disease and who are suitable candidates for surgical resection. The surgery offers the best hope of cure, based on a huge retrospective data (clinical experience). As it has been reported in the literature, neo–adjuvant chemotherapy for stage Ib and II is still considered an experimental modality of treatment because it has been evaluated in only small number of randomized trials. All patients with early stage NSCLC should be seen and evaluated by a thoracic surgeon to determine whether they are candidates for surgical exploration and resection.

**Recommendation:** For patients with clinical stage I and stage II NSCLC and no medical contraindication to operative intervention, surgical resection is recommended. (LOE I, GOR A)

Lobectomy in combination with systematic lymph node dissection or sampling is considered “standard of care” for stage I and II NSCLC, which offers a 5-year survival for patients stage Ia from 69% to 89%, for Ib 52% to 75%, for Ila 45% to 52% and 35% for stage IIb (4).
Pneumonectomy rarely is indicated in stage I or II and is indicated when the lobectomy or one of its modifications is not sufficient to remove all locoregional disease (4). Perioperative mortality (from the day of operation till 30 days postoperatively) is reported to be 3.7% in average and ranges from 1% to 7.6% and the morbidity and mortality are related to the cardio–pulmonary reserves, the co–existence of other risk factors (neo–adjuvant chemotherapy is included) and the experience of a specialized thoracic surgeon (4).

Silvestri et al., from South Carolina, mentioned that mortality was lower for those patients whose operation was performed by a board – certified thoracic surgeon as opposed to general surgeon (5). These results were confirmed by the retrospective review of the Medicare database (6). All patients who have early stage NSCLC need to be evaluated by a Thoracic Surgeon who makes the last decision regarding the safety of surgical therapy or not (1).

**Recommendation:** *For patients with clinical stage I and stage II NSCLC, it is recommended that they be evaluated by a thoracic surgical oncologist with a prominent part of his/her practice focused on lung cancer, even if patients are being considered for nonsurgical therapies.*  
 *(LOE I, GOR B)*

Limited resections (segmentectomy or large wedge resection) are the treatment of choice for patients with NSCLC stage I who have poor lung function and are unfit to undergo typical lobectomy or sleeve lobectomy (7). The results of the lung Cancer Study Group reported in 1995 (a prospective randomized trial) showed a threefold increase in local recurrence, a 75% increase in combined local and distant recurrence and a 50% increase of cancer death in case of limited resections compared with lobectomy (8). A retrospective study from Japan found no significant difference regarding hospital mortality, when compared limited resection to lobectomy (9). Sakurai et al. concluded in their retrospective study that there was no disadvantage for more limited resections when compared to lobectomy for patients with stage I bronchoalveolar carcinoma (tumor <3cm) (10).
Bronchoalveolar carcinoma (BAC) has different characteristics, compared to the other histologic types of NSCLC. T1 Tumor of BAC histologic type with the largest dimension \( \leq 2 \) cm, is treated by means of wedge or segmental resection even if the patient is fit to undergo major resection (11).

**Recommendations**

- **In patients with stage I and stage II NSCLC who are medically fit for conventional surgical resection, lobectomy or greater resection is recommended rather than sublobar resections (wedge or segmentectomy).** (LOE I, GOR A)

- **In patients with stage I NSCLC who may tolerate operative intervention but not a lobar or greater lung resection because of comorbid disease or decreased pulmonary function, sublobar resection is recommended over nonsurgical interventions.** (LOE I, GOR B)

- **In patients with infiltrative mucinous adenocarcinoma or invasive adenocarcinoma of lepidic predominance (former BAC) who are suitable surgical candidates, a limited resection may be performed, provided the surgical margins are free of disease, even if the patients can tolerate major resection.** (LOE I, GOR B)

Minimally invasive video–assisted Thoracoscopic Surgery (VATS) is implemented to perform wedge or segmental resection, lobectomy or pneumonectomy and is continuously more and more applied in many thoracic surgery centers.

Recently a meta-analysis reported similar locoregional recurrences for VATS lobectomy compared to open lobectomy, with lower distant recurrence rate and improved 5-year survival rate in favor of VATS lobectomy. The latter results may be partially related to a selection bias in the VATS group. Also VATS is associated with lower morbidity, shorter hospital stay and facilitates the delivery of adjuvant chemotherapy (12 - 15).
Recommendation: For patients with NSCLC Stage I who are considered appropriate candidates for VATS resection, the implementation of VATS by experienced thoracic surgeons familiar with these techniques is acceptable alternative to open thoracotomy. (LOE I, GOR B)

No randomized trials comparing sleeve lobectomy to pneumonectomy have been reported in the literature. There are only retrospective reviews of the outcomes in patients treated with sleeve lobectomy compared with subjects treated with pneumonectomy. Suen et al. reported a retrospective study with debatable advantages of sleeve lobectomy versus pneumonectomy in terms of operative mortality and survival (16).

Recommendations

➔ For patients with centrally or locally advanced NSCLC in whom a complete resection can be achieved with either technique, sleeve lobectomy is recommended over pneumonectomy. (LOE I, GOR B)

➔ For patients with N1 lymph node metastases (stage II) in whom a complete resection can be achieved with either technique, sleeve lobectomy is recommended over pneumonectomy. (LOE I, GOR B)

The extent of lymph node evaluation at the time of resection for Stage I or Stage II NSCLC remains a controversial issue. Two randomized trials have proved no difference in overall survival in patient undergoing a radical lymphadenectomy compared to those with lymph node sampling (13,14), while a third randomized trial by Wu et al. found improved survival for patients who underwent mediastinal lymph node dissection rather than sampling (15). A meta-analysis of three randomized trials for patients who underwent surgical treatment for early stage (I – IIIA) NSCLC found that 4-year survival was superior in patients with mediastinal lymph node dissection compared with sampling only (15). Lymph node dissection is associated with longer operative time and greater volume of postoperative fluid loss throughout the chest tubes, without alteration in the hospital stay duration. Both procedures
are safe and provide significant staging information, which may affect our
decision regarding the adjuvant chemotherapy. The current minimum
standard is a systematic sampling of each lymph node station draining a
tumor. For right sided resections, nodes should be taken from mediastinal
levels 2, 3, 4, 7, 8, and 9, as well as from the hilar and interlobar area (lymph
node groups 10 and 11). On the left, the lymph node stations that need
sampling are 5, 6, 7, 8 and 9, as well as the hilar and interlobar lymph nodes.
A randomized trial of mediastinal lymph node sampling versus complete
lymphadenectomy during pulmonary resection in patients with N0 or N1 (less
than hilar) NSCLC (ACOSOG Z0030 Trial) was presented at the Annual
meeting of the American Association of Thoracic Surgery in 2010. The
authors concluded that mediastinal lymph node dissection does not improve
survival nor decreases the incidence of local or distant recurrences (17) in
patients with early stage NSCLC when a thorough sampling of the mediastinal
lymph nodes is negative.

**Recommendation:** *Intraoperative systematic mediastinal lymph node
dissection or systematic sampling are recommended in patients who
undergo resection for NSCLC stage I or Stage II, for the need of accurate
pathologic staging. (LOE I, GOR B)*

Pancoast tumors are a relatively unusual presentation of NSCLC that occur at
the apex of the upper lobes and invades the adjacent anatomical structures. A
tumor of the apical segment of the upper lobe is classified as Pancoast tumor
or superior sulcus tumor when it invades the most superior ribs, or the lower
roots of the brachial plexus or the sympathetic chain, or the subclavian
vessels or the vertebrae. These tumors are divided into anterior, middle and
posterior compartment tumors, depending on the location of chest wall
invasion (18). Detailed discussion about the surgical treatment of these
tumors is included in the surgical treatment of stage III, as these tumors are
locally advanced except for the cases with N0 disease, without vertebral
invasion.
Recommendations

➔ Patients with potentially resectable, non-metastatic Pancoast tumor, who have good performance status, are recommended to have neo-adjuvant chemo-radiotherapy. (LOE I, GOR B)

➔ Every effort must be made to achieve a complete resection in case of surgical resection of Pancoast tumor. (LOE I, GOR A)

➔ Resection of Pancoast tumor consists of lobectomy combined with the resection of the involved adjacent anatomic structures instead of limited resection. (LOE I, GOR C)

Conclusions

Clinical experience and randomized trials, as well as meta-analysis, indicate that treatment of choice for patients with NSCLC stage I or stage II remains the surgical resection by means of lobectomy, rarely pneumonectomy, and limited resection for patients who are not able to tolerate major resections.

Summary of Recommendations

1. For patients with clinical stage I and stage II NSCLC and no medical contraindication to operative intervention, surgical resection is recommended. (LOE I, GOR A)

2. For patients with clinical stage I and stage II NSCLC, it is recommended that they be evaluated by a thoracic surgical oncologist with a prominent part of his/her practice focused on lung cancer, even if patients are being considered for non-surgical therapies. (LOE I, GOR B)

3. In patients with stage I and stage II NSCLC who are medically fit for conventional surgical resection, lobectomy or greater resection are recommended rather than sub-lobar resections. (LOE I, GOR A)
4. In patients with stage I NSCLC who may tolerate operative intervention but not a lobar or greater lung resection because of co-morbid disease or decreased pulmonary function, sublobar resection is recommended over non-surgical interventions. (LOE I, GOR B)

5. In patients with BAC, who are suitable surgical candidates, a limited resection may be performed, provided the surgical margins are free of disease, even if the patients can tolerate major resection. (LOE I, GOR B)

6. For patients with NSCLC Stage I, who are considered appropriate candidates for VATS resection, the implementation of VATS by experienced thoracic surgeons who are familiar with these techniques is an acceptable alternative to open thoracotomy. (LOE I, GOR B)

7. For patients with centrally or locally advanced NSCLC in whom a complete resection can be achieved with either technique, sleeve lobectomy is recommended over pneumonectomy. (LOE I, GOR B)

8. For patients with N1 lymph node metastases (stage II) in whom a complete resection can be achieved with either technique, sleeve lobectomy is recommended over pneumonectomy. (LOE I, GOR B)

9. Intraoperative systematic mediastinal lymph node dissection or sampling is recommended in patients who undergo resection for NSCLC stage I or Stage II, for the need of accurate pathologic staging. (LOE I, GOR B)

10. Patients with potentially resectable, non-metastatic Pancoast tumor, who have good performance status, are recommended to have neo-adjuvant chemo-radiotherapy. (LOE I, GOR B)

11. Every effort must be made to achieve a complete resection in case of surgical resection of Pancoast tumor. (LOE I, GOR A)

12. Resection of Pancoast tumor consists of lobectomy combined with the resection of the involved adjacent anatomic structures, instead of sublobar resection. (LOE I, GOR C)
References


4.2 EARLY STAGE, MEDICALLY INOPERABLE NSCLC

Τριχάς Μ.

- Οι θεραπευτικές αποφάσεις πρέπει να λαμβάνονται κατόπιν συμβουλίου ή συζήτησης από ομάδα διαφορετικών ειδικοτήτων που περιλαμβάνει χειρουργό-ογκολόγο, ακτινοθεραπευτή-ογκολόγο, παθολόγου-ογκολόγο, πνευμονολόγο, παθολόγου-ανατόμο, ακτινολόγο.

- Η ακτινοθεραπεία (ΑΚΘ) πρέπει να χορηγείται ως κύρια θεραπεία σε ασθένεις που, για ιατρικούς λόγους, δεν μπορούν να χειρουργηθούν.

- Οι ασθενείς σταδίου I ή II ΜΜΚΠ μη εξαιρέσιμο για ιατρικούς λόγους πρέπει να υποβάλλονται σε Στερεοτακτική Ακτινοθεραπεία ή σε συνεχή υπερκλασιματοποιημένη επιταχυνόμενη ακτινοθεραπεία (CHART regimen). Αν δεν υπάρχει η υποδομή για τις ανωτέρω θεραπείες, τότε υποβάλλονται σε κλασική ριζική ακτινοθεραπεία.
4.3 ADJUVANT CHEMOTHERAPY IN NSCLC

Pathologic staging is the most important prognostic factor determining the likelihood of relapse. The most extensive data correlating stage with prognosis come from a series of over 31,000 cases from the Surveillance, Epidemiology and End Results (SEER) database used to validate the 7th TNM staging system. Survival decreased progressively with more advanced disease. For stages IA, IB, IIA, IIB, IIIA, and IIIB, the median survivals were 59, 48, 30, 24, 14, and 9 months, respectively. These data underscore the need for effective adjuvant therapy in all stages of resected NSCLC.

Stage IA

For patients with completely resected stage IA NSCLC, postoperative chemotherapy is not recommended. There are very little data available on this subset of patients because most randomized adjuvant trials have excluded patients with stage IA disease extent. From the lung adjuvant cisplatin evaluation meta-analysis\(^1\), there was no benefit for postoperative adjuvant cisplatin-based chemotherapy among 347 stage IA NSCLC patients. Patients with stage IA disease did worse with adjuvant chemotherapy (HR 1.40 (95% CI 0.95-2.06).

Are there any stage IA patients with who might benefit from adjuvant chemotherapy?

**Recommendation:** For patients with completely resected stage IA NSCLC, the use of adjuvant chemotherapy is not recommended for routine use outside the setting of a clinical trial. (LOE I, GOR A)

Gene expression profiling — Multiple gene expression profiles are being developed that may be useful in defining favorable and unfavorable prognostic subsets. If these results are validated in prospective trials, gene expression profiles have the potential to identify a high-risk group of patients with stage I disease, including stage IA, who might benefit from adjuvant chemotherapy.
At this time, treatment recommendations based on gene expression profiling cannot be supported by the available data.

Stage IB
For patients with stage IB NSCLC, the majority of recent studies\textsuperscript{2-4} have not found a statistically significant benefit for this subset of patients. One study\textsuperscript{5} has reported benefit, although the results were so different from the other trials as to call into question the validity of its findings. The lung adjuvant cisplatin evaluation meta-analysis\textsuperscript{1} found a trend toward improvement in survival in 1,371 stage IB patients randomized to postoperative cisplatin-based chemotherapy over surgery alone, with an 8\% reduction in the risk of death associated with chemotherapy, but this difference was not statistically significant. The Cancer and Leukemia Group B investigators conducted an exploratory analysis of the effectiveness of adjuvant paclitaxel/carboplatin chemotherapy in those patients with primary tumors >4 cm. In this analysis\textsuperscript{4}, there continued to be a statistically significant benefit for these stage IB patients. This finding opened a still unsolved controversy of whether patients with stage IB tumors should be treated with systemic adjuvant chemotherapy. In the new UICC 7 classification, T2 N0 tumors >5 cm in diameter will be reclassified as stage IIA instead of IB, which could solve this controversy.

Should we treat patients with tumors greater than 4 cm, or grade III, with adjuvant chemotherapy?

Recommendation: For patients with completely resected stage IB NSCLC, the use of adjuvant chemotherapy is not recommended for routine use. In patients with high risk features, adjuvant chemotherapy might be an option. (LOE I, GOR B)

Studies from Japan have evaluated the use of oral uracil/tegafur (UFT) as an adjuvant therapy to surgery in early stage NSCLC. Results from these randomized adjuvant trials have been mixed. The single largest trial\textsuperscript{6} randomized completely resected stage I adenocarcinoma patients to oral UFT
for 2 years or no postoperative therapy. With a median follow-up of >6 years, the 5-year survival rates were 88% in the UFT group and 85% in the control group (p = 0.047). Subset analyses found the greatest benefit in the T2N0, stage IB patients. Of concern was the lack of benefit for disease-free survival. A meta-analysis\(^7\) of the effectiveness of adjuvant UFT has also been conducted. This included results from 2,003 patients and compared outcome of single-agent adjuvant oral UFT to surgery alone. UFT was associated with a significant improvement in overall survival (hazard ratio, 0.74; 95% confidence interval, 0.61 to 0.88; p =0.001). There are no confirmatory data on the use of adjuvant oral UFT outside of Japan.

*Although the results are encouraging, oral UFT or another oral fluoropyrimidine cannot be recommended as adjuvant therapy at this time.*

**Stage II and IIIA**

Data for the use of adjuvant cisplatin-based chemotherapy in stage II and IIIA NSCLC are strong. The International Adjuvant Lung Trial, National Cancer Institute of Canada JBR.10, and Adjuvant Navelbine International Trialist Association (ANITA) studies all found significant benefit for the use of adjuvant chemotherapy in the general population of NSCLC studied, as well as in the stage II and IIIA patient subsets\(^5\). The lung adjuvant cisplatin evaluation meta-analysis\(^1\) of the 1,616 stage II patient subset found a 27% reduction in the risk of death (hazard ratio, 0.83; 95% confidence interval, 0.73 to 0.95) and 27% reduction in the risk of death in stage IIIA (HR 0.83 (95% CI 0.72-0.94).

**Recommendations**

- For patients with stage II and IIIA NSCLC who are willing and able to tolerate adjuvant chemotherapy, treatment with a cisplatin-based doublet is recommended (LOE I, GOR A)
- A reasonable option is the combination of vinorelbine plus
cisplatin as used in the JBR.10 and ANITA trials. (LOE I, GOR A)

- Based on evidence from metastatic setting, other modern cisplatin-based regimens may be considered.
- The role of carboplatin-based combinations as an adjuvant remains uncertain.

ERCC1 expression — Immunochemical detection of ERCC1 expression in a primary NSCLC may be a predictor for lack of benefit from platinum-based adjuvant chemotherapy. This was suggested in an analysis of 761 tumors from patients enrolled in the IALT trial. Adjuvant chemotherapy resulted in a significant improvement in 5-year survival (HR 0.65) for patients whose tumors did not express ERCC1. In contrast, chemotherapy was associated with a non-significant trend toward worse 5-year survival with adjuvant chemotherapy (HR 1.14) when ERCC1 was expressed on the tumor.

K-ras and p53 — Abnormalities in these genes were studied in a subset of 253 patients from the JBR.10 adjuvant chemotherapy trial. Patients with mutations in k-ras in their tumor did not appear to benefit from adjuvant chemotherapy, while those with wild-type k-ras did significantly better.

Overexpression of the p53 gene as assessed by immunohistochemistry was associated with a significantly poorer prognosis compared to those who were negative for p53 overexpression, but the benefit from adjuvant chemotherapy was greater among those with p53 overexpression. Patients with mutations in p53 did not appear to benefit from adjuvant chemotherapy.

DNA methylation markers — Methylation of the promoter region of four genes thought to be important in the pathogenesis of lung cancer (p16, CDH13, APC, and RASSF1A) has been associated with a significantly increased risk of recurrent NSCLC. In a study of 167 patients who underwent potentially curative resection of stage I NSCLC, including 51 who relapsed within 40 months after surgery, the absence of promoter methylation
correlated with higher rates of subsequent recurrence-free survival. As with other molecular markers, these results require confirmation in a larger prospective study before they can be used to select patients for adjuvant therapy.

- **At this time, treatment recommendations based on ERCC1, K-ras, p53 or DNA methylation markers analysis cannot be supported by the available data. Whether these patients would benefit from any form of adjuvant therapy – including non-platinum regimens – is unknown.**

**Molecularly Targeted Agents** — There is no evidence that Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (erlotinib, gefitinib) have a role in an adjuvant setting.

**Elderly patients** — The available data suggest that older adults with resected NSCLC should not be excluded from receiving adjuvant chemotherapy based upon age. The decision to pursue such therapy should consider both the potential benefits of such treatment and the health of the individual patient. The LACE meta-analysis found that efficacy was not significantly different in elderly compared to younger patients, even though older patients received lower doses and fewer cycles of chemotherapy\(^{11}\). In addition, no differences in severe toxicity were observed.

The increased difficulty in administering chemotherapy in older patients is illustrated by the subset analysis of JBR.10, in which 32 percent were more than 65 years of age\(^{12}\). The older patients received fewer cycles of chemotherapy (median three versus four cycles in those ≤65 years). Despite this, adjuvant chemotherapy was associated with a survival benefit in those >65 years that was similar to that in younger patients.

Neither of these analyses can be generalized to assess the role of adjuvant chemotherapy in the broader population of older patients, since those enrolled in
these adjuvant chemotherapy trials represent a group that is probably substantially different than those of similar age who were not enrolled and may even be more fit than some of the younger patients entered into the protocol.

Furthermore, elderly patients have not been well represented in adjuvant trials; as a result, the data are scarce and recommendations must be made on an individual basis.

Recommendations

- For carefully selected older (>70 yrs old) patients with resected stages IB, II, and IIIA NSCLC, adjuvant chemotherapy using the same chemotherapy regimens as for younger patients is suggested. (LOE II, GOR B)
- The decision of whether or not to use adjuvant chemotherapy in elderly adults must be individualized.
- A comprehensive geriatric analysis may be useful prior to making a decision about whether or not to proceed with adjuvant chemotherapy.
References


4.4 NEOADJUVANT CHEMOTHERAPY IN EARLY STAGE NSCLC

Μπριασούλης Β., Παπακοτούλας Π.

Neoadjuvant or preoperative chemotherapy is still considered an experimental modality of treatment mainly because it has been evaluated in only a small number of randomized trials, exploring the safety and activity of different platinum regimens. Theoretically, the neoadjuvant approach has a number of advantages: it can reduce the tumor volume and facilitate the control of micrometastatic diffusion or prevent it; the neoadjuvant treatment allows a careful evaluation of chemotherapy response giving critical information on tumour biology in adequate tumour samples; the compliance of chemotherapy in untreated patients is certainly better than after surgery and its dose intensity higher. On the other hand, its toxicities and a delay to surgery could be disadvantages, although up to now these issues seem to be scarcely relevant.

A meta-analysis based upon seven trials involving 988 patients suggested that neoadjuvant chemotherapy improved survival with a HR of 0.82 (95% CI 0.69–0.97), equivalent to an absolute benefit of 6% at 5 years. They furthermore found an incremental benefit by stage: stage IA: + 4%, stage IB: 6%; stage II–III: + 7%, but did not observe any interaction between the kind of platinum-containing regimen, or the kind of adjuvant treatment (chemo- or radiotherapy). The exploratory nature of these subgroup analyses warrants an IPD approach, which is ongoing. When the mature results of the European Intergroup trial added to the previous meta-analysis a shift of the hazard ratio observed to 0.87, with loss of the significance of the improvement in outcome.

The range of results observed with neoadjuvant chemotherapy is illustrated by several contemporary phase III trials:

In a French trial, 355 patients with NSCLC (stage IB, II, or IIIA, including 35 percent with N2 disease) were randomly assigned to surgery with or without two cycles of preoperative cisplatin-based chemotherapy. Responding patients were eligible for postoperative chemotherapy as well. Neoadjuvant
chemotherapy was associated with a trend toward a longer median disease-free survival (p=0.15). At a median follow-up of 14 years, the 10-year recurrence-free survival rate was significantly increased with chemotherapy plus surgery compared to surgery alone (HR 0.78 95% CI 0.62-0.98). There was a trend toward increased overall survival with neoadjuvant chemotherapy compared to surgery alone (p=0.12), and the difference was statistically significant when multivariate analysis incorporated age, T stage, and N stage (HR 0.69 95% CI 0.64-0.90).

In the multicenter European LU22 trial, 519 patients with resectable NSCLC were randomly assigned to three cycles of platinum-based chemotherapy followed by surgery or to immediate surgery. At randomization, 93 percent of patients had clinical stage I or II disease. The chemotherapy regimen varied at different sites; the two most widely used combinations were vinorelbine plus cisplatin and gemcitabine plus cisplatin. Overall 75 percent of patients completed all three cycles of chemotherapy, and the objective response rate to chemotherapy was 47 percent. Despite the observed antitumor activity from chemotherapy, there was no improvement in PFS with neoadjuvant treatment (HR for recurrence 0.96, 95% CI 0.77-1.21). Similarly, there was no improvement in overall survival with preoperative chemotherapy (five-year survival 44 versus 45 percent, HR for death 1.02, 95% CI 0.80-1.31). Results were not reported as a function of stage. The negative results in this trial may be attributed to the very high percentage of patients enrolled with stage I disease. This trial also underscores the difficulties in accurately staging patients preoperatively, as 59 percent of patients on the control arm (surgery alone) had either pathological upstaging or downstaging at the time of surgery.

In Southwest Oncology Group trial SWOG 9900, 354 patients with resectable stage IB-IIIA NSCLC were randomly assigned to three cycles of chemotherapy with paclitaxel plus carboplatin followed by surgery or immediate surgery. PFS was prolonged with neoadjuvant chemotherapy compared to immediate surgery (HR 0.80 95% CI 0.619-1.04). Overall
survival was also non-significantly longer with neoadjuvant chemotherapy (median 62 versus 41 months, HR 0.79, 95% CI 0.60-1.06). The trial was terminated prematurely when positive results were obtained in large trials using adjuvant chemotherapy.

Neoadjuvant and adjuvant chemotherapy were compared to surgery alone in the three-armed NATCH trial. In this trial, 624 patients with IA, IB, II, or III (T3N1) NSCLC were randomly assigned to surgery alone, neoadjuvant chemotherapy followed by surgery, or surgery followed by adjuvant chemotherapy. Chemotherapy consisted of three cycles of paclitaxel plus carboplatin. Compliance with chemotherapy was significantly higher with neoadjuvant rather than adjuvant chemotherapy (90 percent versus 61 percent receiving three cycles of chemotherapy). Despite this, there were no significant differences in the five-year disease-free survival rates (34, 38, and 37 percent for surgery alone, neoadjuvant chemotherapy, or adjuvant chemotherapy, respectively) or five-year overall survival rates (44, 47, and 46 percent, respectively) possibly due to the predominance of stage I patients.

A smaller European trial randomly assigned 141 patients to chemotherapy with gemcitabine plus cisplatin followed by surgery or to surgery alone. There was a trend toward improved overall three-year survival with the combined modality approach (p=0.053). In a subset analysis, the benefits appeared to be limited to patients with stage IIB/IIIA disease (three-year overall survival 70 versus 47 percent). The trial was terminated prematurely when positive results were obtained in large trials using adjuvant chemotherapy.

A common feature of these trials is that they have all been confronted with accrual problems, leading in some studies to their early closure, when the results of randomized trials showing a benefit of adjuvant chemotherapy were published.
Besides their low power and accrual, these trials have two further weaknesses in common: the survival in their control arms treated with immediate surgery is better than initially estimated, confounding the underpowering caused by the early closure of these trials; stage I (clinical or pathological) accounted for >50% of the enrolment and, hence, of the better than expected survival.

As the accumulated evidence in the adjuvant setting has not found a statistically significant survival benefit for adjuvant chemotherapy in stage I disease, the implication of this finding in the neoadjuvant setting might imply that a possible benefit for higher stages has been diluted by the majority of stage I cases.

Decisions on giving neoadjuvant chemotherapy depend upon accurate clinical staging, while the decision to give adjuvant therapy is based upon the more accurate pathologic staging. Although 98 percent of patients in the NATCH trial had clinical stage I or II disease at protocol entry, 28 percent of those who underwent immediate surgery (with or without adjuvant chemotherapy) were reclassified as pathologic stage III based upon surgical findings.

The results of these trials and the meta-analysis do not support the use of a neoadjuvant approach in stage I, II rather than immediate surgery with postoperative adjuvant chemotherapy for patients with resectable NSCLC.

Can preoperative cisplatin-based combination chemotherapy be considered in patients with stage IIIA–N2 disease?
References


4.5 FOLLOW-UP AND SURVEILLANCE OF THE LUNG CANCER PATIENT TREATED WITH CURATIVE INTENT

Kosmas Ch.

→ In lung cancer patients treated with curative intent therapy, follow-up for complications related to the curative intent therapy should be managed by the appropriate specialist and should probably last at least 3 to 6 months. At that point, the patient should be reevaluated by the multidisciplinary tumor board for entry into an appropriate surveillance program for detecting recurrences and/or metachronous tumors. (LOE II, GOR C)

→ In lung cancer patients treated with curative intent therapy, and those having adequate performance and pulmonary functions, surveillance with a history, physical examination, and imaging study (CT of chest and upper abdomen) is recommended every 6 months for 2 years and then annually. All patients should be counseled on symptom recognition and be advised to contact their physician if worrisome symptoms were recognized. (LOE I, GOR C)

→ Ideally, surveillance for recognition of a recurrence of the original lung cancer and/or development of a metachronous tumor should be coordinated through a multidisciplinary team approach. If possible, the physician who diagnosed the primary lung cancer and initiated the curative intent therapy should remain as the health-care provider overseeing the surveillance process. (LOE II, GOR C)

→ In lung cancer patients following curative intent therapy, use of blood tests, PET scanning, sputum cytology, tumor markers, and fluorescence bronchoscopy is not currently recommended for surveillance. (LOE II, GOR C)

→ Lung cancer patients who smoke should be strongly encouraged to stop smoking, and offered pharmacotherapeutic and behavioral therapy, including follow-up. (LOE I, GOR A)
5 STAGE III NSCLC

5.1 THE ROLE OF POST-OPERATIVE RADIOTHERAPY

Kouloulias V, Trichas M.

Recommendations

➔ For patients with completely resected stage IA or IB NSCLC, postoperative radiotherapy is associated with a decreased survival and is not recommended. (LOE I, GOR B)

➔ For patients with completely resected stage II NSCLC, postoperative radiotherapy decreases local recurrence but a survival benefit has not been clearly shown; therefore, postoperative radiotherapy is not recommended. (LOE I, GOR B)

➔ In patients with resected NSCLC who were found to have incidental (occult) N2 disease (IIIA1–2), adjuvant postoperative radiotherapy should be considered after adjuvant chemotherapy to reduce local recurrence. (LOE II, GOR C)
5.2 NEO-ADJUVANT CHEMOTHERAPY, CHEMORADIOOTHERAPY

Mountzios J.

5.2.1 Neoadjuvant chemotherapy versus surgery alone

Locally advanced or stage III disease accounts for <30% of patients with NSCLC. Locally advanced NSCLC has been for many years divided into stage IIIA with a 24% 5-year survival, and stage IIIB with a worse prognosis and 5-year survival of 9%. Stage IIIA NSCLC represents a heterogeneous group of patients whose tumour extension is restricted to the affected lung (T3 N1) but also includes patients with metastatic disease to the ipsilateral mediastinal lymph nodes (T1-3 N2). The poor survival with surgery alone has led to efforts to add chemo- and/or radiotherapy to the locoregional treatment in locally advanced disease, either in the adjuvant or the neoadjuvant setting. Neoadjuvant chemotherapy and chemo-radiotherapy have been evaluated mainly in the stage IIIA setting, since stage IIIB disease is treated with definitive chemoradiotherapy.

Two large individual-data meta-analyses [1, 2] comparing neoadjuvant [1, 7 trials] or peri-operative [2, 5 trials] chemotherapy to surgery alone suggested a significant survival benefit from the addition of chemotherapy, ranging at 5 years from 6% to 14% albeit weakened by confounding factors as the non-homogeneity of the patients included, the inadequate sample size and the variable addition of postoperative treatments. The analysis by stage shows a 6%–7% absolute benefit in 5-year survival in CIIIA patients, improving their outcome from 15%–35% to 21%–42%. Specific data regarding the subset IIIA–N2 are, however, lacking.

- Neoadjuvant chemotherapy is mostly applied in stage IIIA-N2 (TNM 7th edition) disease since IIIA-N1 disease is usually treated by surgical resection and IIIB disease is generally treated with definitive chemoradiotherapy.

- A significant survival benefit in favor of neoadjuvant platinum-based chemotherapy as compared to surgery alone is present in stage IIIA NSCLC ranging from 6% to 14% at 5 years.
5.2.2 Neoadjuvant versus perioperative chemotherapy

In a recent meta-analysis of 10 trials using pooled data [3], a marginal survival benefit of adding platinum-based neoadjuvant chemotherapy in resectable IIIA NSCLC patients treated with surgical resection and adjuvant chemotherapy was demonstrated (HR=0.81, 95%CI: 0.67-0.97). However, this was a pooled-data meta-analysis in heterogenous populations treated with various regimens of platinum-based chemotherapy and there were no specific data regarding the subset IIIA–N2.

- Addition of neoadjuvant cisplatin-based chemotherapy offers a marginal survival benefit in patients with resectable IIIA disease treated with surgical resection and adjuvant chemotherapy.

5.2.3 Induction chemotherapy followed by surgical resection or definitive radiotherapy

In a large EORTC trial [4], patients with documented IIIA due to unresectable (bulky) N2b disease NSCLC received as induction chemotherapy three cycles of platinum-based chemotherapy: 332 responding patients were then randomly allocated to receive surgery or radiotherapy, the latter consisting of at least 60 Gy to the primary tumour and 40–46 Gy to mediastinum; PORT was later given to 62 (40%) patients in the surgical arm. Median survival time and 5-year overall survival rates were 16.4 months and 16% in the surgical arm, and 17.5 months and 14% in the radiotherapy arm. In the surgery arm only 50% resulted in complete resection due to the study design.

- Surgery does not improve overall or progression-free survival compared with radiotherapy in stage IIIA-N2b patients responding to induction chemotherapy.
5.2.4 Induction chemo-radiotherapy followed by surgical resection or radiotherapy

In the phase III randomized North American Intergroup Trial [5], 492 patients with pathologically documented stage IIIA–N2 NSCLC were randomly assigned to either concurrent chemoradiation therapy (two cycles of cisplatin and etoposide, plus radiotherapy interrupted at 45 Gy) followed by surgery (trimodality treatment), or the same chemoradiotherapy regimen with uninterrupted definitive radiotherapy up to 61 Gy. Two additional consolidation cycles of cisplatin and etoposide were given in both groups. Overall survival was not significantly improved with the addition of surgery even though progression-free survival was significantly better and local-only relapse rates were lower in patients who underwent trimodality treatment. The most probable reason for the observed lack of improved outcome with surgery relates to the exceedingly high mortality rate after pneumonectomy, mainly attributable to acute respiratory distress syndrome and other respiratory causes, and not observed in other centers or single institutional series. The authors did an exploratory matching analysis between resected and not resected patients, which led to the hypothesis that trimodality treatment could be beneficial if a complete resection with lobectomy is done after induction chemoradiotherapy, and if the increased surgical mortality associated with pneumonectomy is avoided. This type of analysis is, however, prone to bias because of the absence of matching for other possible prognostic factors such as gender, age and different biomarkers.

- In patients with stage IIIA-N2 disease and PS<2, induction chemoradiotherapy with cisplatin-etoposide followed by either surgical resection or thoracic radiotherapy are both valid options with comparable outcomes.
- Surgery should be avoided in low volume centers when pneumonectomy will be required because of increased post-operative morbidity and mortality.
- In downstaging mediastinal IIIA-N2 disease after induction CRT, surgery could be an option in multidisciplinary team approach.
In both trials local control with surgery is better than with radiotherapy, as the locoregional relapse rate in the EORTC study was higher with radiotherapy and progression-free survival was better in the Intergroup trial. Although this observation can be credited to the surgical resection only, it cannot be excluded that the administration of PORT in the EORTC trial and an imbalance in the consolidation chemotherapy in the Intergroup trial are responsible for this finding, as both modalities have been shown to reduce local control. This finding suggests a role for resection as consolidation after definitive chemoradiotherapy. Exploratory subgroup analyses of both trials show an improved outcome in patients who are downstaged, and/or in whom a complete resection can be obtained with a lobectomy, as compared with either operated patients without these features, or matched irradiated patients. This finding requires further validation in an adequately designed trial in which patients downstaged after definitive chemoradiotherapy are randomly allocated to either consolidation resection or not.

**Question:** Is the role of resection as a “consolidation” treatment to reduce local relapse after downstaging from definitive chemoradiotherapy?

### 5.2.5 Induction chemotherapy followed by chemo-radiotherapy versus chemoradiotherapy followed by consolidation chemotherapy

Recent data from four randomized phase III trials have suggested that there is no survival advantage to adding induction chemotherapy (various regimens) prior to concurrent chemo-RT. In two other studies conducted by SWOG and the Hoosier Oncology Group, it was reported that there is no survival benefit to adding consolidation chemotherapy after concurrent chemo-RT. The two strategies (induction and consolidation chemotherapy) have been compared in two randomized trials. In the first one, unresectable stage III NSCLC patients received CDDP (60 mg/m²), GEM (1g/m², days 1 and 8) and VNR (25mg/m², days 1 and 8) with reduced dosage of GEM and VNR during
radiotherapy (66 Gy). Two cycles of CT with radiotherapy followed by two further cycles of CT alone were administered in arm A or the reverse sequence in arm B. The study, which was prematurely closed due to poor accrual, showed that chemoradiotherapy with CDDP, GEM, and VNR appears feasible both as initial treatment, or after induction chemotherapy. Induction chemotherapy followed by chemoradiotherapy seemed less toxic with better observed response rates. In the second randomized phase II study [6], patients were randomly assigned to receive two cycles of docetaxel (D) 75 mg/m² on day 1 and cisplatin (C) 40 mg/m² on days 1 and 2, either preceding (IND arm) or following (CON arm) concurrent CT-RT, where 66 Gy was delivered using involved-fields concurrent with weekly D 20 mg/m² and C 20 mg/m².

The study showed that both modalities shared similar efficacy and toxicities, since the rate of grade III-IV esophagitis did not differ significantly between the two groups.

- **Induction, or consolidation chemotherapy in inoperable stage III NSCLC, has not shown survival benefit as compared to definite chemoradiotherapy alone.**
- **Induction and consolidation chemotherapy associated with definitive chemoradiotherapy in inoperable stage III NSCLC share similar efficacy and toxicity profiles.**
Recommendations

→ Neoadjuvant chemotherapy is mostly applied in stage IIIA-N2 (TNM 7th edition) disease, since IIIA-N1 disease is usually treated by surgical resection and IIIB disease is generally treated with definitive chemoradiotherapy. (LOE I, GOR A)

→ Neoadjuvant platinum-based chemotherapy is strongly recommended as compared to surgery alone in stage IIIA NSCLC (LOE I, GOR A)

→ Neoadjuvant cisplatin-based chemotherapy in patients with resectable IIIA disease followed by surgical resection and adjuvant chemotherapy may represent an alternative to upfront surgical resection in selected patients (LOE II GOR C)

→ Surgery does not improve overall or progression-free survival compared to definitive radiotherapy in stage IIIA-N2b patients responding to induction chemotherapy. (LOE II, GOR B)

→ In patients with stage IIIA-N2 disease and PS<2, induction chemoradiotherapy (CRT) followed by either surgical resection or thoracic radiotherapy are both valid options with comparable outcomes. Surgery should be avoided in low volume centers when pneumonectomy will be required because of increased post-operative morbidity and mortality. In downstaging mediastinal IIIA-N2 disease after induction CRT, surgery could be an option in multidisciplinary team approach. (LOE II, GORC)

→ Induction or consolidation chemotherapy in inoperable stage III NSCLC have not shown survival benefit as compared to definite chemoradiotherapy alone and are generally not recommended. Induction and consolidation chemotherapy associated with definitive chemoradiotherapy in inoperable stage III NSCLC share similar efficacy and toxicity profiles. (LOE II, GOR C)
III NSCLC

III A-N1

Surgery

Adjuvant chemotherapy

Surgery + adjuvant chemotherapy

Thoracic radiotherapy

III A-N2

Induction chemotherapy± radiotherapy

IIIB

Definitive chemoradiotherapy
References


The majority of patients with NSCLC have advanced disease at initial diagnosis, representing 28% of all lung cancer cases. Treatment of this interesting group continues to be controversial and challenging and has been the subject of a wide variety of clinical trials. Recommendations for this stage are generally weak because of lack of large randomized trials and inhomogeneity in the population included in this stage. According to the TNM staging system, proposed by the International Association for the Study of Lung Cancer (IASLC) (1), stage III is separated into IIIA and IIIB. Patients who have $T_{1-2}N_{2}M_{0}$, $T_{3}N_{1-2}M_{0}$, $T_{4}(\text{ipsilateral nodule/s})N_{1-2}M_{0}$, belong to stage IIIA, while patients with $T_{1-4}N_{3}M_{0}$, and $T_{4}(\text{invasion})N_{0-2}M_{0}$, belong to stage IIIB.

**Stage IIIA N1-2, Chest wall invasion**

Patients with NSCLC that invades the chest wall, rarely have N1 or N2 disease (Pancoast tumors included), and whenever surgery is performed, every effort must be made to achieve a complete resection. Yokoi et al. reported on $T_{3}N_{1-2}M_{0}$, with a 5-year survival rate of 18% (2). Long-term survival is affected positively by the completeness of resection and the absence of N1 or N2 disease (3).

**Recommendations**

1. **For patients with chest wall invasion and N2 disease, surgical resection is not recommended.** (LOE II, GOR C)
2. **Pancoast tumor stage IIIA, because of N2 disease, is not recommended to be treated surgically.** (LOE II, GOR 2)
3. **In case of NSCLC that invades the chest wall, every effort must be made to achieve a complete resection.** (LOE I, GOR B)
**Stage IIIA- N2 disease**

Patients with NSCLC stage IIIA, because of N₂ disease, are sub-classified into four groups (4). 1. Group IIIA₁ represents patients with incidental node metastasis found on the final histology examination. 2. Group IIIA₂ represents patients with the nodal invasion limited to one level of N₂ disease, recognized intraoperatively. 3. Group IIIA₃. The patients have N₂ disease at one or more levels of mediastinal lymph nodes confirmed during the staging procedure. 4. Group IIIA₄ includes patients who have bulky or fixed multistation N₂ disease.

**Group IIIA₁-2:** Despite thorough preoperative staging, some patients are found unexpectedly to have N₂ disease during the operation or at the final pathologic examination. About 25% of all patients submitted to thoracotomy are found to have unexpected N2 disease (5). In the case that complete resection is feasible, surgeons should then proceed to the planned lung resection with lymph node resection or sampling, otherwise the resection should be aborted. The 5-year survival rate after complete resection ranges between 14% - 30% with the best results seen in minimal N₂ disease (6-8).

In case of left upper lobe tumors with infiltration of the lymph nodes at the aortopulmonary window and the para-aortic area (lymph node stations 5, 6), the 5-year survival averages 40%. About 27% to 36% of patients will have skipped metastatic disease (N₂ disease exists without N1-2 disease) (9). Systematic lymph node resection or sampling is essential for accurate staging, while there is still controversy, whether this procedure improves long-term survival or not.

**Recommendations**

- **Patients with NSCLC stage IIIA₁₂, in whom complete resection is feasible, the planned lung resection and mediastinal lymph node resection is recommended. (LOE II, GOR C)**
- **Patients who have complete resection of the primary tumor, radical lymph node dissection or sampling is recommended. (LOE I, GOR B)**
**Group IIIA3:** These patients are potentially candidates for surgical treatment, and several studies suggested combined chemotherapy and/or radiotherapy followed by surgery, because of the poor survival rates provided by surgery alone, or in combination with adjuvant chemo–radiotherapy. The confirmation of N2 disease is mandatory because up to 40% of the moderately enlarged lymph nodes have no malignancy, especially in patients who have recent lung infection or atelectatic lung parenchyma. There are many phase II non–randomized clinical trials on neoadjuvant chemotherapy followed by surgery (10). Also plenty of randomized, phase III trials compared the results of neoadjuvant therapy followed by surgery versus surgery alone (11-13). Some of these trials have no pathological confirmation of N2 disease, while others included patients with stage IIB, a subgroup with favorable outcome or patients with stage IIIB who have poor prognosis. Finally most trials have small number of patients. With all the above negative factors, the authors concluded that neoadjuvant chemotherapy followed by surgery is more effective than surgery alone (14).

The meta-analysis of Berghman et al. in 2000 evaluating neoadjuvant chemotherapy (four randomized trials) found only very marginal benefit in favor of neoadjuvant chemotherapy (15). The EORTC randomized trial compared chemo–radiotherapy to chemotherapy followed by surgery. The patients had preoperative proven N2 disease and the authors concluded that there was no difference in overall survival or progression free disease (16).

The North American Intergroup study included patients with histologically confirmed N2 disease, compared chemo–radiotherapy (concurrently), followed by surgery versus chemo-radiotherapy alone (17) There was very high mortality rate in pneumonectomies, which reached the level of 26% and there was no difference in 5 year survival, in the two arms. This unacceptable high mortality is in disagreement with the 5% mortality rate for pneumonectomy when performed by experienced thoracic surgeons.


Recommendations

➔ In patients with NSCLC who have N2 disease identified preoperatively (IIIA3), referral for multidisciplinary evaluation (thoracic surgeon included) is recommended before any definitive treatment. (LOE I, GOR C)

➔ In patients with NSCLC, with N2 disease identified preoperatively (IIIA3), induction chemotherapy with or without radiotherapy, followed by surgery, preferably lobectomy, is an acceptable treatment. (LOE I, GOR B)

➔ In patients with NSCLC who have IIIA3, identified preoperatively, who do receive induction chemoradiotherapy as part of clinical trials, pneumonectomy is not recommended. The surgical treatment should be limited to lobectomy. (LOE I, GOR C)

➔ In patients with NSCLC who have IIIA3, identified preoperatively, surgery alone is not recommended. (LOE I, GOR A)

Siegenthaler et al. at MD Anderson reported that neo-adjuvant chemotherapy does not increase mortality (18). Careful evaluation for surgery after neo–adjuvant chemo–radiotherapy is necessary because incomplete resection or open–close thoracotomy is aggravating for the patient’s survival.

➔ Recommendation: Surgical debulking procedures in case of NSCLC stage IIIA3 are not recommended. (LOE I, GOR A)

Group IIIA4: Patients with bulky or fixed N2 disease are not surgical candidates.

➔ Recommendation: Surgical resection or surgical debulking procedures in case of NSCLC stage IIIA4 is not recommended. (LOE I, GOR A)
Stage IIIB: About 10% to 15% of the patients with NSCLC have stage IIIB at the initial diagnosis. Most patients with T4 tumor because of the involvement of mediastinal structures usually have N2 disease (19).

Although there are no randomized trials comparing the effectiveness of chemotherapy followed by surgery versus chemotherapy alone, these patients in general are recommended to receive chemoradiotherapy. Taking account of the low survival rate and the high mortality, any patient who has NSCLC stage IIIB and is considered a potential surgical candidate, would be best evaluated by multi-disciplinary team. Surgery may be offered to highly selected patients as a single therapy or after neo-adjuvant chemotherapy with or without radiotherapy, while chemo-radiotherapy is recommended for all cases. Carefully selected patients, when treated with induction chemotherapy followed by surgical resection, have the same results as the patients with stage IIIA treated in the same manner (20, 21). Almost all Thoracic Surgery centers with large volume of lung cancer surgery, have experience in the resection of NSCLC invading vital structures (main carina, superior vena cava, aorta, left atrium, main pulmonary artery, vertebral body and the esophagus). Although the resection of NSCLC stage IIIB is feasible, the long term survival continues to be very low, and the perioperative mortality remains high.

Patients who have T4 tumor with N2 disease are believed to be unsuitable candidates for surgical therapy and this is in agreement with the guidelines recommended by the American College of Chest Physicians (ACCP), the British Thoracic Society (BTS), and the National Comprehensive Cancer Network (NCCN) (5, 20, 23).

The largest experience in the resection for T4 tumors has been achieved for tumors involving the main carina, especially those patients with \(T_4N_{0-1}M_0\). Carinal resection and reconstruction offer 20% to 28% 5-year survival rate, with 7% to 29% mortality in experienced centers (5, 20). The highest survival rate and the lowest mortality come from experienced centers (3).
Also, surgery has been applied to carefully selected patients with superior vena cava (SVC) invasion (3, 20). There are no randomized trials to compare the effectiveness of surgery compared to conservative treatment, while Spaggiari et al. have reported 5-year survival rates up to 15% (24).

The treatment options for stage IIIB, NSCLC, because of nodule/s at a different lobe of the same lung (T4 tumor), are the same with the other T4 tumors. Biopsy (either by VATS or CT-FNA) is recommended to exclude or to confirm the presence of synchronous lung cancer. The preoperative staging procedure must include whole body PET/CT scan and mediastinoscopy or VATS, or FNA under the guidance of EBUS or EUS, in order to exclude N2 disease. The mortality is around 7%, the median survival is 32 months and the 5-year survival rate is 34% (it raises up to 57% in case of N0 disease).

Klepetko, as well as others, reported on patients with NSCLC invading the aorta (25) but the number of patients was small, the morbidity high and the long term survival rates very low.

Patients with NSCLC stage IIIB because of vertebral body invasion are rarely cured and the majority of these patients are considered unresectable. Grunenwald et al. reported on patients with radiographic evidence of destruction treated by limited or total vertebrectomy (26).

Superior sulcus tumors, when considered potentially respectable are treated with multimodality treatment which includes preoperative chemo-radiotherapy (27, 28).

The 5-year survival rates from two studies were 44% and 56% respectively. Invasion of the vertebral body, the subclavian vessels and the evidence of clinical N2 disease are considered contra-indication to surgery, and should be addressed only in the context of a clinical trial.
Recommendations

➔ In selected patients with clinical T4N0-1 NSCLC, stage IIIB, who are candidates for curative surgical treatment, invasive mediastinal evaluation and extensive extrathoracic staging procedure are recommended. (LOE I, GOR C)

➔ In selected patients with clinical stage T4N0-1 NSCLC as a result of satellite tumor nodule/s in the ipsilateral lung, carinal or SVC evaluation is recommended to be performed by a multidisciplinary team, to determine whether the tumor is operable or not. In case of N2 disease, surgery is not recommended. (LOE I, GOR C)

➔ For patients with stage IIIB NSCLC, when being considered as surgical candidates, it is recommended that the resection be undertaken only at specialized centers. (LOE I, GOR C)

Conclusions

Treatment of patients with locally advanced NSCLC (Stage IIIA and IIIB) continues to be controversial and challenging and has been the subject of a wide variety of clinical trials. Recommendations for the surgical treatment are generally weak because of the lack of large randomized trials and because of the inhomogeneity in the population included in this stage. There is a prevailing opinion that every patient with locoregional NSCLC should be approached as a potential candidate for surgical therapy, and multidisciplinary evaluation (thoracic surgeon included), is essential before embarking on definitive treatment.

It is recommended that clinician seeking to apply or consult the guidelines use personal independent medical judgments in the context of individual clinical circumstances to determine any patient care or treatment.
Summary of Recommendations:

1. **For patients with chest wall invasion and N2 disease, surgical resection is not recommended.** (LOE II, GOR C)

2. **Pancoast tumor stage IIIA because of N2 disease is not recommended to be treated surgically.** (LOE II, GOR C)

3. **In case of NSCLC that invades the chest wall, every effort must be made to achieve a complete resection.** (LOE I, GOR B)

4. **For patients with NSCLC in whom N2 disease (IIIA2) is found intraoperatively, the planned lung resection and mediastinal lymph node resection are justified.** (LOE II, GOR C)

5. **Patients who have complete resection of the primary tumor, radical lymph node dissection or systematic sampling is recommended.** (LOE I, GOR B)

6. **In patients with NSCLC who have N2 disease identified preoperatively (IIIA3), referral for multidisciplinary evaluation (which includes a thoracic surgeon) is recommended before embarking on definitive treatment.** (LOE I, GOR C)

7. **In patients with NSCLC, who have N2 disease identified preoperatively (IIIA3), induction chemotherapy with or without radiotherapy followed by surgery preferably lobectomy is an acceptable treatment in selected patients with mediastinal downstaging.** (LOE I, GOR B)

8. **In patients with NSCLC who have IIIA3, identified preoperatively, who do receive induction chemoradiotherapy, pneumonectomy in high volume centers, whenever feasible, could be an option.** (LOE I, GOR C)

9. **In patients with NSCLC who have IIIA3, identified preoperatively, surgery alone is not recommended.** (LOE I, GOR A)

10. **Surgical debulking procedures in case of NSCLC stage IIIA3 is not recommended.** (LOE I, GOR A)

11. **Surgical resection or surgical debulking procedures in case of NSCLC stage IIIA4 is not recommended.** (LOE I, GOR A)
12. **In selected patients with clinical T4N0-1 NSCLC, stage IIIA, who are candidates for curative surgical treatment, it is recommended that invasive mediastinal evaluation and extensive extrathoracic staging procedure be undertaken.** (LOE I, GOR C)

13. **In selected patients with clinical stage T4N0-1 NSCLC as a result of satellite tumor nodule/s in the ipsilateral lung, carinal or SVC, evaluation is recommended to be performed by a multidisciplinary team to determine whether the tumor is operable or not. Surgery is not recommended when there is N2 disease.** (LOE I, GOR C)

14. **For patients with NSCLC, stage IIIB, when being considered surgical candidates, it is recommended that the resection be undertaken only at specialized centers, by experienced thoracic surgeons.** (LOE I, GOR C)

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5.4 MEDIASTINAL STAGING AFTER INDUCTION THERAPY

Iliadis K, Stratakos Gr, Chatziioannou S.

NSCLC is staged according to the TNM-classification and rules, AJCC/UICC 7th edition (2010). The N₂ positivity is related with poor prognosis, so the accurate mediastinal nodal staging is of paramount importance. Unfavorable prognostic factors include the presence of radiological N2 disease, the extranodal expansion, the number of lymph node stations involved, and the infiltration of subcarinal lymph node (LN No 7).

Persistent mediastinal lymph node involvement after induction therapy is associated with poor prognosis, and lung resection in this group of patients does not add any survival benefit. Therefore, techniques providing cytohistological information (restaging the mediastinum) are advisable to avoid unnecessary thoracotomies with no therapeutic value and restaging of the mediastinum after induction therapy is obligatory.

At the present time, neither CT, PET nor PET/CT are accurate enough for further therapeutic decisions. CT scan has shown disappointing results for mediastinal nodal staging. The accuracy of CT in restaging the mediastinal LNs are very low and are reported around 50%. The reason for this is that a complete histological response is possible without any radiological response. In the other hand, PET scan is more accurate than CT but clearly not as accurate as in untreated patients. At restaging, the sensitivity of PET scan is around 70% and false negative rate, although better than CT, is still around 30%. The reason for this poor sensitivity is not clear. A very small mass of residual tumor, such as post-treatment microscopic foci surrounded by fibrosis, may be more difficult to detect. Changes in the micro-environment of the tumor, such as altered perfusion due to post-chemotherapy changes, may also impair presentation of FDG to the metastatic LNs.

However, PET/CT should be performed at least 3 weeks after the end of the induction treatment to exclude disease progression and the development of new foci. Persistent positive mediastinal findings on PET should be histopathologically proven.
The mediastinum can be principally restaged by the same techniques as applied in primary staging. These include invasive surgical and non-surgical techniques.

Invasive surgical restaging consists of mediastinoscopy and VATS restaging of the mediastinum. Re-mediastinoscopy or video-mediastinoscopy after induction treatment, although technically feasible, is more difficult and more inaccurate than the first procedure due to severe adhesions and fibrosis. It seems that the degree of adhesions and mediastinal fibrosis is mainly secondary to pre-induction mediastinoscopy rather than induction treatment itself. It also offers the advantage of providing histological evidence of response after induction therapy. The accuracy of this technique exceeds 85%.

Invasive non-surgical restaging techniques consist in transbronchial needle aspiration (TBNA), Endobronchial Ultrasound (EBUS) needle aspiration and Esophageal Ultrasound (EUS) needle aspiration. EBUS-TBNA in a study of 124 patients during restaging showed a sensitivity of 76% and specificity of 100%.[8] However, because of the low negative predictive value, tumor-negative findings should be confirmed by surgical staging before thoracotomy. EUS-FNA seem to yield similar results as VATS and re-mediastinoscopy.

A suggested approach is to use EBUS or EUS-FNA for primary staging and reserve mediastinoscopy for mediastinal restaging after induction therapy.

- **The mediastinum has to be restaged by the same techniques as applied in the primary staging.**
- **PET CT is less accurate than in primary staging. It can be used to exclude disease progression or the development of new foci.**
- **PET positive mediastinal lymph nodes have to be confirmed.**
- **Mediastinoscopy is technically feasible but more difficult than in primary staging due to fibrosis and adhesions.**
• **EBUS/EUS TBNA is less accurate and offers an alternative in restaging.**

• **EBUS should be used in the initial evaluation of mediastinum and mediastinoscopy should be kept for restaging where its role is mandatory.**

### References


PROPOSED ALGORITHM OF SURGICAL MEDIASTINAL RE-STAGING AFTER INDUCTION THERAPY FOR N2 NSCLC
5.5 ΑΚΤΙΝΟΘΕΡΑΠΕΙΑ ΤΟΥ ΠΝΕΥΜΟΝΑ

Κουλουλίας Β.

5.5.1 Γενικά

Η ακτινοθεραπεία του μη μικροκυτταρικού καρκίνου του πνεύμονα (ΜΜΚΠ) περιλαμβάνει τη ριζική ακτινοθεραπεία, την παρηγορητική και τη στερεοτακτική ακτινοθεραπεία. Οι τεχνικές αφορούν την τρισδιάστατη σύμμορφη ακτινοθεραπεία (3D-CRT), τη στερεοτακτική ακτινοβόληση και την ακτινοθεραπεία διαμορφούμενης έντασης δέσμης με απεικονιστική καθοδήγηση (IMRT-IGRT). Η επιλογή ανάμεσα στις 3D-CRT και IMRT-IGRT αφορά το μέγεθος και την τοπογραφία της νόσου, ώστε να μπορεί να συμπεριληφθεί εντός ακτινοβολητέων περιοχών χωρίς αυξημένο κίνδυνο επιπλοκών από τους γειτνιάζοντες φυσιολογικούς ιστούς, καθώς και ανάλογα με το αποτέλεσμα αναπνευστικών δοκιμασιών (FEV1) προ της χορήγησης ριζικής ακτινοθεραπείας.

1 Η ριζική ακτινοθεραπεία ενδείκνυται για τους ασθενείς σταδίου I, II και IIIa.

2 Οι ασθενείς σταδίου I ή II ΜΜΚΠ μη εξαιρέσιμου για ιατρικούς λόγους πρέπει να υποβάλλονται σε Στερεοτακτική Ακτινοθεραπεία.

3 Οι ασθενείς σταδίου IIIa ΜΜΚΠ οι οποίοι δεν είναι κατάλληλοι για χειρουργική αντιμετώπιση πρέπει να εκτιμώνται στο πλαίσιο ογκολογικού συμβουλίου, με σκοπό τη ριζική αντιμετώπιση και θεραπεία. Η θεραπεία εκλογής είναι η σύγχρονη συνδυασμένη χημειο-ακτινοθεραπεία.

4 Σε ασθενείς με καρκίνο IIIβ-IV, η θεραπεία εκλογής είναι ο επιπαχυνόμενος υποκερματισμός δόσης σύμφωνα με τα πρωτόκολλα MRC.
5.5.2 Γενικές αρχές ακτινοθεραπείας

- Το πλάνο ΑΚΘ πρέπει να γίνει βασιζόμενο στην αξονική σχεδίασμο.
- Το PTV πρέπει να καθορίζεται με βάση τις κατευθυντήριες γραμμές της ICRU-62, που βασίζεται στο GTV, συν το περιθώριο του CTV για τη μικροσκοπική νόσο, τα περιθώρια του ITV για την κίνηση του όγκου-στόχου και τα περιθώρια για τις καθημερινές ανακρίβειες της τοποθέτησης.
- Συστήνεται η διόρθωση της ετερογένειας στα ακτινοθεραπευτικά πλάνα όλων των ασθενών.
- Το μακροσκοπικό μέγεθος όγκου-στόχου (gross tumor volume, GTV) πρέπει να περιορισθεί στην ορατή νόσο (συμπεριλαμβάνοντας η πρωτοπαθής εστία και η λεμφαδενική νόσος) στην αξονική ± στο PET/CT.
- Όσον αφορά το CTV των λεμφαδενικών χωρών, η εκλεκτική ακτινοβόλησή τους (elective nodal irradiation) παραμένει αδιευκρίνιστη. Η συνεισφορά του PET/CT σε αυτό κρίνεται σημαντική για τη μείωση της ακτινικής πνευμονίτιδας-οισοφαγίτιδας. Ωστός, η ακτινοβολία εμπλεκομένου πεδίου (Involved field) με τη χρήση PET/CT χωρίς εκλεκτική ακτινοβόληση αποτελεί πλέον κοινή πρακτική. Γενικώς, πρέπει να ελαχιστοποιηθούν οι δόσεις σε πνεύμονες, καρδιά, οισοφάγο, βραχιόνιο πλέγμα, νωτιαίο μυελό και θωρακικό τοίχωμα.
- Πρέπει να εξατομικεύεται ανάλογα με την ανατομική περιοχή των όγκων και την πορεία της δέσμης. Γενικώς, η ενέργεια της δέσμης φωτονίων πρέπει να κυμαίνεται μεταξύ 4 και 10 MeV, κυρίως λόγω των ανομοιογενειών του αέρα που υπάρχει κατά τη διέλευση της δέσμης.
- Γενικώς, όταν χρησιμοποιείται θεραπεία με πρωτόνια ή τεχνική IMRT, πρέπει να γίνεται καθημερινή απεικονιστική καθοδήγηση προς την θεραπεία (IGRT – Image Guided Radiation Therapy), για τη διασφάλιση της ποιότητας. Σημαντικός, επίσης, είναι ο υπολογισμός της κίνησης του όγκου σύμφωνα με τις κατευθυντήριες γραμμές του.
ΑΑΡΜ Task Group. Ούτως, τέτοιες τεχνικές είναι η αξονική
tομογραφία αργής σάρωσης (slow CT scanning), η αξονική
tομογραφία με κράτημα της αναπνοής (inhale exhale breath hold CT)
kαι η τετραδιάστατη αξονική (4-D respiration-correlated CT).

- Οι δόσεις ακτινοθεραπείας στον ΜΜΚΠ κυμαίνονται ανάμεσα σε 60-
  74+Gy, ενώ σε ταυτόχρονη χημειοθεραπεία φαίνεται ότι η συνολική
dόση είναι έως 60Gy. Οι δόσεις της στερεοτακτικής ακτινοθεραπείας
ραδιοβιολογικά ισοδύναμες είναι άνω των 100Gy. Οι δόσεις της
παρηγορητικής ακτινοθεραπείας κυμαίνονται από 30 έως 50Gy,
αναλόγως των δόσεων που χρησιμοποιούνται ανά συνεδρία (300-
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5.6 ΡΙΖΙΚΗ ΑΚΤΙΝΟΘΕΡΑΠΕΙΑ ΤΟΥ ΠΝΕΥΜΟΝΑ

Τριχάς Μ.

5.6.1 Επιδημιολογικά στοιχεία

Ο καρκίνος του πνεύμονα αποτελεί την κύρια αιτία θανάτου από καρκίνο στις Ηνωμένες Πολιτείες Αμερικής. Εκτιμάται ότι συνολικά 225.500 νέες περιπτώσεις (116.750 άνδρες και 108.750 γυναίκες) διαγνώστηκαν το 2010 με καρκίνο (βρογχογενή + πνεύμονος) και 157.300 θάνατοι (86.200 άνδρες, 71.100 γυναίκες). Μόνο το 15,8% όλων των ασθενών θα είναι ζωντανοί στα 5 έτη από τη διάγνωση.

Κοινά συμπτώματα εμφάνισης αποτελούν ο βήχας, η δύσπνοια, η απώλεια βάρους και το θωρακικό άλγος. Οι περισσότεροι συμπτωματικοί ασθενείς πάσχουν και από χρόνια αποφρακτική πνευμονία.

Ο κύριος παράγοντας κινδύνου είναι το κάπνισμα και συνδέεται με περισσότερο από το 85-90% όλων των θανάτων που αφορούν τον καρκίνο του πνεύμονα. Ο κίνδυνος αυξάνεται με τον αριθμό των τσιγάρων καθώς και με τον αριθμό των ετών κατά τα οποία καπνίζει ο ασθενής.

Οι παθητικοί καπνιστές έχουν αυξημένο σχετικό κίνδυνο ανάπτυξης καρκίνου του πνεύμονα.

Το ραδόνι παράγεται από τη διάσπαση του ραδίου 226 και είναι η δεύτερη κύρια αιτία ανάπτυξης καρκίνου του πνεύμονα. Η διάσπαση του οδηγεί στην παραγωγή ενώσεων που εκπέμπουν α-σωματίδια, τα οποία μπορούν να προκαλέσουν βλάβη σε κυτταρικό επίπεδο και, κατά συνέπεια, να αυξήσουν τον κίνδυνο κακοήθους εξαλλαγής.

Δεδομένα υποστηρίζουν ότι μετεμμηνοπαυσικές γυναίκες που καπνίζουν ή ήταν πρώην καπνιστές δεν θα πρέπει να λαμβάνουν ορμονική θεραπεία υποκατάστασης, διότι αυτό αυξάνει τον κίνδυνο θανάτου από μη μικροκυτταρικό καρκίνο πνεύμονα (ΜΜΚΠ).

Οι μικρές ίνες αμιάντου αποτελούν γνωστό καρκινογόνο παράγοντα και αυτός ο κίνδυνος αυξάνεται στα άτομα που καπνίζουν. Υπολογίζεται ότι περίπου 3-4 % των καρκίνων του πνεύμονα προκαλούνται εξαιτίας της έκθεσης σε αμίαντο.
Επιπροσθέτως, υπάρχουν και άλλοι παράγοντες κινδύνου που προκαλούν πνευμονική φλεγμονή, μεταξύ αυτών η φυματίωση, το οικογενειακό ιστορικό και η έκθεση σε ουσίες όπως ο διχλωρομεθυλαιθέρας, οι πολυκυκλικοί αρωματικοί υδρογονάνθρακες (ΠΑΥ), το χρώμιο, το νικέλιο και οι οργανικές ενώσεις του αρσενικού.

5.6.2 Κύριοι παθολογοανατομικοί τύποι
Σύμφωνα με τον Παγκόσμιο Οργανισμό Υγείας, ο Μη Μικροκυτταρικός καρκίνος του πνεύμονα αποτελεί περίπου 85% όλων των περιπτώσεων καρκίνου του πνεύμονα. Αυτός διαιρείται σε 2 τύπους: (1) Μη πλακώδης (αδενοκαρκίνωμα, καρκίνωμα από μεγάλα κύτταρα κ.ά.) και (2) Πλακώδης (επιδερμοειδής) καρκίνος. Το αδενοκαρκίνωμα είναι ο πιο συχνός τύπος που συναντάται στις Ηνωμένες Πολιτείες και ο πιο κοινός σε μη καπνιστές. Με τη χρήση των μικροσυστοιχιών του DNA, όπου καταγράφεται η έκφραση του γονιδιακού προφίλ, έχουν εντοπισθεί υπότυποι του αδενοκαρκίνωματος (π.χ. βρογχοειδείς, επιθηλιοειδείς) που συνδέονται με αυξημένη επιβίωση στα αρχικά στάδια της νόσου, ενώ το επιθηλιοειδές συνδέεται με αυξημένη επιβίωση στα προχωρημένα στάδια της νόσου.

5.6.3 Διαγνωστική προσέγγιση πριν από την ακτινοθεραπεία
Ακτινοθεραπευτής-Ογκολόγος εξειδικευμένος στην ογκολογία θώρακος πρέπει να καθορίζει τη δυνατότητα χορήγησης ριζικής ακτινοθεραπείας, λαμβάνοντας υπ’ όψιν την κλινική εικόνα και τη συννοσηρότητα του ασθενούς.

- Πνευμονικός λειτουργικός έλεγχος
- Βρογχοσκόπηση (προτιμάται η διεγχειρητική)
- Μεσοθωρακοσκόπηση
- EBUS
- PET / CT
5.6.4 Ριζική ακτινοθεραπεία

5 Η ριζική ακτινοθεραπεία ενδείκνυται για τους ασθενείς σταδίου I, II και III ΜΜΚΠ που είναι σε καλή κλινική κατάσταση (performance status WHO 0, 1) και η νόσος τους μπορεί να συμπεριληφθεί εντός ακτινοβολητέων περιοχών χωρίς αυξημένο κίνδυνο επιπλοκών από τους γειτνιάζοντες φυσιολογικούς ιστούς.

6 Όλοι οι ασθενείς πρέπει να υποβάλλονται σε αναπνευστικές δοκιμασίες προ της χορήγησης ριζικής ακτινοθεραπείας για ΜΜΚΠ.

7 Οι ασθενείς με πτωχή αναπνευστική λειτουργία, αλλά παρά ταύτα ικανοί να υποβληθούν σε ριζική ακτινοθεραπεία, μπορούν να υποβληθούν εάν ο ακτινοβολούμενος όγκος υγιούς πνεύμονα είναι μικρός.

8 Οι ασθενείς σταδίου I ή II ΜΜΚΠ μη εξαιρέσιμου για ιατρικούς λόγους πρέπει να υποβάλλονται σε στερεοτακτική ακτινοθεραπεία ή σε συνεχή υπερκλασματοποιημένη επιπταχυνόμενη ακτινοθεραπεία (CHART regimen). Αν δεν υπάρχει η υποδομή για τις ανωτέρω θεραπείες, τότε υποβάλλεται σε κλασική ριζική ακτινοθεραπεία.

5.6.5 Ριζική χημειο-ακτινοθεραπεία σταδίου III ΜΜΚΠ

Οι ασθενείς σταδίου III ΜΜΚΠ οι οποίοι δεν είναι κατάλληλοι για χειρουργική αντιμετώπιση πρέπει να εκτιμώνται στο πλαίσιο ογκολογικού συμβουλίου, με σκοπό τη ριζική αντιμετώπιση και θεραπεία.

Η θεραπεία ελκυστήρης είναι η συνδυασμένη σύγχρονη χημειο-ακτινοθεραπεία (ΧΜΘ με βάση την πλατίνα).

ΑΡΧΕΣ ΑΚΤΙΝΟΘΕΡΑΠΕΙΑΣ

- Το GTV πρέπει να περιοριστεί στην ορατή νόσο (συμπεριλαμβάνονται η πρωτοπαθής εστία και η λεμφαδενική νόσος) στην αξονική ± στο PET/CT.
- Όσον αφορά το CTV των λεμφαδενικών χωρών, η εκλεκτική ακτινοβόληση τους (elective nodal irradiation) παραμένει αδιευκρίνιστη.
- Η εκλεκτική ακτινοβόληση (elective nodal irradiation) πρέπει να βασίζεται στον όγκο-στόχο, στις παραμέτρους των γειτονικών φυσιολογικών...
δομών και την πιθανή συννοσηρότητα του ασθενούς. Εντοπισμένο στη διήθηση πεδίο ΑΚΘ (Involved field) χωρίς εκλεκτική ακτινοβόληση αποτελεί κοινή πρακτική, επειδή έχει δείξει ότι επιτρέπει τη χορήγηση υψηλότερης δόσης στον όγκο, με αποδεκτή τοξικότητα και χαμηλή πιθανότητα κινδύνου μεμονωμένης λεμφαδενικής υποτροπής.

• Στους ασθενείς που υποβάλλονται σε ΧΜΘ εισαγωγής, πρέπει να γίνεται μία αξονική σχεδιασμού αναφοράς πριν από την έναρξη της ΧΜΘ εισαγωγής. Εάν είναι εφικτό, τα αρχικά ακτινοθεραπευτικά πεδία πρέπει να καλύπτουν τον όγκο-στόχο πριν από τη ΧΜΘ, και τα περιορισμένα πεδία (cone-down) να καλύπτουν τον όγκο-στόχο μετά τη ΧΜΘ. Εντούτοις, σε ασθενείς με επηρεασμένη καρδιακή ή πνευμονική λειτουργία, εάν ο αρχικός όγκος ήταν μεγάλος και αναμένεται μεγάλη τοξικότητα, ο όγκος πρέπει να χρησιμοποιείται μετά την εισαγωγή ΧΜΘ.

• Η ενέργεια της δέσμης φωτονίων πρέπει να εξατομικεύεται ανάλογα με την ανατομική περιοχή των όγκων και την πορεία της δέσμης. Γενικά, να χρησιμοποιούνται δέσμες φωτονίων με ενέργειες που κυμαίνονται μεταξύ των 4-10 MeV. Εάν η πορεία της δέσμης διασχίζει χαμηλής πυκνότητας πνευμονικό ιστό προτού εισέλθει στον όγκο, τότε πρέπει να χρησιμοποιούνται ενέργειες 15 ή 18 MeV για την επίτευξη καλύτερης κατανομής της δόσης.

• Είναι σημαντικό να εκτιμηθεί στο DVH (Dose Volume Histogram), στο πλαίσιο της τρισδιάστατης ακτινοθεραπείας, η κάλυψη των όγκων στόχων GTV, CTV και PTV, καθώς και των φυσιολογικών ιστών. Πρέπει να ελαχιστοποιηθούν οι δόσεις σε φυσιολογικά οργάνα, καρδιά, οισοφάγο, βραχιόνιο πλέγμα, νωτιαίο μυελό και θωρακικό τοίχωμα.

• Μέθοδος σχεδιασμού είναι η τρισδιάστατη σύμμορφη ακτινοθεραπεία (3D-CRT). Σε περιπτώσεις όπου υπάρχει μεγάλο ποσοστό του φυσιολογικού πνεύμονα που θα ακτινοβοληθεί ή όταν ο όγκος γειτνιάζει με ευαίσθητα φυσιολογικά όργανα, πρέπει να εκτιμηθεῖ το ενδεχόμενο
χρήσης της διαμορφούμενης έντασης ΑΚΘ (IMRT). Σημαντικά μικρότερος κίνδυνος πρόκλησης ακτινικής πνευμονίτιδας και βελτίωση της συνολικής επιβίωσης έχουν παρατηρηθεί κατά τη σύγκριση IMRT με τρισδιάστατη σύμμορφη ΑΚΘ (3-D CRT). Όταν χρησιμοποιείται η IMRT τεχνική, πρέπει να τηρούνται οι κατευθυντήριες γραμμές NCI IMRT.

- Η διαχείριση της αναπνευστικής κίνησης πρέπει να λαμβάνεται υπ’ όψιν σε όλους τους ασθενείς με ΜΜΚΠ όταν υποβάλλονται σε ΑΚΘ θώρακος. Αποδεκτές μεθόδους υπολογισμού της κίνησης του όγκου για τις κατευθυντήριες γραμμές του AAPM Task Group αποτελούν οι εξής: α) Αξονική τομογραφία αργής σάρωσης (slow CT scanning), Αξονική τομογραφία με εισπνοή-εκπνοή και κράτημα της αναπνοής (inhale exhale breath hold CT), Τετραδιάστατη αξονική (4-D respiration-correlated CT), β) Μέθοδοι του Respiratory gating, που εκμεταλλεύονται ένα εξωτερικό αναπνευστικό σήμα ή τα εσωτερικά fiducial markers, γ) Μέθοδοι κρατήματος της αναπνοής (breath-hold methods) με διατήρηση-κράτημα της βαθιάς εισπνοής (deep-inspiration breath-hold), ενεργό έλεγχο της αναπνοής (active-breathing control - ABC) συσκευής, αυτορρύθμιση της αναπνοής χωρίς παρακολούθηση των αναπνευστικών κινήσεων, δ) Forced shallow breathing, με κοιλιακή πίεση και ε) Μέθοδοι παρακολούθησης σε πραγματικό χρόνο (Real-time tumor tracking).
Δόσεις που χορηγούνται στη συμβατική κλασματοποιημένη ΑΚΘ
Συνιστώμενες δόσεις: 60 – 74 Gy (60 – 70 Gy επί ΧΑΘ)

<table>
<thead>
<tr>
<th>Τύπος Θεραπείας</th>
<th>Συν. Δόση</th>
<th>Δόση/κλάσμα</th>
<th>Διάρκεια Θεραπείας</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ριζική</td>
<td>60-74 Gy</td>
<td>2 Gy</td>
<td>6-7,5 εβδομάδες</td>
</tr>
<tr>
<td>• ΑΚΘ μόνο ή</td>
<td>60-70 Gy</td>
<td>2 Gy</td>
<td>6-7 εβδομάδες</td>
</tr>
<tr>
<td>Διαδοχική ΧΜΘ+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ταυτόχρονη ΧΜΘ</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Όρια ανοχής φυσιολογικών ιστών στη συμβατική κλασματοποιημένη ΑΚΘ (3-D CRT)

<table>
<thead>
<tr>
<th>Φυσιολογικές ευαίσθητες δομές</th>
<th>Όρια Ανοχής</th>
</tr>
</thead>
<tbody>
<tr>
<td>Νωτιαίος Μυελός</td>
<td>46 Gy με 1,8-2 Gy / Συν</td>
</tr>
<tr>
<td>Πνεύμονας</td>
<td>V20 &lt;30 %</td>
</tr>
<tr>
<td></td>
<td>MLD &lt;20 Gy</td>
</tr>
<tr>
<td>Καρδιά</td>
<td>V40 &lt;100%</td>
</tr>
<tr>
<td></td>
<td>V45 &lt;67 %</td>
</tr>
<tr>
<td></td>
<td>V60 &lt;33 %</td>
</tr>
<tr>
<td>Οισοφάγος</td>
<td>Μέση δόση &lt;34 Gy</td>
</tr>
<tr>
<td>Βραχιόνιο πλέγμα</td>
<td>66 Gy με 1,8-2 Gy / Συν</td>
</tr>
</tbody>
</table>
Εναλλακτικά σχήματα χορήγησης ΑΚΘ
- 55 Gy σε 20 fx (2,75 Gy ημερήσια δόση) (NICE 2005)

**ΒΙΒΛΙΟΓΡΑΦΙΑ:**


6 STAGE IV NSCLC

6.1 MOLECULAR ANALYSIS OF NSCLC

Murray S, Boukouinas J.

Introduction
Lung cancer represents the most common cancer in the world today. It is also the leading cause of cancer-related deaths worldwide. There are some 1.35M newly diagnosed cases annually and of those approximately 1.18M result in death due to disease (2002 statistics). Every year, in Europe, >200,000 new cancer cases are diagnosed, accounting for >20% of all cancer deaths in the region [1]. In the USA, there was an estimated 222,500 new cases of lung cancer diagnosed and >157,000 deaths from the disease [2].

Non-small-cell lung cancer (NSCLC) comprising adenocarcinoma, squamous carcinoma and large-cell carcinoma, make up >80%–85% of all lung cancer types. In terms of their presentation (initial diagnosis), about 70% of patients are diagnosed with advanced disease [3]. Due in part to the late diagnostic presentation of NSCLC a large proportion of cases are unsuitable for curative treatment. For this reason, the majority of patients are offered systemic therapy as a standard approach, with palliation, the patients’ quality of life (QOL) incorporated into endpoints typically set at prolongation of life rather than the otherwise higher expectation of survival improvements [3, 4].

Although small improvements have been made, for virtually all therapeutic strategies, many patients have and eventually almost all patients will develop tumors that are non-responsive to our current treatment strategies whether they are of the so called ‘targeted’ or ‘non-targeted’ class [5]. The application of molecular targeted therapeutics into daily clinical practice has identified the need for biomarkers of patient stratification and clinical decision-making. Predictive (and prognostic) biomarkers, if appropriately developed, validated and employed, can identify patients who are most likely to benefit from treatment or spare patients that have tumors with ‘de novo’ resistance to a given agent from ineffective or toxic treatments. In this way they can improve clinical outcomes and assist in reducing healthcare costs [6, 7].
1. Is there sufficient evidence to support the routine application of EGFR somatic mutation assessment?

The epidermal growth factor receptor (EGFR), one of the earliest identified oncogenes, has been implicated in processes such as cell proliferation, resistance to apoptosis, angiogenesis and cell motility [8]. It is highly expressed in non-small-cell lung cancer (NSCLC), with the highest expression being observed in the histological subtype of squamous cell carcinoma [9]. Increased EGFR expression, both at the messenger RNA and protein levels, has been correlated with adverse disease characteristics such as advanced stage at diagnosis and resistance to treatment [8,10]. It has also been suggested to be a prognostic factor associated with reduced survival [9, 11]. The central role of EGFR in lung cancer carcinogenesis provided the rationale for the development of drugs that would target the receptor, abrogate receptor signaling and, thus, inhibit cancer growth [12, 13]. During the early clinical development of the EGFR TKIs, one of the central questions was the relationship between the target (EGFR protein) expression and treatment effectiveness.

After the first clinical results became available, the observation that certain patients demonstrated rapid objective tumor responses led to the identification of EGFR gene copy number gain [14, 15] and somatic EGFR mutations [16–18] as candidate biomarkers of response and survival. Compared with PCR-based methods, scoring EGFR gene copy number is fairly assessor dependent. In an attempt to standardize EGFR gene copy number in NSCLC, and to overcome differences between EGFR in NSCLC and the routinely assessed c-erbB2 gene in breast cancer [14, 19], an alternative scoring system was proposed by Cappuzzo et al. [14]: the Colorado Classification System (CCS) is fairly well acknowledged and routinely used for the assessment of EGFR gene copy number. The utility of EGFR gene copy number as a predictive biomarker for stratification to TKI administration is not, however, of clinical significance. A recent meta-analysis of its predictive significance indicated that it is not suggested for clinical implementation [20]. One of the largest studies conducted investigating EGFR GCN as a predictive
biomarker, the INVITE study, suggested that patients with increased EGFR GCN benefitted more from vinorelbine than gefitinib [21].

In 2004, three groups offered further insight into the mechanisms that underlie NSCLC sensitivity to TKIs and correlated responses to gefitinib or erlotinib with the presence of somatic mutations clustered in exons 18 to 21 of the tyrosine kinase domain of EGFR [17-19] This distinct, clinically relevant molecular subset of lung cancer is essentially mutually exclusive from other molecular subsets that may characterize >50% of NSCLC. Subsequent reports indicated that the somatic mutational status of EGFR correlated with female sex, smoking history, adenocarcinoma histology and Asian ethnic origin, which corresponded well with the results from previous retrospective analyses [22-24].

Since the first reports of somatic EGFR mutations in NSCLC, a plethora of publications have described EGFR mutations in patients treated with TKIs that correlated with an improved response, and studies have documented the existence of such mutations in TKI-naive patients [25-30]. Two major databases of EGFR mutations are in existence, the COSMIC database that catalogues all reports and the Somatic mutations-EGFR database that catalogues based upon non-overlapping datasets [31-33].

Amongst the multitude of mutations found in the EGFR gene (Table 1) most common cluster in two regions, these have been termed ‘classical’ mutations. These classical mutations are namely in-frame deletions around the LREA motif (residues 746–750) located in exon 19 (corresponding to approximately 50% of all EGFR mutations), and the L858R point mutation of exon 21 (accounting for approximately 40% of EGFR mutations) [25, 32, 34, 35, 36].

The overall spectrum of mutations can be seen in Table 2, and accounts for >350 different mutations across the four exons (18, 19, 20, 21), with distributional frequencies of 53, 133, 104 and 69 per exons 18 through 21 [31]. Further, to this are the commonly correlated factors of female gender, smoking history, histological type and ethnicity as indicated in Table 3. Note
here that the most common mutations represent only a handful of specific mutations, but that the drift across each hot-spot accounts for some 100 different mutations [31]. Ethnicity plays a role with total reported frequencies at: 17.1% of all NSCLCs in western Europeans, and 35.5% in East Asians, however, the relative distribution of mutations according to the other factors by ethnicity are not different.

Most patients with exon 19 deletions or L858 mutations demonstrate substantial clinical responses to monotherapy with the reversible 4-anilinoquinazoline, ATP-mimetic EGFR tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib [29, 31]. In 2009, trials in EGFR-mutant lung cancer with EGFR tyrosine kinase inhibitors (TKIs) reported the longest survival rates currently seen for metastatic NSCLC [16, 22].

Several alternative mutations, such as G719 of exon 18, and L861Q in exon 21, account for 2.5% of EGFR mutations and also demonstrate similar response rates. Analysis of all published reports suggests response rates of 61%, 73%, 60% (less T790M) and 63% for exons 18,19,20,21 respectively [31]. The T790M “acquired resistance mutation” has been reported as a mechanism of resistance in several studies. Its presence has been linked to shorter PFS times when the tumors harboured concomitant yet small amounts of T790M before EGFR TKI therapy [37-39]. However, virtually all reported cases of T790M positive cancers have demonstrated responses to TKIs characterised by shorter relapsing times [5]; implying that sensitive tumors regress and resistant clones gain an advantage.

In respect to pre-selection of patients for mutational testing utilising gender, smoking history and ethnicity the largest US based population studied indicated that it is the presence of the mutation and not the clinical characteristic that underlies the clinical outcomes seen after EGFR TKI treatment [40]. Overall survival of men and former/current smokers with EGFR mutations was similar to that seen in women and never smokers. In their analysis, EGFR mutations occur with an incidence of 23% in 2,142 patients with stage I through IV lung adenocarcinoma. Sensitizing mutations were
detected in 19% of men and 13% of current/former smokers. Although there is a decrease in the incidence of mutations with increased number of pack-years smoked, a substantial number of \textit{EGFR} mutations were found in patients with a significant history of smoking, as indicated from the somatic \textit{EGFR} database Table x. In the US study \textit{EGFR} mutations in men and former/current smokers represented 31% and 40% of all mutations, respectively. These results were comparable to the results reported among patients from East Asia [38, 39, 41] (Table 3). Furthermore, similar results were reported in a multi-institutional study conducted in Spain, \textit{EGFR} mutations were found 350 (17\%) of 2,105 patients; and the incidence was 8\%, 10\%, and 6\% in men, former, and current smokers, respectively. [42]

Although clinical selection factors to choose \textit{EGFR} TKIs have guided the care of individual patients and facilitated research for a decade, this strategy has been eclipsed by our ability to use the presence of \textit{EGFR} sensitizing mutations as the basis for treatment. If we only perform mutation testing in selected patients based on clinical features, we will fail to detect a substantial number of mutations in smokers, men and in histologies other than adenocarcinoma. In the US study 31\% of all \textit{EGFR} mutations would be missed if testing were restricted to women, 40\% would be missed if testing were restricted to never smokers, and 57\% would be missed if testing were restricted to women who never smoked cigarettes. The somatic \textit{EGFR} database indicates that restriction to adenocarcinomas 8.3\% would be missed (Table 3). These common findings suggest support the growing consensus that all patients with NSCLC should be offered to undergo mutation testing at diagnosis if tissue is available. [43]

\textit{Recommendation 1.1 – EGFR somatic mutation testing should be carried out to identify patients eligible for first-line treatment with EGFR TKIs. (LOE I, SOR A)}

\textit{Recommendation 1.2 – All patients, irrespective of histology, smoking status or gender should be tested for EGFR mutation status. (LOE I/II, SOR A)}
Recommendation 1.3 – Patients harbouring sensitizing EGFR mutations should be treated with EGFR TKIs regardless of the genotype of the sensitizing mutation. (LOE I, SOR A)

Recommendation 1.4 – IHC (protein expression) and ISH (gene copy number) of EGFR are not recommended for routine clinical use (this requires update due to approval of Cetuximab based on IHC by the FDA.) [LOE I/II, SOR A]

Other recommendations: 1.5 – The concomitant presence of T790M (resistance) mutation should not preclude the use of EGFR TKIs in the first-line setting (or at first administration of TKI.) [LOE II, SOR B]

2. What is the optimal source of material for molecular analysis, and which method is appropriate?

Although not standardized, 10% neutral-buffered formalin is the optimum fixative [44]. Bouin's fluid should not be used, and other fixatives have yet to be validated against formalin. Fixation times should be prolonged, as they may result in reduced quality and quantity of extracted DNA.

Biopsy of the primary tumor is the most appropriate material for EGFR analysis (and other molecular analysis), following appropriate pathological review. However, NSCLC is commonly diagnosed using minimally invasive sampling of CT scan-guided fine needle aspirates, bronchoalveolar aspirates, bronchoalveolar lavages, or pleural effusions. In a significant proportion of cases, these procedures will provide insufficient material for molecular analysis. Few studies have assessed the PPV, NPV of such surrogate materials compared to primary tumor biopsies (currently under investigation).

It may be advisable in certain cases to make efforts to perform biopsies in different areas of the tumor and considering biopsies of metastases, if more easily accessible compared to primary tumor, taking into account the potential discrepancies in EGFR status between primary tumor and metastasis that
might influence treatment outcome. There is, however, little evidence of large discordances between metachronous or synchronous tumors [Japanese study, + Meta Review]. *EGFR* mutation testing using other samples such as on cytology samples may be improved by manual micro-dissection or, because of the stochastic distribution of malignant and non-malignant cells using laser capture micro-dissection [45].

Due to issues identified in the availability and reproducibility of NSCLC biopsies from several of the largest phase III studies conducted in NSCLC ASCO has suggested the following: “It is also recommended that in order to obtain tissue for more accurate histologic classification or for investigational purposes, efforts to obtain more tissue than what is contained in a routine cytology specimen. Properly fixed material from cytology cell block preparations is generally required for analysis, as opposed to cytology smear preparations.” [Keedy et al. JCO, 2011].

When assessing the *EGFR* mutation status, it is important to use a well-validated and robust method, in order to minimize the risk of false negative or false positive results. False positive result would increase the risk of first-line gefitinib, which has been demonstrated to be worse than standard chemotherapy in *EGFR* mutation negative patients. On the contrary, false negative result would deny the chance of receiving the optimal treatment option for a mutation positive patient. Techniques for *EGFR* mutational analysis can be widely divided in two categories: (1) screening techniques [e.g. polymerase chain reaction (PCR) followed by direct sequencing] that can potentially detect both known and novel mutations; and (2) targeted mutation detection (e.g. ARMS or PNA-LNA), that are generally characterized by a higher sensitivity but allow the detection pre-specified mutations only. The most commonly reported method of mutation detection is PCR-based amplification and direct sequencing [46]. Direct DNA sequencing has a limited sensitivity for the detection of tumor cells containing an *EGFR* mutation against a background of WT alleles. Therefore, the sensitivity of DNA
sequencing is dependent on the percentage of tumor cells in the sample that can be significantly influenced by tumor heterogeneity.

Several studies have investigated concordance between various techniques. Due in part to the spectrum of mutations and in part to the accepted heterogeneity of NSCLC samples (intra- and inter-), there is a common understanding that the utility of more than one technique may be valuable in identifying the larger percentage of individuals harbouring somatic EGFR mutations. The most sensitive of techniques includes ARMS, with the commercially available DxS kit being the most commonly utilized. The specificity of this commercially available mutation specific PCR detection kit (TheraScreen® EGFR29 Mutation Kit; DXS Ltd., Manchester, UK) was examined in a German study of reference centers, comparing it to direct sequencing [47].

Their study identified 163 mutation-positive tumors from 1,047 samples representing a mutation rate of 15.6%. They addressed the question which mutations detected by the sequencing approach would have been identified by the commercially available mutation-specific PCR test. A total of 67 of the 169 mutations (40%) would have been missed by the mutation-specific PCR analysis. Incidences per exon missed were 17/21 (81%) exon 18; 33/82 (40%) exon 19; 9/9 (100%) exon 20; 8/57 (14%) exon 21. According to the Somatic Mutation-EGFR-Database [31], 47 of the 67 mutations (70%) are characterised as “activating” mutations. In summary, they reported that 47 of all 149 activating mutations (32%) detected by routine diagnostic sequencing of exons 18–21 would have been missed by sole application of mutation-specific PCR testing. However, there is also sufficient data from the somatic EGFR database and numerous articles that sequencing is limited by its sensitivity, typically 20% mutant allelic content required compared to 1% for ARMS (Table 4). Therein, the utility of two complementary techniques is expected to capture at least 10% extra activating mutation positive patients.

Several other PCR and non-PCR based analytical techniques have been investigated however there is little data to support their utilisation. One last
technique is that of mutation specific antibody detection. Although several studies have been conducted to address their PPV and NPV, the rate of diss-concordance is currently too high to suggest their utility in standard practice. Furthermore, considering the limited availability of biopsy, the use of surrogate samples- including plasma and pleural effusion- has also been explored. Circulating DNA derived from tumor tissue, derived either from serum, plasma or CTCs could be representative of EGFR mutations status of the primary tumor [48-52]. However, the false negative rate remains high, and further validation is mandatory before these procedures can be used in routine clinical practice.

**Recommendation 2.1** – DNA derived from tumor biopsy material is the optimal source for EGFR somatic mutation testing; repeat biopsy may be indicated to gain sufficient material to test. There is no evidence to mandate testing for an EGFR somatic mutation outside the first-line setting. (LOE II, SOR A)

**Recommendation 2.2** – Alternative biopsy material other than tumor biopsy, cytology, BAL, FNAs, ascites, brushings, have all been reported to harbour EGFR mutations. Insufficient data exists to classify concordance with a tumor biopsy, and as such they may be utilised for molecular classification subsequent to 2.1. [LOE II/II (under investigation), SOR B]

**Recommendation 2.3** – Other surrogate sources of tumor derived DNA, including serum, plasma or CTCs, have not demonstrated sufficient correlative concordance to warrant their use outside of exploratory analyses (or in cases devoid of available biopsy material). [LOE II/III, SOR B/C]

**Recommendation 2.4** – Sensitizing mutations in EGFR are present in all four exons (18-21). Screening practices for clinical studies have utilised several techniques for their identification. Concerns have been raise about inadequacies of certain testing methodologies. Utility of more
than one technique to allow high sensitivity (detection of limited allelic content) and high specificity (wide mutational spectrum coverage) is suggested to maintain a low NPV. [LOE II, SOR B]

Other recommendations 2.5 – The use of alternative techniques (other than robust PCR based methods such as ARMS or sequencing) including mutation specific MoAbs demonstrate high false positive rates and are not recommended for EGFR mutation analysis outside of research use. [LOE II, SOR B/C]

3. Guidance on tissue handling, analysis and reporting of somatic EGFR mutational analysis.

Recommendation 3.1 – Pathological review should be performed by a registered pathologist and reporting should specify the component(s) according to standard nomenclature.

Recommendation 3.2 – A pathologist (or molecular pathologist) should be involved in sample preparation and interpretation of EGFR mutation status result reporting. Micro- or macro-dissection of samples are intended to maximize tumor cell content (typically not less than 50%) before DNA extraction. The report should include comment(s) on biopsy source and processing, quantity and quality of tested sample, and should follow guidance on genetic test reporting such as that provided by the EMQN, UKNEQAS and the Human Genome Variation Society for nomenclature and reporting guidelines (http://www.hgvs.org)

4. The importance of participation in quality assurance programs for genetic testing?

Outside of the US there are heterogeneous standards and requirements for laboratories to perform and report on molecular testing. This lack of harmonisation throughout the EU has seen the development of local bodies that aim to regulate certain components of molecular genetic techniques that
have been included in many areas of clinical practice. Due to the complexity of the processes involved in molecular oncology several specialties are often brought together through new collaborations to deliver such testing. Country specific standards are at times more rigid and auditable as well as being clear and transparent to participants and public. Several quality assurance schemes dealing with EGFR mutational analysis have been initiated across the EU. The aim of all schemes is to provide a means of monitoring compliance with best practice procedures [52].

The most advanced of such schemes that also offer external audit and offer participating laboratories accreditation and not only certification for such complex testing include the EMQN and the UKNEQAS. The UKNEQAS is a government regulated non-profit organisation specifically set up to audit UK based laboratories. The EMQN is a global non-profit organisation offering equally audited EQA schemes. Recently a global imitative has been established between EMQN, ESP, ESMO, UKNEQAS and several country specific schemes to offer one harmonising EQA for EGFR mutational analysis [53]. These schemes ensure basic standards are met with respect to material handling, processing, reporting and interpretation of molecular testing. Supplemental schemes are available to cover techniques, and associated processes. Guidelines for all testing, molecular or not, stipulate the use of EQA certified laboratories.

**Recommendation 4.1 – Somatic mutation tests that are required for clinical decision making should only be carried out in laboratories that are compliant with country-specific standards for clinical diagnostic testing (UK, Clinical Pathology Accredited Laboratories; USA, CLIA Laboratories). The laboratory should have accreditation to conduct the test and should participate in internal and external quality assurance programs to maintain such accreditation (EMQN, UKNEQAS, CAP) on a routine basis. [LOE II, SOR A]
5. Testing guidelines for EML4-ALK

Oncogenic fusion genes consisting of EML4 and anaplastic lymphoma kinase (ALK) are present in a subgroup of NSCLC, representing 2%–7% of tumors [5]. According to limited data, Echinoderm micro-tubule associated protein-like 4 (EML4)-ALK is more prevalent in patients who have never smoked or who have a history of light smoking and in patients with adenocarcinomas, particularly those with the rare signet-ring appearance. Here again EML4-ALK is mutually exclusive from both EGFR and KRAS positive tumors. Due to the absolute low numbers of ALK positive NSCLCs identified to date it is difficult to assign clinicopathological factors that may assist in their identification, much of the published data to date are heterogeneous.

Crizotinib is an oral selective ATP inhibitor of the ALK and MET tyrosine kinases. It was recently approved by the FDA (July 2011) for patients with advanced NSCLC who are positive for the ALK gene rearrangement, based on dramatic responses (>80%) seen in ongoing phase II trials in patients with the molecular change who had previously progressed. Patients otherwise devoid of EGFR mutations can potentially harbor the EML4-ALK gene rearrangement. Testing using the only FDA approved format, FISH, should be conducted in an appropriately accredited pathology or molecular pathology facility compliant with country-specific standards for clinical diagnostic testing. Few centers in the EU have such accreditation and efforts to ensure correct molecular analysis for the detection of this rare subgroup should be considered by the treating physician and patient alike.

Recommendation 5.1 – Routine testing for EML4-ALK is recommended. (LOE II, SOR A)

Recommendation 5.2 – All recommendations concerning EGFR testing relevant for laboratory and clinical implementation are essentially the same for EML4-ALK. (LOE II, SOR A)

Recommendation 5.3 – Current recommendation is that EML4-ALK testing is conducted by FISH in a certified laboratory. (LOE II, SOR A)
6. Guidelines for testing of other somatic mutations or gene aberrations for treatment selection.

Several authors have proposed that KRAS mutational analysis in order to select patients unlikely to benefit from treatment with EGFR-directed therapy could be included into a screening algorithm for NSCLC. KRAS mutations are known to be mutually exclusive with EGFR mutation and EML4-ALK. They have been shown in a meta-analysis to be good predictors on non-response to EGFR TKIs [10, 31]. Inclusion of KRAS into a screening algorithm would reduce the number of patients tested for the presence of EGFR mutation by approximately 25%. Several centres actually utilize such screening algorithms; however, the reporting of KRAS raises questions regarding treatment of NSCLC in the absence of an EGFR mutation. At present there is no prospective randomised trial powered sufficiently to conclude if it is a negative predictor with respect to PFS or OS. There are several trials that have included KRAS analysis as secondary and exploratory endpoints and we await a meta-analysis to determine if KRAS mutant patients are deleteriously affected by treatment with a TKI compared to chemotherapy.

Furthermore, the only two studies that have addressed the prognostic significance of KRAS in NSCLC have contradictory results not allowing us to understand its potential role as a clinically relevant biomarker for NSCLC. Utilisation of KRAS during EGFR screening should be left to the decision of the diagnostic laboratory. If it is included into a screening algorithm, the same sample, reporting, quality control and sample access issues as indicated for EGFR pertain.

Several other somatic mutations have been identified in NSCLC, however, to date they do not appear to have any clinical utility either with respect to prediction, prognosis or utility in screening algorithms. Until sufficient evidence supports their clinical utility they are not recommended outside of clinical trials.
Recommendation 6.1 – Routine testing for somatic KRAS mutations, has not entered clinical routine despite evidence of that KRAS is a negative predictive factor for TKIs. Although not advised for routine testing several laboratories utilize it in screening algorithms due to its mutual exclusivity from EGFR mutations. Recommendations as per testing for EGFR and EML4-ALK apply. (LOE II, SOR B)

Recommendation 6.2 – The routine testing for BRAF, ERBB2, PIK3CA somatic gene mutations is not currently recommended outside of clinical trials. (LOE IV, SOR C)

7. What is the role of customising chemotherapy based on mRNA levels of ERCC1, RRM1, TS and BRCA1?

Recommendation 7.1 – Routine testing for mRNA levels of ERCC1, RRM1, TS and BRCA1 is not currently recommended outside of clinical trials.

8. How does histology affect the molecular screening algorithm or therapeutic decision?

For EGFR, although there are recent recommendations from an international pane that few patients with squamous cell carcinoma harbour EGFR mutations [ref], the largest database of somatic EGFR mutations [31] indicates that the rate of EGFR mutations in non-adenocarcinomas is 8.3% (7-11%, whites and Asians respectively). Data provided by NCCN represent only individual studies. Similarly grouping of non-adenocarcinomas may overestimate the incidence of mutations in squamous histologies [currently under investigation]. One point of note: by German law diagnostic laboratories must report on any subgroup/measure that has an incidence of >1% in the
general population. For this reason they are obliged to screen all patients for mutations in all exons (18-21).

In respect to EML4-ALK, there is insufficient evidence to pre-screen patients based upon their histology.

For current treatment regimens, pemetrexed/cisplatin and bevacizumab/chemotherapy are recommended for patients with non-squamous NSCLC who are EGFR mutation negative (or with unknown mutation status). For such reasons the previous comments regarding the preference of tumor biopsy over cytological samples should be stressed.

Recommendation 8.1 – Biopsy is preferential to cytology for molecular analysis. (LOE II, SOR A)

Recommendation 8.2 – Certain therapies (chemotherapy or biological) may have approval based upon histological stratification. (LOE III, SOR A)

<table>
<thead>
<tr>
<th>Recommendation 1</th>
<th>Is there sufficient evidence for routine somatic EGFR mutation analysis?</th>
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<tbody>
<tr>
<td>1.1</td>
<td>EGFR somatic mutation testing should be carried out to identify patients eligible for first-line treatment with EGFR TKIs.</td>
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<td>1.2</td>
<td>All patients, irrespective of histology, smoking status or gender should be tested for EGFR mutation status.</td>
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<td>1.3</td>
<td>Patients harbouring sensitizing EGFR mutations should be treated with EGFR TKIs regardless of the genotype of the sensitizing mutation.</td>
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<td>1.4</td>
<td>IHC (protein expression) and ISH (gene copy number) of EGFR are not recommended for routine clinical use.</td>
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<td>1.5</td>
<td>The concomitant presence of T790M (resistance) mutation should not preclude the use of EGFR TKIs in the first-line setting (or at first administration of TKI).</td>
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## Recommendation 2

### What is the optimal source of material for molecular analysis?

2.1 DNA derived from tumor biopsy material is the optimal source for *EGFR* somatic mutation testing; repeat biopsy may be indicated to gain sufficient material to test. There is no evidence to mandate testing for an *EGFR* somatic mutation outside the first-line setting.

2.2 Alternative biopsy material other than tumor biopsy, cytology, BAL, FNAs, ascites, brushings, have all been reported to harbour *EGFR* mutations. No clear evidence suggests that such biopsies are not concordant with a tumor biopsy, and as such they may be utilised for molecular classification.

2.3 Other surrogate sources of tumor derived DNA, including serum, plasma or CTCs have not demonstrated sufficient correlative concordance to warrant their use outside of exploratory analyses (or in cases devoid of available biopsy material).

2.4 Sensitizing mutations in *EGFR* are present in all four exons (18-21). Screening practices for clinical studies have utilised several techniques for their identification. Concerns have been raise about inadequacies of certain testing methodologies. Utility of more than one technique to allow high sensitivity (detection of limited allelic content) and high specificity (wide mutational spectrum coverage) is suggested to maintain a high PPV.

2.5 The use of alternative techniques (other than robust PCR based methods such as ARMS or sequencing) including mutation specific MoAbs demonstrate high false positive rates and are not recommended for *EGFR* mutation analysis outside of research use.
**Recommendation 3**  
Guidance on tissue handling, analysis and reporting of somatic *EGFR* mutational analysis

3.1 Pathological review should be performed by a registered pathologist and reporting should specify the component(s) according to standard nomenclature.

3.2 A pathologist (or molecular pathologist) should be involved in sample preparation and interpretation of *EGFR* mutation status result reporting. Micro- or macro-dissection of samples are intended to maximize tumor cell content (typically >50%) before DNA extraction. The report should include comment(s) on biopsy source and processing, quantity and quality of tested sample, and should follow guidance on genetic test reporting such as that provided by the EMQN, UKNEQAS and the Human Genome Variation Society for nomenclature and reporting guidelines (http://www.hgvs.org).

**Recommendation 4**  
The importance of participation in quality assurance programs for genetic testing?

4.1 Somatic mutation tests that are required for clinical decision making should only be carried out in laboratories that are compliant with country-specific standards for clinical diagnostic testing (UK, Clinical Pathology Accredited Laboratories; USA, CLIA Laboratories). The laboratory should have accreditation to conduct the test and should participate in internal and external quality assurance programs to maintain such accreditation (EMQN, UKNEQAS, CAP) on a routine basis.

**Recommendation 5**  
Testing guidelines for *EML4-ALK*

5.1 Routine testing for *EML4-ALK* is recommended.

5.2 All recommendations concerning *EGFR* testing relevant for laboratory and clinical implementation are essential the same for *EML4-ALK*.

5.3 Current recommendation is that *EML4-ALK* testing is conducted by FISH in a certified laboratory.
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<tr>
<th>Recommendation 6</th>
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<th>IMAGE 3</th>
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<tr>
<td>Other (veristrat)</td>
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<td>Prognostic markers IALT, JBR.10</td>
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<td>Predictive markers P53, p27, ERCC1, MSH2</td>
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References


36. US abstract


6.2 FIRST-LINE THERAPY

Linardou E, Samantas E.

Introduction
Non-small-cell lung cancer (NSCLC) accounts for 80%–85% of all lung cancer cases. The majority of patients present with advanced disease. Five-year age- and area-adjusted relative survival of all lung cancer patients in Europe continues to be low at 11%. The majority of patients diagnosed with NSCLC are unsuitable for curative treatment due to advanced disease, thus systemic therapy is the standard approach with palliation, patients’ quality of life (QOL) and prolongation of life being the goal of therapy. Decisions on the treatment strategy should take into account disease, histology, age, performance status, comorbidities and patient’s preferences. Generally, treatment should be initiated after interdisciplinary discussion, ideally at a multidisciplinary oncology board. Systemic treatment should be guided by an experienced medical oncologist and selection of agents should take into account the patient’s situation, the treatment goal and potential side-effects of treatment. In any stage of NSCLC, smoking cessation should be encouraged as it may increase treatment efficacy and decrease risk of complications.

Pleural or pericardial effusion is a criterion for Stage IV, M1a disease (7th edition AJCC, T4 with effusion has been re-classified as M1a disease). In patients with effusions positive for malignancy, local treatment (paracentesis, drainage, pericardial window) should supplement systemic treatment as for stage IV disease. For patients with distant metastases, M1b, treatment algorithm takes into account the location of the metastasis, ie. solitary nodule in the brain or the adrenal. Patients with solitary brain metastasis may benefit from surgical resection.
Chemotherapy – The evidence

Patients with stage IV disease and a good PS, benefit from chemotherapy, usually with a platinum-based regimen. Drugs that have proved useful for stage IV NSCLC include platinum agents (cisplatin, carboplatin), taxanes (paclitaxel, docetaxel), vinorelbine, vinblastine, etoposide, pemetrexed, gemcitabine. Combinations using many of these produce 1-year survival rates of 30-40% and are superior to single agents. Phase III randomized trials have shown that many of the platinum-doublet combinations yield similar objective response rates and survival, differing slightly for toxicity, convenience and cost. A recent meta-analysis of 16 trials with a total of 2,714 patients, of which 12 trials used platinum-based regimens, compared the efficacy of chemotherapy with BSC in patients with NSCLC. It showed a benefit to chemotherapy in reduction of risk of death (hazard ratio=0.77;95%CI, 0.71 to 0.83;\(P\leq0.0001\)) and an increase in 1-year survival. In patients with a PS of 0 or 1, evidence supports using a combination of two cytotoxic drugs for first-line therapy. Recent trials and an MA comparing two drugs vs one drug demonstrated improvement in radiologic response rate for patients receiving two drugs, and one trial and the MA found statistically significant improvements in OS. None of the individual trials, or the MA, testing combinations of three cytotoxic drugs versus two drugs demonstrated a survival benefit with the use of three cytotoxic drugs, but they all demonstrated increases in toxic AEs with three cytotoxic drugs. In the last 10 years, 15 RCTs and 4 literature-based MAs compared platinum- with non–platinum-containing regimens. Seven trials and the 4 MAs reported a significant advantage in response to platinum-based therapy compared with non–platinum-based regimens, and the 4 MAs and one individual study showed a significant survival advantage with platinum-based therapy. Contraindications to platinum-based therapy include allergy to cisplatin or carboplatin, baseline hearing loss, renal insufficiency, intolerable nausea despite optimal emesis prophylaxis, intolerance to corticosteroids, and patient refusal to take a platinum drug. For these patients, non-platinum combinations are acceptable alternatives.
Data on alternative schedules of administration is limited to two studies of paclitaxel/carboplatin regimens which demonstrated no difference in weekly versus every-3-week administration of paclitaxel/carboplatin. Hematologic toxicities were greater in the every-3-week schedules.

Some cisplatin-based combinations lead to better outcomes than others. Observations that docetaxel/cisplatin was superior to vinorelbine/cisplatin in a general NSCLC population, that pemetrexed plus cisplatin was superior to gemcitabine plus cisplatin for patients with non-squamous NSCLC, and that gemcitabine plus cisplatin was superior to pemetrexed plus cisplatin for patients with squamous NSCLC were based on individual clinical trials or retrospective (although preplanned) subgroup analyses. The data are not sufficient to narrow down the selection of a platinum-based doublet to only two choices based on efficacy alone, and the clinician must often choose one chemotherapy regimen over another based on other factors, including drug schedule and AEs.

The choice of either cisplatin or carboplatin is acceptable. Drugs that may be combined with platinum include the third-generation drugs docetaxel, gemcitabine, irinotecan, paclitaxel, pemetrexed, and vinorelbine. The evidence suggests that cisplatin combinations have a higher response rate than carboplatin and may improve survival when combined with third-generation agents. Carboplatin is less likely to cause nausea, nephrotoxicity, and neurotoxicity than cisplatin but is more likely to cause thrombocytopenia. There is a lack of consistent superiority of either agent in terms of OS, toxicity, or QoL across the literature. In recent MAs, cisplatin was superior to carboplatin in terms of survival in certain subgroups, including non-squamous NSCLC, and when combined with third-generation agents. Data on neurotoxicity are confounded by a preponderance of trials that combine carboplatin with taxanes, which are among the most neurotoxic drugs.

In patients with stage IV NSCLC, first-line cytotoxic chemotherapy should be stopped at disease progression or after four cycles in patients whose disease is not responding to treatment. Two-drug cytotoxic combinations should be administered for no more than six cycles.
Targeted agents – The evidence for use in first-line

Specific targeted therapies have been developed and gained approval for the treatment of advanced NSCLC. Bevacizumab is a recombinant mab that blocks the VEGF. Erlotinib and gefitinib are small molecule (tyrosine kinase) inhibitors of EGFR. Crizotinib is a small molecule inhibitor that targets ALK and MET.

Erlotinib was FDA approved in 2004 for the treatment of advanced NSCLC after failure of at least one prior chemotherapy regimen. Gefitinib was recently approved as first-line therapy of advanced NSCLC harboring EGFR mutations regardless of the patient’s PS. In unselected patients with stage IV NSCLC, erlotinib or gefitinib should not be used in combination with cytotoxic chemotherapy as first-line therapy. In unselected patients, evidence is insufficient to recommend single-agent erlotinib or gefitinib as first-line therapy. The first-line use of gefitinib is recommended for patients with activating EGFR mutations. If EGFR mutation status is negative or unknown, then cytotoxic chemotherapy is preferred. Four trials examined using erlotinib or gefitinib in combination with cytotoxic chemotherapy doublets in the first-line setting, and all four found no advantage in survival, PFS, or response with the addition of an EGFR TKI to chemotherapy. In three of the four trials, there were more AEs in the arm with the EGFR TKI (primarily skin toxicities and diarrhea). In the phase III IRESSA Pan-Asia Study (IPASS), investigators compared gefitinib with carboplatin/paclitaxel as first-line treatment in populations specific to East Asia, all of whom had adenocarcinoma and were light or never smokers. The primary end point was PFS, which was statistically significantly longer with gefitinib; OS, as secondary end point, was not. Hematologic AEs, alopecia, neuropathy, and nausea were greater with chemotherapy, whereas diarrhea and skin toxicities were greater with gefitinib. The results of analysis of PFS by EGFR mutation status found that patients with mutations experienced a better outcome with gefitinib and patients without mutations benefited more from chemotherapy. The EGFR mutation status of most patients’ tumors is negative or unknown, in which case
cytotoxic chemotherapy is preferred. The American Society of Clinical Oncology recommends that patients be tested for whether they have an *EGFR* mutation, however, the NCCN and ESMO guidelines specify that only patients with nonsquamous histology (e.g. adenocarcinoma) be assessed for *EGFR* mutations, since patients with squamous cell carcinoma are unlikely to have *EGFR* mutations.

**Crizotinib** was recently approved by the FDA (July 2011) for patients with advanced NSCLC who are positive for the ALK gene rearrangement, based on dramatic responses (>80%) seen in ongoing phase II trials in patients with the molecular change who had previously progressed.

There are three RCTs (two phase III) published on the antiangiogenesis agent bevacizumab. The phase III trial that added bevacizumab to carboplatin/paclitaxel and reported OS found statistically significant increases for OS, as well as for PFS and response. The second phase III trial, of bevacizumab with cisplatin/gemcitabine, confirmed the PFS benefits. The primary AEs with bevacizumab included grade 4 and 5 hematologic events, as well as non-hematologic toxicities. Serious bleeding was initially seen in the phase II trial with certain tumors, leading to a narrowing of eligibility criteria in phase III to patients with non–squamous cell carcinoma, as well as excluding patients with certain criteria. Toxic deaths have occurred in all trials, including a trial of bevacizumab as second-line therapy with and without chemotherapy or erlotinib. For the recommendations on the use of bevacizumab we take into account the fact that the addition of bevacizumab to gemcitabine/ cisplatin did not improve OS and the lack of phase III data on combining bevacizumab with other cytotoxic regimens.

Based on the results of one large phase III RCT (phase III FLEX; First-Line Erbitux in Lung Cancer study), clinicians may consider the addition of cetuximab to cisplatin/vinorelbine in first-line therapy in patients with an *EGFR*-positive tumor as measured by immunohistochemistry (IHC).
Cetuximab may be continued, as tolerated, until disease progression. Positive EGFR protein expression assessed by IHC was an eligibility criterion of the FLEX trial. These results have not yet been validated in a prospective study. The results of these studies suggest that cetuximab may add benefit in terms of survival when combined with cisplatin/vinorelbine. As in the case of bevacizumab, there are insufficient data to recommend the addition of cetuximab to other chemotherapy regimens. The duration of cetuximab is recommended to continue until intolerance or progression of disease, based on the design of the studies. However, the optimal duration of treatment with cetuximab beyond chemotherapy is not known.

Patients with solitary metastases (brain, adrenal, lung)

For patients with solitary brain metastasis, resection or stereotactic radiosurgery (SRS) are the primary alternatives. The addition of whole brain radiotherapy (WBRT) to surgery or SRS improves local control but not overall survival. Therefore an individual assessment should be applied. If the primary tumour is resectable (i.e. T1–3 N0–1) surgery with or without chemotherapy is an option in highly selected, fit patients. Alternatively, radiotherapy or chemoradiation is an option in selected patients with localized thoracic disease. In other patients chemotherapy is recommended. For patients with isolated adrenal metastasis, systemic chemotherapy is recommended. In selected fit patients adrenalectomy can be considered, if lung disease is resectable as well. Solitary lesions in the contralateral lung should be considered as secondary primary and treated with curative intention if both tumours are potentially curable.
Summary of Recommendations

1. Should first-line chemotherapy be offered to all patients with advanced NSCLC?

Recommendation 1: Systemic treatment as first-line therapy should be offered to all patients with metastatic NSCLC according to their PS status. (LOE I, GOR A)

2. What is the most effective first-line chemotherapy for the treatment of patients with stage IV NSCLC?

Recommendation 2: Platinum-based chemotherapy with a doublet is preferred to non-platinum-based chemotherapy in eligible patients with metastatic NSCLC. There is no standard platinum-based doublet for metastatic NSCLC in general. (LOE I, GOR A)

3. Is there a preferred combination based on histological subtype?

Recommendation 3: Histology of the tumor should guide our therapeutic options. (LOE I, GOR B)

4. Is cisplatin preferred to carboplatin-based chemotherapy?

Recommendation 4: cisplatin should be used in fit patients with PS 0-1 who have adequate organ function. (LOE I, GOR B)

5. What is the optimal duration of first-line chemotherapy for stage IV NSCLC?

Recommendation 5:

a. First-line cytotoxic chemotherapy should be stopped at disease progression or after four cycles in patients whose disease is not responding to treatment.

b. Four cycles of chemotherapy appear sufficient in most NSCLC patients but six cycles may be considered depending on response and toxicity. Two-drug cytotoxic combinations should be administered for no more than six cycles.
6. When should bevacizumab be used and with which chemotherapy should it be combined?

Recommendation 6: Bevacizumab combined with platinum-based chemotherapy is a treatment option in eligible patients with nonsquamous NSCLC. (LOE I, GOR B)

7. What is the preferred first-line treatment in patients with advanced NSCLC harboring an activating EGFR mutation?

Recommendation 7: An EGFR TKI (gefitinib, erlotinib) is the preferred first-line treatment in patients whose tumor harbors an activating EGFR mutation. (LOE I, GOR A)

8. What is the preferred treatment option for patients with the EML4-ALK rearrangement?

Recommendation 8: In patients with the EML4-ALK gene rearrangement, crizotinib is the option of choice. (LOE II, GOR A)

9. Is there a role for cetuximab?

At present cetuximab is not approved by regulatory agencies in Europe for the treatment of NSCLC.

Recommendation 9: cetuximab added to platinum-based chemotherapy could be considered as a treatment option for patients with EGFR immunohistochemistry positive metastatic NSCLC, in particular when cisplatin/vinorelbine is the chemotherapy backbone. (LOE I, GOR B)

10. What is the optimal treatment and sequence for patients with brain metastases at diagnosis?

Recommendation 10: local treatment to brain followed by systemic therapy is the standard approach for patients with brain metastases at diagnosis. The type of local treatment depends on the number and site of brain lesions. Local treatment may be delayed in asymptomatic patients. (LOE II, GOR B)
Stage IV NSCLC - First-line therapy algorithm

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Establish histologic subtype

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1. Adenocarcinoma, large cell, NOS

   EGFR mutation test
   
   Positive
   gefitinib
   erlotinib
   
   Negative
   ALK test
   
   Positive
   crizotinib
   
   Negative
   1\textsuperscript{st} line chemo

   - Platinum-based doublet
     - Bevacizumab+carboplatin/paclitaxel
     - Cisplatin/pemetrexed
   - Cetuximab/cisplatin/vinorelbine

2. Squamous cell carcinoma

   - Platinum-based doublet
   - Cisplatin/gemcitabine
   - Cetuximab/cisplatin/vinorelbine
References


6.3 MAINTENANCE THERAPY

Pallis A, Aggelaki S.

Several phase III trials have intensively investigated the role of maintenance treatment in the field of stage IV NSCLC, in order to improve the results in this devastating disease.

Two different approaches have been evaluated; the so-called continuation maintenance when the maintenance agent was part of initial therapy and is continued in the absence of disease progression ("maintained") or switch maintenance when a third agent is initiated after a defined number of cycles chemotherapy in the absence of disease progression. Several phase III trials with both chemotherapeutic and targeted agents have demonstrated PFS prolongation (continuation maintenance) or both PFS and OS benefit (switch maintenance).

Several other phase III studies have demonstrated a PFS (gemcitabine in unselected population, pemetrexed in patients with non-squamous histology) or OS (pemetrexed in patients with non-squamous histology) benefit with continuation maintenance. Switch maintenance has demonstrated PFS (docetaxel in unselected population, erlotinib and gefitinib in unselected population, pemetrexed in patients with non-squamous histology) and OS benefit (erlotinib in unselected population, pemetrexed in patients with non-squamous histology).

Currently, erlotinib and pemetrexed are registered as maintenance treatment in patients with NSCLC not progressing after four cycles of standard platinum-based doublet chemotherapy. The US Food and Drug Administration (FDA), and the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) approved pemetrexed (Alimta®; Eli Lilly and Company, Indianapolis, IN) for maintenance treatment of patients with locally advanced or metastatic non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based doublet induction.
chemotherapy. EMA recommends erlotinib (Tarceva, OSI Pharmaceuticals Inc and Genentech, Inc) maintenance treatment for unselected patients with locally advanced or metastatic NSCLC who had stable disease after four cycles of standard platinum-based first-line chemotherapy. FDA has approved erlotinib for the first-line maintenance treatment in unselected patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based chemotherapy.

Recommendations

➔ For patients with stable disease or response after four cycles of standard platinum-based doublet chemotherapy, immediate treatment with an alternative, single-agent chemotherapy such as pemetrexed in patients with non-squamous histology, should be considered.

➔ Erlotinib should be considered in patients of any histology with stable disease after four cycles of platinum-based doublet chemotherapy.

➔ However, a break from cytotoxic chemotherapy after a defined number of chemotherapy cycles is also acceptable, with initiation of second-line chemotherapy at documented disease progression. (LOE IB, GOR A)
6.4 SECOND-LINE THERAPY IN NSCLC

Makatsoris Th.

In patients treated with first-line chemotherapy for advanced NSCLC, disease progression usually occurs within 3–5 months. Second-line therapy can be defined as any treatment following first-line therapy for metastatic NSCLC, irrespective of any maintenance or adjuvant therapy. The goal of second- or third-line treatment is prolongation of life and symptom control. Factors that influence treatment decisions include: histology, age, PS, comorbidities, previous therapy, molecular features, potential side effects, goal of treatment and patients’ preferences.

The decision to administer second and third-line therapy should be based on a number of factors: histology, age, performance status (PS), comorbidities, previous therapy, molecular features, potential side effects, ultimate goal of the treatment and patients’ preferences.

Age alone is not considered to be an exclusion criterion for second- or third-line therapy. In a retrospective study of 461 patients <70 years versus >70 years there was no difference in median PFS (P=0.08) and no statistical difference in toxicity (Wu, 2010).

6.4.1 Cytotoxic chemotherapy

Second-line therapy at progression palliates tumor-related symptoms and improves survival (Barlesi, 2006). Second-line cytotoxic chemotherapy for advanced NSCLC should be considered in patients with a good performance status with progression after initial chemotherapy or treatment with a targeted agent. Various studies have shown response rates of around 10%. Both docetaxel and pemetrexed have been approved for second-line monotherapy. Docetaxel: The efficacy of second-line chemotherapy was first shown in a phase III trial in which 104 patients with previously treated stage IIIB or IV NSCLC were randomly assigned to docetaxel monotherapy (100 mg/m² or 75 mg/m² every three weeks) or best supportive care (BSC) (Shepherd 2000).
Patients receiving docetaxel had a significantly better median survival (7.5 versus 4.6 months with BSC) and one-year survival (37 versus 11 percent). Side effects such as febrile neutropenia were less common in patients treated with the 75 mg/m² regimen. There was also improvement in the quality of life. Docetaxel was compared to vinorelbine or ifosfamide in a trial of 373 patients who had failed a platinum-containing regimen (Fossella, 2000). The patients were randomly assigned to docetaxel (100 mg/m² every three weeks), docetaxel (75 mg/m² every three weeks), vinorelbine (30 mg/m² weekly), or ifosfamide (2 g/m² daily for three days, every three weeks). Although the median survival was similar in all groups (5.6 months), 32 percent of patients treated with docetaxel (75 mg/m²) survived one year versus 21 percent with docetaxel (100 mg/m²) and 19 percent of those receiving vinorelbine or ifosfamide.

6.4.2 Pemetrexed

The multi-targeted antifolate pemetrexed appears to be as active and have less toxicity than docetaxel for second-line therapy in patients with nonsquamous NSCLC. In a phase III trial, 571 patients with recurrent NSCLC were randomly assigned to docetaxel (75 mg/m²) or pemetrexed (500 mg/m²), each given every three weeks (Hanna, 2004). Treatment was continued until there was disease progression or unacceptable toxicity. Pemetrexed was combined with folic acid (350 to 1000 mcg daily) and vitamin B12 (1000 mcg every nine weeks) to decrease the incidence of hematologic toxicity. Additionally dexamethasone (4 mg twice daily for three days) was given to minimize cutaneous toxicity. The objective response rates were similar (9 percent for both agents), as was median survival (eight months in each group). However, pemetrexed was associated with significantly less grade 3 or 4 neutropenia (5 versus 40 percent), febrile neutropenia (2 versus 13 percent), use of granulocyte colony-stimulating factor support (3 versus 19 percent), and hair loss (6 versus 38 percent).

Subset analyses from this trial suggested that pemetrexed was more active than docetaxel in patients with nonsquamous tumors (overall survival median
9.3 versus 8.0 months, hazard ratio [HR] 0.78, 95% CI 0.61-1.00) (Scagliotti, 2009). In contrast, pemetrexed was less effective than docetaxel in patients with squamous carcinomas (median overall survival 6.2 versus 7.4 months, HR 1.56, 95% CI 1.08-2.26). This effect is consistent with the findings of the preferential activity of pemetrexed in patients with nonsquamous histology in the first-line setting. This has led to the restriction of pemetrexed in patients with nonsquamous NSCLC.

6.4.3 Combination chemotherapy

Combination chemotherapy does not appear to improve overall survival compared to single agent chemotherapy in the second-line setting. A meta-analysis that included 847 patients from six trials, in which patients were randomly assigned to either single agent chemotherapy or a chemotherapy doublet was performed (Di Maio, 2009). It was shown that doublet chemotherapy as second-line treatment of advanced NSCLC significantly increased response rate and progression-free survival, but it was more toxic and did not improve overall survival compared to single-agent chemotherapy.

6.4.4 Epidermal growth factor receptor inhibitors

Erlotinib and gefitinib were investigated for efficacy in pretreated patients. A phase III study comparing erlotinib with placebo in stage IIIIB or IV NSCLC patients who had received one to two prior combination chemotherapy regimens and were not candidates for further cytotoxic treatment demonstrated significant, although moderate, clinical benefit of erlotinib (median OS of 6.7 and 4.7 months for erlotinib and placebo, P <0.001) (Shepherd, 2005). Patients treated with erlotinib had also improvements in pain, cough and dyspnea.

Another phase III study evaluated gefitinib versus placebo in patients with advanced NSCLC who had disease progression after one or two prior chemotherapy regimens (ISEL study). In this study there was no statistically significant difference in overall survival (HR 0.89, P=0.087) (Thatcher, 2005).
In preplanned subgroup analyses, there was significant prolongation in OS in patients who had never smoked and were of Asian ethnicity. In contrast to the ISEL trial, another trial (INTEREST), found that OS with gefitinib was not inferior compared to docetaxel (7.6 months versus 8.0 months for gefitinib and docetaxel respectively, p=0.62) (Kim, 2008).

In the case that \textit{EGFR} sensitizing mutations are present, the use of an \textit{EGFR} TKI is recommended if it has not been used previously. In this case, even in patients with poor performance status (PS 3 or 4) an \textit{EGFR} TKI could be considered as such patients could benefit from this treatment.

\textbf{6.4.5 ALK inhibition}

The identification of the novel fusion oncogene EML4-ALK specific molecular abnormality in a subset of patients with NSCLC has led to the development of crizotinib, an ALK inhibitor. In a retrospective study comparing survival outcomes in crizotinib-treated patients and crizotinib-naive controls screened during the same time period it was seen that in patients with advanced, ALK-positive NSCLC, crizotinib therapy was associated with improved survival compared with that of crizotinib-naive controls. Additionally, survival in 30 ALK-positive patients who were given crizotinib in the second-line or third-line setting was significantly longer than in 23 ALK-positive controls given any second-line therapy (median overall survival not reached vs 6 months, 1-year overall survival 70\% vs 44\% and 2-year overall survival 55\% vs 12\%; hazard ratio 0.36, 95\% CI 0.17–0.75; p=0.004) (Shaw 2011). Crizotinib was approved by the US Food and Drug administration in August 2011 independently of whether or not the patient has received previous treatment for advanced NSCLC.
Recommendations

1. **Patients eligible for second-line therapy should be in relatively good condition (PS 0-2) (LOE I, GOR A)**

2. **Agents that can be used as second-line therapy in previously treated patients with advanced NSCLC include:**
   a. Docetaxel for **squamous NSCLC** (LOE II, GOR B)
   b. Pemetrexed for **non-squamous NSCLC** (LOE II, GOR B)
   c. Erlotinib (LOE II, GOR B)
   d. Gefitinib

3. **Age alone is not an exclusion criterion for second-line therapy (LOE III, GOR A)**

4. **When EGFR sensitizing mutations are present, it is recommended to use an EGFR TKI if not previously used (LOE II, GOR B)**

5. **In patients with poor PS who have an EGFR sensitizing mutation, EGFR TKIs can be considered.**

6. **In anaplastic lymphoma kinase (ALK) fusion gene positive advanced non-small cell lung cancer therapy with crizotinib is recommended if not previously used.**
References


6.5 THIRD-LINE THERAPY

Panopoulos Ch.

Introduction

Patients, who progress after second-line treatment for non-small cell lung cancer, may be candidates for third-line treatment. Treatment decisions in third-line treatment should take into account a number of factors, like age, PS, histology, comorbidities, molecular biology factors, markers, side effects and finally patient preferences. The choice of drugs should also take into account previous first and second-line treatments.

Aim of third-line treatment

Available data do not support the routine use of 3rd treatment. The selection of patients for third-line treatment should be done in base of PS.

1. Selection of drugs

Only erlotinib has been approved in the U.S. and Europe for third-line treatment. (LOE II, GOR B)

Inclusion in clinical trials, supportive care and various agents could be an option in individualized basis.

There is one randomized trial, which compared erlotinib with placebo in previously treated patients with first and second-line chemotherapy and who were EGFR TKI naïve and who were not eligible for further cytotoxic therapy. In this study, erlotinib, while having a good tolerability profile without hematologic toxicity, also showed good results according with the PS. For patients with a PS 0-1, the response rate was 8% and 11% for those with PS 2-3, and the median survival was 8.3, 4.3 and 1.9 months for patients with PS 0-1, 2 and 3 respectively. According to the results of this study, the use of erlotinib is suggested as third-line treatment where the PS of the patients is usually diminished.
In a retrospective Japanese study of efficacy and toxicity of pemetrexed as a third-line treatment the overall and PFS where 3.03 months, with response rate 12% and a favorable toxicity profile. PS significantly influenced PFS

According to a retrospective study of 700 patients, survival and response rates decreased with each subsequent line of treatment. For these patients supportive care should be the treatment of choice. Therefore in third-line treatment an \textit{EGFR} TKI should be considered naïve for \textit{EGFR} TKI patients.

2. Which patients should receive third-line treatment?

Patients with clinical or laboratory signs of disease progression after second-line treatment are candidates for third-line treatment. The results of erlotinib studies showed that PS plays a crucial role in patient’s selection for third-line treatment

According to these studies third-line treatment should be offered to patients with good PS with a disease progression

From a retrospective analysis of 131 patients treated with third-line treatment, it seems that the best candidates can be identified using standard prognostic factors like PS and disease control after first and second-line treatments (LOE I, GOR A)

3. Is \textit{EGFR} mutation status a crucial criterion for treatment choice?

In case of \textit{EGFR} mutated, the use of \textit{EGFR} TKIs is recommended if not received in first or second-line. (LOE II, GOR B)

4. Patients with symptomatic brain metastases

Brain metastases are frequent enough in advanced NSCLC (20-30%). Patients who remain or become asymptomatic after the adequate treatment (Irradiation, anticonvulsive and anti-edematous treatment) could benefit from treatment with \textit{EGFR} TKI.
There is only one phase II Japanese study with response in 6 of 14 patients with brain metastases\textsuperscript{6} (LOE V, GOR B)

### 5. Is age alone an exclusion criterion for third-line treatment?

There is a study which compared pemetrexed versus docetaxel in second-line treatment. In this study there was no statistically difference in survival for patients $>70$ years of age versus those $<70$ years\textsuperscript{7}.

In another retrospective study, there was no difference in PFS between the two age groups ($>70$ and $<70$) for various treatments\textsuperscript{8}

The results of these studies show that age alone should not be considered as exclusion criterion for third-line treatment (LOE III, GOR A)
References


6.6 NSCLC IN THE ELDERLY

Pallis A, Vamvakas L.

6.6.1 Introduction

As a result of an increasing life expectancy, the incidence of lung cancer diagnosed in the elderly population is rising. About 50% of newly diagnosed NSCLC cases occur in patients older than 65 years, while 30-40% of cases are diagnosed in patients older than 70 years. Data from the Surveillance, Epidemiology, and End Results (SEER) registry indicate that the median age at diagnosis in NSCLC patients is 69 years. Based on these observations, it is clear that NSCLC represents a significant health problem in elderly. The cut-off point at which an adult is considered ‘elderly’ has not been well defined. This is because aging is a highly individualized process that can not be predicted solely on the basis of chronological age. Thus, in clinical practice, biologic instead of chronologic age should be considered. Unfortunately, to date, laboratory tests and geriatric evaluation are inadequate in defining aging. Thus, it is clear that there is an emerging need for developing tools to better evaluate a patient’s functional age rather than chronologic age. Practically, age of 70 years is considered a reference point and is commonly used in clinical trials in oncology. Based on available literature, especially at or around 70 years of age, a number of age-related physiologic changes occur (decrease in bone marrow reserves, renal function, and drug clearance), which increase the risk of toxicity related to systemic therapy; hence age 70 is widely accepted as cut-off for elderly-specific analyses.

Another important issue encountered by oncologists treating elderly cancer patients is the heterogeneity that characterizes patients of the same chronological age in everyday clinical practice. Many patients are likely to benefit from standard treatment approaches in a similar manner to patients of a younger age, however, others who present with multiple co morbidities and significant functional impairment, are at higher risk of experiencing severe treatment-related toxicity, and may require a more individualized approach. Thus it is crucial for oncologists to have a valid and reliable tool for evaluating...
a patient’s “functional” rather than chronological age to guide treatment selection. The Comprehensive Geriatric Assessment (CGA) is a thorough method used for evaluating fitness in elderly patients. According to the CGA, patients are categorized into three groups for treatment decisions; a) fit patients b) vulnerable patients c) frail patients. Patients in group A are good candidates for almost all forms of cancer treatment, with similar survival outcomes and levels of tolerability when compared to their younger counterparts. Patients in group C are usually offered appropriate supportive care or single-agent palliative chemotherapy only, due to significant co-morbid disease and poor overall functional levels. Patients in group B, however, are often the most challenging to treat due to wide-ranging variability in disease state and functional level, and an individualized approach is therefore recommended. It has been proven that CGA offers additional information to chronological age and Performance Status (PS) and often evaluates a higher percentage of elderly patients as being unfit for chemotherapy when compared to physicians’ judgment.

- The major characteristic of elderly patients with non-small cell lung cancer (NSCLC) is heterogeneity, and a precise definition of elderly patients is difficult.
- Functional capacity and organ function are more important than age, and a useful tool for treatment choice in the elderly population is to perform some kind of comprehensive geriatric assessment at baseline.

6.6.2 Surgical treatment

In patients with early stage non-small cell lung cancer, surgical resection provides the best form of treatment regarding survival rates and residual quality of life. Many surgeons, however, will not offer surgery to patients >70 years because of the additional risk associated with operating on this cohort, and limited long-term benefits they perceive this will offer. Here, several prospective and large population studies have shown unanimously, that
patients >70 years of age respond as well as younger patients in all outcome measures pertaining to morbidity, mortality and quality of life post-operatively, and should receive aggressive surgical management if considered fit for surgery.\textsuperscript{11,12}

Older patients should receive surgical treatment according to disease stage and according to preoperative selection based on cardiac evaluation studies and assessment of pulmonary function are required in order to further improve results.

\textit{Whether elderly patients should be offered lobectomy as a “standard of care” or more limited procedures (i.e. wedge resection) is not clear, although retrospective data indicate that both these procedures yield similar outcomes.}\textsuperscript{13} \textit{Pneumonectomy should be avoided or performed with caution, given the higher rate of mortality reported with this procedure.}\textsuperscript{12,14} Careful patient selection with preoperative evaluation based on cardiac and respiratory assessment is mandatory and could significantly improve the results. (LOE III/IV, GOR B)

\subsection*{6.6.3 Radical radiotherapy for potentially resectable tumors}
Radical radiotherapy appears to result in a better survival than might be expected when compared with no treatment.\textsuperscript{15} The optimal radiation dose and treatment technique (particularly with respect to mediastinal irradiation) remain uncertain. (LOE III/IV, GOR B)

\subsection*{6.6.4 Adjuvant chemotherapy after surgical resection}
There is a complete lack of prospective data regarding the role of adjuvant chemotherapy in elderly NSCLC patients after surgical resection. \textit{Elderly patients with stage II and IIIA NSCLC should be considered for adjuvant chemotherapy after surgical resection.} \textsuperscript{16} Adjuvant chemotherapy should not be withheld from patients on the basis of
chronological age alone. Treatment decisions should take into account the estimated absolute benefit, life expectancy, treatment tolerance, cognition, presence of comorbidities and patient preferences. (LOE II, GOR B)

Little information is available regarding the real benefit and tolerability of these regimens for patients over 75 years of age and further data is required to elucidate the risk versus benefit ratio.

6.6.5 Adjuvant RT after surgical resection

There is a lack of prospective data regarding the role of adjuvant RT in completely resected NSCLC patients and particularly in older patient populations. Given that adjuvant RT has been demonstrated to have a negative impact on survival and is not routinely recommended for the general population, it should not be recommended for older population groups with NSCLC.

Locally advanced disease

Four studies reported the results of age-based retrospective subgroup analyses of randomized phase III trials, which evaluated concurrent chemoradiotherapy (CMRT) in one arm. All four studies concluded that elderly and younger patients derive similar survival benefit from CMRT, but also found that there is a significantly greater risk of short-term hematologic and non-hematologic toxicity for elderly patients, which may outweigh the observed benefit.

One phase III elderly-specific trial has evaluated CMRT versus RT alone. The study was prematurely closed after enrolment of only 46 of the 190 originally planned patients (23 in the RT arm and 23 in the CMRT arm), because four treatment-related deaths occurred (three in the CMRT arm; two deaths were considered due to pneumonitis). At that time, OS was 428 days on the RT arm versus 554 days on the CMRT arm. Unfortunately, because of
its premature closure and the small number of patients randomized no definitive conclusions can be drawn from this study.

**Recommendation**

*Concurrent CMRT approach should be offered to fit elderly patients with locally advanced NSCLC. However, given the lack of adequate prospective randomized trials, specifically designed for the elderly population, and given the higher risk of toxicity in elderly patients, treatment decision should be based on performance status, absence of significant comorbid diseases and patient life expectancy. For patients who are not suitable for concurrent CMRT sequential chemotherapy-RT could be considered. (LOE II, GOR C)*

**Metastatic disease**

**Single-agent treatment**

For the elderly population the available data suggest that third generation single-agent is the standard first-line treatment for unselected NSCLC pts.

*Published data support the use of vinorelbine*\(^{22}\), *gemcitabine*\(^{23}\) or *docetaxel monotherapy*\(^{24}\). *Docetaxel produces higher PFS when compared to vinorelbine, but without a difference in OS. Very limited data are published regarding octogenarians, and thus no specific recommendations can be made for this particular age group. (LOE I, GOR A)*

**Carboplatin-based doublets**

A recently published phase III trial demonstrated a significant PFS and OS prolongation in favour of a carboplatin/paclitaxel doublet compared to gemcitabine or vinorelbine single-agent treatment. However, the higher toxicity and toxic death rate indicate that we should consider these results with caution. The selection of suitable patients should be based on patients PS, functional dependence, absence of significant comorbid diseases and patient life expectancy.
A carboplatin-based doublet chemotherapy is a valid option for fit elderly patients (PS 0 to 1 with an adequate organ function and without main comorbidities). (LOE I, GOR A)

Cisplatin-based doublets
Age-specific subgroup analyses of several phase III trials have been performed (Table 3) and all indicate outcome measures, namely response rate, PFS and OS, do not differ significantly among age groups. A recent phase III trial of cisplatin/docetaxel doublet versus single-agent docetaxel failed to demonstrate any benefit in favour of the combination arm.

Recommendations
→ Randomized, phase III, elderly-specific prospective data do not support the use of cisplatin in older patients.
→ Cisplatin-based chemotherapy with cisplatin at attenuated doses has been shown to be an active and feasible option in phase II trials and deserves prospective phase III comparison against monochemotherapy.
→ Cisplatin-based doublets could be considered as an option in fit older patients on the basis of retrospective data. (LOE I, GOR B)

Targeted agents
Given that the addition of bevacizumab to standard cytotoxic chemotherapy in elderly population is associated in some cases with significant toxicity, while it is not clear whether it offers a survival benefit or not, prospective studies to assess the therapeutic index in combination with chemotherapy are needed, before definitive recommendations regarding their use can be made.

There very limited data regarding the role of bevacizumab in older NSCLC pts with non-squamous histology. Because of the risk of contrasting toxicity data, bevacizumab should be used with caution in selected older NSCLC patients. (LOE II, GOR B)
Erlotinib or gefitinib monotherapy is active and relatively well tolerated in elderly patients with advanced NSCLC \[^{30,31}\]. However, because these data are based on phase II trials, further investigation in the context of randomized phase III trials of selected patients based on validated molecular markers (e.g. EGFR mutations \[^{32,33}\]) are needed.

**EGFR TKIs (gefitinib, erlotinib) should be used as 1st line treatment in older patients according to their indication. (LOE II, GOR B)**

**Second-line treatment**

There is lack of prospective data regarding the role of second-line treatment in elderly NSCLC population.

On the basis of retrospective data, age alone should not prevent the administration of second-line therapy and docetaxel, pemetrexed \[^{34}\] or erlotinib \[^{35}\] could be considered as second-line treatment for elderly NSCLC patients.

**Pemetrexed produces a more tolerable toxicity profile compared to docetaxel. A thorough evaluation of the patient should be done on the basis of life expectancy, expected benefit, comorbidities and patient's preferences. (LOE II, GOR B)**
References


6.7 TREATMENT OF NSCLC PATIENTS WITH PS2

Papakotoulas P, Kosmas Ch.

PS has been shown to be an independent prognostic parameter. Median overall survival of patients with PS2, whatever the treatment under investigation, is always substantially shorter than that of PS0 or PS1 patients, and rarely exceeds 5 months, with 1-year survival rates <20%.

The greatest part of the evidence available on PS2 patients comes from small sub-groups of patients with PS2, enrolled in clinical trials usually including patients with a PS ranging from 0 to 2. The proportion of patients with PS2 in these trials is often <20% of the whole study population, suggesting the existence of a selection bias determining the exclusion of PS2 patients with worse general conditions and co-morbidities.

Consequently, it is not surprising that the proportion of PS2 patients in population-based studies, not biased by inclusion criteria and not restricted by the characteristics of experimental treatment, is consistently higher (30%-40%) than that reported in the majority of clinical trials.

- PS: independent prognostic factor
- PS 2 patients have shorter survival than PS 0-1
- The prevalence of poor PS is quite high in lung cancer patients
- Providers tend to underestimate poor PS
- Specific clinical trials and treatment guidelines for this patient population are urgently needed.

CHEMOTHERAPY VERSUS TARGETED THERAPY

Whenever possible, therapy should be individualized based upon the molecular and histologic features of the tumor. If feasible, patients should have tumor tissue assessed for the presence of a somatic mutation in the epidermal growth factor receptor (EGFR), which confers sensitivity to EGFR tyrosine kinase inhibitors (erlotinib or gefitinib), and for the anaplastic lymphoma kinase (ALK) fusion oncogene, which confers sensitivity to crizotinib.
EGFR somatic mutation testing should be carried out to identify patients eligible for first-line treatment with EGFR TKIs (LOE I, GOR A)

**EGFR TKIs in unselected patients**

A randomized trial in previously untreated patients with a PS 2 who were not selected based upon EGFR mutation status observed worse overall survival with erlotinib compared with chemotherapy. However patients who crossed over to erlotinib had the best outcome (a median survival of 14.9 months). The subgroup analyses identified sex and histology as predictors of outcome, with females having a better PFS on erlotinib and squamous cell carcinoma patients having a better PFS when treated with chemotherapy. Lastly, patients who had never smoked had a better outcome with erlotinib.

This subset analysis was based on small numbers of patients and cannot be used to guide decisions but is raising questions:

*Is selection or “enrichment” based on clinical features helpful in identifying unselected patients who tend to benefit the most from TKIs, and are not candidates for cytotoxic chemotherapy?*

*What is the outcome of patients crossing to TKIs after chemotherapy?*

Two other trials in previously untreated patients not selected based upon EGFR mutation status, showed that erlotinib and gefitinib did not improve overall survival compared with best supportive care.

*Are EGFR inhibitors appropriate for poor performance status patients in whom the EGFR mutation status has not been assessed but who are not candidates for cytotoxic chemotherapy?*

**EGFR MUTATION POSITIVE PATIENTS**

Single agent EGFR TK inhibitors may have a dramatic benefit in carefully selected poor performance status patients with known mutations in EGFR. Patients with tumors harboring these mutations had an extraordinary outcome with EGFR TKIs, including response rates >60% and a median survival three- to four-fold higher than that generally observed with conventional cytotoxics.

As an example, in a Japanese study, gefitinib (250 mg/day) in patients with
previously untreated, advanced NSCLC and an **EGFR** mutation resulted in a response rate 66%. The median progression-free survival, median overall survival, and one-year survival rates for the entire cohort were 6.5 months, 18 months, and 63 percent, respectively. Among the patients with a performance status $\geq 3$, 68% improved to a performance status $\leq 1$.

> **For patients with a poor performance status with a known sensitivity mutation in the EGFR receptor, single agent therapy with an EGFR inhibitor (erlotinib or gefitinib) (LOE I, GOR B).**

**ALK FUSION ONCOGENE POSITIVE**

Oncogenic fusion genes consisting of EML4 and anaplastic lymphoma kinase (ALK) are present in a subgroup of NSCLC, representing 2%–7% of tumors. The presence of the ALK fusion oncogene conferred sensitivity to crizotinib, a specific inhibitor of the anaplastic lymphoma kinase (ALK) tyrosine kinase, in phase II studies.

In a recent phase II trial\(^4\), the response rate to crizotinib was 57% in patients with FISH-positive EML4-ALK rearrangements, and 77% of patients were continuing to receive crizotinib at the time of data cut-off. The estimated probability of 6 months PFS was 72%, with no median for the study reached.

Although these studies contained only a limited number of patients with a poor performance status, this approach is preferred for these patients.

> **For poor performance status patients whose tumors contain an ALK fusion oncogene, therapy with crizotinib is recommended (LOE II, GOR B).**
NO EGFR MUTATION AND NO ALK FUSION ONCOGENE

Systemic chemotherapy

It is now well accepted that cisplatin-based chemotherapy confers an improvement in overall survival and offers substantial palliation for patients with metastatic non-small cell lung carcinoma (NSCLC) compared with best supportive care. However, these advances apparently are confined to patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1.

A worse PS is characterised by lower response rates to chemotherapy, shorter time to treatment failure and shorter progression-free survival\(^5\). Moreover, it is a widely held opinion that these unfit patients are at higher risk for severe toxicity, which would counterbalance the eventual small benefit expected.

However, more recent trials and analyses\(^5\) that have focused specifically upon patients with a poor performance status indicate that some patients do benefit from treatment and the overall rate of toxicity does not differ significantly from the rate of toxicity in the PS-0 or PS-1 cohorts. Furthermore it was suggested that the untoward incidence of adverse events is not all drug-related and is secondary, at least in part, to the comorbidities that often are associated with an impaired PS.

\(\rightarrow\) **For patients with PS2 and without a sensitizing molecular abnormality, cytotoxic chemotherapy should be offered as an option. (LOE I, GOR B)**
Single agent chemotherapy

On the basis of current evidence, chemotherapy appears justified in patients with advanced NSCLC and a PS of 2. Subgroup analyses from several randomized trials suggest that several new-generation cytotoxic drugs are superior to BSC alone in this category of patients. Therefore, single agent chemotherapy with these drugs (e.g. gemcitabine, vinorelbine, and taxanes) represents an historical option for palliative treatment of these patients. The choice of the drug should be based on the toxicity profile of each agent and type of co-morbid conditions.

→ Treatment with a single agent is generally recommended. (LOE II, GOR C)

Single agents versus two-drug combinations

Combination chemotherapy usually results in significantly higher objective response rates than single agent therapy. Toxicity is more severe with combination regimens, including the incidence of serious or life-threatening adverse events and treatment-related deaths.

One randomized controlled phase III trial designed exclusively for patients with PS 2 and a phase III trial (comparing docetaxel with the combination of docetaxel plus gemcitabine) with planned subgroup analysis by PS found no survival benefit between comparators for patients with PS 2, whereas another phase III trial (paclitaxel with or without carboplatin) with planned subgroup analysis by PS and a randomized phase II trial comparing traditional cytotoxic chemotherapy with erlotinib in patients with PS 2 found that patients with PS 2 had a survival benefit from a doublet versus a single agent.

The only analysis reporting on quality of life parameters showed no evidence of a detrimental impact from combination as compared to single agent therapy. Based upon these results, a general approach is to use single-agent chemotherapy.
Because of heterogeneity among patients classified as PS 2, subjectivity of scoring PS, inter-observer variability and lack of consistent data in favor of an optimal chemotherapy regimen, it is unable to recommend a combination of two cytotoxic drugs for patients with PS 2.

It is conceivable that those with compromised PS on the basis of concomitant illnesses may fare better on a single agent and on the other hand patients with rapidly expanding disease burden may profit most from combination. Should we distinguish the underline reasons for compromised PS: disease burden versus comorbidities versus both?

The role of platinum-based chemotherapy
At present, platinum-based combination chemotherapy is considered the standard treatment for advanced NSCLC, but it is still unclear if the benefit achieved with this treatment is restricted only to PS0 and PS1 patients, or also applies to PS2 patients.

In the meta-analysis published in 1995, a significant benefit was demonstrated for cisplatin-based trials, and a sub-group analysis confirmed this benefit for both good and poorer PS patients.

The survival benefit of PS-2 patients in the subgroup analyses of phase III trials comparing platinum-based combinations vs single agents (eg paclitaxel plus carboplatin versus paclitaxel alone) should be interpreted with caution, in view of the substantial risk of selection bias (18% of the population).

Data from phase II trials showed that doublets such as carboplatin plus paclitaxel and cisplatin plus gemcitabine, administered at attenuated doses, proved to be feasible in PS 2 patients.
Are carboplatin-based or low-dose cisplatin-based doublets representing alternative options?

High priority should be dedicated to prospective clinical trials evaluating tolerability and efficacy of platinum-based combinations (carboplatin-based or low dose cisplatin-based doublets).

The role of platinum-free chemotherapy

As expected, platinum-based treatment is often associated with a higher occurrence of toxicity. Gemcitabine, vinorelbine, paclitaxel and docetaxel, administered as single agents characterised by a good tolerability, with a low incidence of severe adverse events. Most of the studies with these drugs show some advantage of chemotherapy in terms of overall survival.

Most of the studies comparing platinum free combinations containing new cytotoxic agents versus platinum-based treatment show no significant interaction between treatment and PS in terms of overall, and platinum-free combination chemotherapy could represent a reasonable, less toxic option for PS 2 patients.

However, there is no consistent evidence that combination chemotherapy without platinum is better than third generation drugs given as single agents.

- No data justify the use of platinum-free or high-dose (>100 mg/m²) cisplatin-based combination chemotherapy instead of single-agent treatment in this group of patients.
Recommendations

→ Whenever possible, therapy should be individualized based upon molecular and histologic features of the tumor. If feasible, patients should have tumor tissue assessed for the presence of a somatic mutation in the epidermal growth factor receptor (EGFR) that confers sensitivity to the EGFR tyrosine kinase (TK) inhibitors.

→ For patients with PS 2 and without a sensitizing molecular abnormality, cytotoxic chemotherapy is recommended. (LOE I, GOR B)

→ Treatments with a single agent or platinum-based doublet are acceptable options. (LOE II, GOR C)

→ A combination regimen using reduced-doses is a reasonable alternative.

→ For patients with a poor performance status (PS ≥2) and a known sensitivity mutation in the EGFR receptor, single agent therapy with an EGFR inhibitor (erlotinib or gefitinib) rather than chemotherapy is recommended. (LOE II, GOR B)

→ This approach may also be appropriate for poor performance status patients in whom the EGFR mutation status has not been assessed but who are not candidates for cytotoxic chemotherapy.

→ For poor performance status patients whose tumors contain an ALK fusion oncogene, initial therapy with crizotinib rather than chemotherapy is recommended. (LOE I, GOR B)
References


6.8 **SURGICAL TREATMENT OF OLIGO-METASTATIC NON-SMALL CELL LUNG CANCER**  
*Barbetakis N.*

Patients with stage IV metastatic non-small cell lung cancer (NSCLC) are generally believed to have an incurable disease. They have an overall median survival time of 7-11 months\(^1\). The most common extrapulmonary sites of distant metastases are the brain, bone, liver and adrenal gland\(^2\). Approximately 7% of patients with metastatic disease from NSCLC primary tumor will have a solitary metastasis after full evaluation\(^3\). These solitary metastases include synchronous or metachronous satellite nodules in different pulmonary lobes or solitary extrapulmonary metastases. The term “oligometastases” was used initially by Hellmann and Weichselbaum to describe a restricted locoregional tumor load\(^4\). It has now become synonymous with isolated distant metastases.

**6.8.1 Brain metastases**

Approximately one third of patients with NSCLC and brain metastases present initially with neurologic symptoms, with the lung cancer being found only after a search for the primary tumor has been carried out. It is now accepted that patients with solitary brain metastases from NSCLC are best treated by resection of the brain lesion followed by postoperative whole-brain radiation therapy. Using this strategy the 5-year survival rate in these patients should approach 20%\(^5\). Even if a cure is not obtained, survival is prolonged and quality of life improved when compared with a non-surgical approach. Advances in surgical techniques have made resection of solitary brain metastasis a standard treatment with low morbidity and mortality (0-3%)\(^6\).

When patients present with NSCLC and a single synchronous brain metastasis and both lesions are resectable, the brain tumor should be resected prior to the primary tumor, provided that no urgent intrathoracic process is occurring. If the resectability of either lesion is in question prior to surgery, one should approach the questionable lesion first, to ensure that both
lesions can be completely resected prior to undertaking a potentially unnecessary operation. If a brain metastasis is found but a search for the primary tumor is negative, one should proceed with resection of the intracranial tumor.

**Recommendation:** In patients with a good performance status and synchronous oligometastasis of the brain, craniotomy and tumor removal should be performed before pulmonary resection of the primary lung cancer. If the resectability of either lesion is in question prior to surgery, one should approach the questionable lesion first, to ensure that both lesions can be completely resected prior to undertaking a potentially unnecessary operation. If a brain metastasis is found but a search for the primary tumor is negative, one should proceed with resection of the intracranial tumor. The alternative approach with radiosurgery is recommended for surgically inaccessible lesions or generally medical inoperable patients. **WBRT is recommended after local treatment of brain metastasis.**

### 6.8.2 Adrenal metastases

The adrenal gland is a common site of metastatic disease in NSCLC, with involvement ranging from 18-42% in autopsy series. The incidence of solitary adrenal metastases is reported to be 1.62% and 3.5%. However, the presence of a radiological adrenal mass itself does not necessarily represent metastasis because a considerable portion of the general population has benign adenomas (2-9%). Because of the uncertainties in diagnostic staging even using a PET/CT or MRI, Kim et al suggested histopathologic confirmation of suspected adrenal masses before lung resection.

Besides one prospective study that examined a protocol with combined chemotherapy and surgical resection, only retrospective case series have been reported on adrenalectomy for NSCLC. Given the obvious limitations of the published retrospective data the results of surgical resection of isolated
adrenal metastases from lung cancer are certainly better than that typically associated with metastatic lung cancer. These data may support further investigation of this aggressive treatment strategy in oligometastatic disease confined to the adrenal gland.

**Recommendation**

→ *Indication for surgery should be based on respectability of the primary tumor (T1-2N0-1, T3N0) absence of other distant metastatic lesions, unilateral and completely resectable adrenal metastasis and good physical condition of the patients. The role of laparoscopic adrenalectomy remains to be defined. SBRT or RFA are acceptable options for local control.*

### 6.8.3 Lung metastases

Patients who present with lung cancer and are found to have an intrapulmonary metastasis in the same lobe are according to the 7th edition of IASLC, considered to have T3 disease. If the metastasis is located within an ipsilateral nonprimary lobe, it is classified as T4. Pulmonary metastasis in a contralateral lobe is considered M1a disease. However, controversies remain regarding the precise differentiation from second primary lung cancer and metastatic disease from other primary tumors. To characterize these different entities clinicopathologic criteria defined by Martini and Melamed are still in use. Recent advances in histologic assessment may help to differentiate multiple lung primaries from metastases. Both contemporary molecular and comprehensive histologic assessment seem to more accurately classify multiple tumors than the Martini-Melamed criteria.

In cases of bilateral lung cancer in oligometastatic disease, bilateral staged thoracotomy is the favored approach. In cases of synchronous metastatic disease, the side of first resection depends on the anticipated surgical resection and preoperative pulmonary function of the patient. Segmentectomy or wedge resection of the pulmonary metastases on the contrary side should
be performed first if the primary tumor requires a lobectomy or bilobectomy. Mortality rates between 0% and 2.5% in pulmonary metastasectomy for extrapulmonary primary tumors have been reported. Thus it can be expected that a sequential approach for lung cancer and oligometastatic disease can be done with a comparable low mortality rate\(^\text{13}\).

Based on these findings, even patients with oligometastases on the contralateral side should be considered for surgical resection, provided that there is no evidence of lymph node involvement and distant metastasis after an extensive preoperative work-up. Their survival is much higher than the survival of patients who are assumed to have stage IV disease and are treated with palliative chemotherapy\(^\text{13}\). The role of pre- or postoperative chemotherapy in the management of oligometastatic disease remains unclear due to the lack of data.

**Recommendation**

\[\text{Patients with oligometastasis on the contralateral side should be considered for surgical resection, provided that there is no evidence of lymph node involvement and distant metastasis after an extensive preoperative work-up. The role of chemotherapy pre- or post-surgically should be an option.}\]

### 6.8.4 Other extrathoracic metastases

There are two retrospective case series with 4 patients\(^\text{14}\) and 14 patients\(^\text{3}\) specifically addressing this issue. Long-term survival was unexpected high, with a 5-year overall survival rate of 55.6% in the report by Ambrogi et al. And a 10-year survival rate of 86% in the series by Luketich et al. These results likely reflect the careful patient selection who displayed a benign course compared with the typical patient with metastatic NSCLC. Based on the suggestions by Luketich et al. three factors are important in selecting patients for resection of isolated metastases within this oligometastatic category: a. The primary NSCLC needs to be completely resected, b. Metastases need to
have a metachronous onset, c. A thorough and comprehensive staging is required to exclude disseminated metastatic disease.

**Recommendation**

*Patients with non-brain, non-adrenal and non-lung isolated metastases are surgical candidates following a very careful selection. Three factors are important in selecting patients within this oligometastatic category: a) the primary NSCLC needs to be completely resected, b) metastases need to have a metachronous onset, and c) a thorough and comprehensive staging is required to exclude disseminated metastatic disease.*

**Conclusions**

The retrospective methodology used in most studies concerning the role of surgery in oligometastatic NSCLC disease makes it difficult to draw definitive guidelines. Given the rarity of oligometastatic disease in patients with NSCLC, it is unlikely that larger randomized prospective studies will be conducted to compare different treatment strategies. Therefore, our knowledge is built from retrospective case series to elaborate prognostic factors that could predict survival benefit from an aggressive treatment regimen.
Summary of recommendations

1. In patients with a good performance status and synchronous oligometastasis of the brain, craniotomy and tumor removal should be performed before pulmonary resection of the primary lung cancer. If the resectability of either lesion is in question prior to surgery, one should approach the questionable lesion first, to ensure that both lesions can be completely resected prior to undertaking a potentially unnecessary operation. If a brain metastasis is found but a search for the primary tumor is negative, one should proceed with resection of the intracranial tumor. The alternative approach with radiosurgery is recommended for surgically inaccessible lesions or generally medical inoperable patients.

2. Concerning adrenal oligometastatic NSCLC disease, indication for surgery should be based on controlled or controllable primary tumor, no evidence of other distant metastatic lesion, unilateral and completely resectable adrenal metastasis and good physical condition of the patients. The role of laparoscopic adrenalectomy remains to be defined.

3. Concerning lung metastases, patients with oligometastases on the contralateral side should be considered for surgical resection, provided that there is no evidence of lymph node involvement and distant metastasis after an extensive preoperative work-up. The role of chemotherapy in the management of oligometastatic disease pre- or post-surgically remains unclear due to the lack of data.

4. Patients with non-brain, non-adrenal and non-lung isolated metastases are surgical candidates following a very careful selection. Three factors are important in selecting patients within this oligometastatic category: a. Primary NSCLC needs to be completely resected, b. Metastases need to have a metachronous onset, c. A thorough and comprehensive staging is required to exclude disseminated metastatic disease.
References


SCLC

1. Routine staging of SCLC includes the following: history and physical examination, FBC and comprehensive chemistry panel, CT scan of the chest and abdomen CT or MRI of the brain, and bone scan. (LOE I, GOR B)

2. PET scanning is not recommended in the routine staging of SCLC. (LOE II, GOR B)

3. Patients with limited-stage SCLC (broadly corresponding to T1–4, N0–3, M0) and a WHO performance status of 0 or 1 if they present with disease that can be encompassed in a radical thoracic radiotherapy volume should be treated with combined concurrent chemo-radiotherapy. Start the radiotherapy during the first or second cycle of chemotherapy. Patients require referral to a radiation oncologist and a medical oncologist for the consideration of combined modality treatment. (LOE I, GOR A)

4. Offer sequential radical thoracic radiotherapy to patients with limited-stage disease SCLC (broadly corresponding to T1–4, N0–3, M0) who are unfit for concurrent chemoradiotherapy but who have disease control by chemotherapy.

5. In patients eligible to receive early concurrent chemoradiotherapy, patients should be treated with accelerated hyperfractionated radiation – where it is possible – therapy concurrently with platinum-based chemotherapy plus etoposide. (LOE I, GOR B)

6. Patients with limited-stage SCLC achieving a complete or partial response or resected patients with stage I disease should be offered PCI. (LOE I, GOR B)

7. Patients with extensive-stage disease should receive four to not more than six cycles of cisplatin- or carboplatin-based combination chemotherapy. Cisplatin could be combined with either etoposide or irinotecan. (LOE I, GOR B)

8. After chemotherapy, patients achieving a complete response outside the chest and a complete or partial response in the chest could be offered consolidative thoracic radiation therapy in the chest. (LOE II, GOR C)
9. Patients with extensive stage SCLC achieving any response should be offered PCI and WHO performance status 2 or less. (LOE I, GOR C)

10. In patients with SCLC and stage I disease who are being considered for curative intent surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI, abdominal CT plus bone scan, followed by a platinum-based chemotherapy should be offered. (LOE I, GOR A)

11. Outside of a clinical trial, maintenance treatment for patients with extensive-stage or limited-stage disease achieving a partial or complete remission is not recommended. (LOE I, GOR B)

12. Relapsed or refractory patients with SCLC should be offered further chemotherapy. (LOE I, GOR B)

13. Outside of a clinical trial, there is no role for either dose dense/intense initial/induction or maintenance treatment for extensive-stage or limited-stage SCLC. (LOE I, GOR A)

14. Patients with mixed SCLC/NSCLC histology should be treated the same as patients with SCLC. All treatment recommendations made for SCLC should apply to this category of patients. (LOE II, GOR C)

15. Elderly patients with good PS (Eastern Cooperative Oncology Group PS of 0 or 1) with intact organ function should be treated with platinum-based chemotherapy. (LOE I, GOR A)

16. Elderly patients with poor prognostic factors such as poor PS or medically significant still be considered for chemotherapy. (LOE II, GOR C)

17. The standard treatment option of limited stage SCLC should be 3dCRT. (LOE I, GOR A)

18. The involved Field Technique instead of elective nodal irradiation should be administered for toxicity reasons.

19. The dose should be prescribed at the biological equivalent range of 45 Gy b.i.d or 60-70Gy daily. (LOE II, GOR C)
6.9 MALIGNANT PLEURA MESOTHELIOMA

Dahabreh J, Charpidou A.

Malignant pleura mesothelioma is a rare neoplastic disease with poor outcome and no defined optimal treatment. The incidence of MPM is estimated to be increased in the next decade.

6.9.1 Epidemiology

Mesothelioma is an occupational disease in the majority of cases, and the exposure to asbestos is the main cause. It can be occupational, environmental or para-occupational. Primary exposure is most common in male workers of raw asbestos material. Over the last decade there is a shift of MPM occurrence to a larger group of subjects at risk, such as those exposed to asbestos products (construction workers, electricians, plumbers etc). There is no secure cut-off point for asbestos exposure \(^1\) and the mean latency of MPM is 40 years (15-67 years) \(^2\).

Agents other than asbestos are recognized or considered as potential risk factors.

- Asbestos exposure is the main cause of MPM.
- Erionite exposure and therapeutic irradiation have strong level of evidence as causal agents.
- SV40 virus infection has lower level.

6.9.2 Methods to evaluate asbestos exposure

Evaluation of asbestos exposure can be done through specific occupational and environmental questionnaires. Mineral analyses of lung tissue or BAL can reveal high levels of asbestos fibers or bodies, especially when exposure history is uncertain.

⇒ Exposure assessment is important and should be done but has not therapeutic relevance and is not required in the clinical management of mesothelioma (LOE I, GOR A)
Is there a rationale for screening in MPM?

Neither imaging tests nor biological markers can be proposed as screening tools for MPM. Low-dose CT is not effective and PET or MRI are not available for screening purposes. Biological markers as soluble mesothelin related peptide (SMRP) and osteopontin have low sensitivity and high number of false-positive results.

Furthermore to date, according to the available data, there is no proof that early discovery of MPM will cure or improve patient survival for many months.

→ There is no place for screening of MPM (LOE 1, GOR B)

6.9.3 MPM Diagnosis

There are no clear clinical or radiological criteria for mesothelioma’s diagnosis. When mesothelioma is suspected based on clinical or radiological data, thoracoscopy is the best method to obtain diagnosis. The accurate diagnosis of mesothelioma is based on histopathological examination. Differential diagnosis can be difficult and should be done from benign pleura lesions, other malignant tumors (thymomas, carcinomas, lymphomas, angiosarcomas) and metastatic lesions in pleura from lung or breast cancer.

→ Thoracoscopy is the best method for MPM diagnosis except in patients with high pre-operative risk and /or pleural symphysis. (LOE I, GOR A)
→ We should not make diagnosis of mesothelioma based on cytology alone, cytological findings should be histological confirmed (LOE I, GOR B)
→ FNBs are associated with low sensitivity and thus they are not primarily recommended. (LOE I, GOR A)
→ Thoracoscopy should be preferred for diagnosis and visual examination of the pleura (LOE I, GOR A)
6.9.4 Classification
International Mesothelioma Interest Group has recently completed an updated classification\(^{10}\) of the recommended WHO 2004 classification for mesothelial tumors\(^ {9}\).

**Immunohistochemistry**
To separate epithelioid mesothelioma from adenocarcinoma we must use two positive diagnostic markers (nuclear or membrane) and two negative diagnostic markers for mesothelioma. To separate sarcomatoid mesothelioma from squamous or transitional cell carcinoma we must use two broad-spectrum anti-cytokeratin antibodies and two markers with negative predictive value. Differentiating mesothelioma from pulmonary adenocarcinoma can be achieved by using two or more mesothelial markers and two or more carcinoma markers (WHO 2004, Ordonez 2007, Gordon 2009). Based on specificity and sensitivity, the most useful mesothelial markers are cytokeratin 5/6 (WHO 2004, Ordonez 2007, Gordon 2009), calretinin (WHO 2004, Ordonez 2007, Gordon 2009), podoplanin (Ordonez 2007) and Wilms tumor gene-1 (WT-1) (WHO 2004, Ordonez 2007, Gordon 2009) and the most useful markers for adenocarcinoma of the lung are thyroid transcription factor-1 (TTF-1) (WHO 2004, Ordonez 2007, Gordon 2009), MOC 31 (WHO 2004, Ordonez 2007, Gordon 2009), BG-8 (Ordonez 2007, Gordon 2009), monoclonal CEA (WHO 2004, Ordonez 2007), CD15(WHO 2004), BER EP4 (WHO 2004, Ordonez 2007) and B72.3 (WHO 2004, Ordonez 2007). If the differential includes adenocarcinomas of other origin the panel should be modified accordingly.

→ MPM diagnosis should be based on immunohistochemical examination. *(LOE I, GOR A)*
6.9.5 **Staging System**

There is no uniform, validated staging system.

- **International Mesothelioma Interest Group TNM system, which is approved by Union International Corte le Cancer (UICC, 6th edition) and American Join Committee on Cancer (AJCC 7th edition) can be used.** *(LOE I, GOR C)*

6.9.6 **Management**

Patients with MPM should be managed by multidisciplinary team with experience in mesothelioma.

- **Pre-treatment assessments should be based on good clinical practice and the treatment intent.** *(LOE I, GOR C)*

Demographics, clinical history, physical examination, CXR and blood tests should be made to all patients at presentation. Adequate biopsy for histological confirmation and subtype definition, PFTs and proper staging with: CT scans of chest and upper abdomen (with contrast), bone scan and brain CT/MRI (on clinical suspicious only), and FDG-PET could be done to those who are candidates for surgery or multimodal treatment. VATS can be considered if contra-lateral hemithorax disease is suspected. Mediastinoscopy, EBUS-FNA and laparoscopy are optional and only in surgery candidates.

Treatment options for patients with MPM are surgery, radiation and/or chemotherapy.

- **Selected patients with stages II-III disease who are medically operable are candidates for tri-modality approach.** *(LOE II, GOR A)*
- **Patients with clinical stage IV or sarcomatoid histological subtype are candidates for chemotherapy.** *(LOE II, GOR A)*
- **Definitive RT alone is not recommended in unresectable cases.** *(LOE II, GOR A)*
Chemotherapy

Chemotherapy is recommended alone in medically inoperable patients or sarcomatoid subtype MPM. It can also be part of regimen in multimodality approach. Medically operable patients with stage II-III can receive chemotherapy before or after surgery. Two randomized trials \(^{11,12}\) suggested that cisplatin combination with antifolate (pemetrexed or raltitrexed) improves survival. Several phase II trials have evaluate other combination like carboplatin-pemetrexed\(^{13}\), cisplatin-gemcitabine\(^{14}\) or monotherapies with pemetrexed\(^{15}\), or vinorelbine\(^{16}\). There are limited data about optimal chemotherapy after recurrence.

- For patients with good performance status, a combination of cisplatin and pemetrexed is considered as the gold standard. (LOE I, GOR B)
- Administration of chemotherapy should be done as soon as diagnosis. (LOE I, GOR C)
- Chemotherapy should not extent 6 cycles for patients who responds or have stable disease and must be stopped earlier if unacceptable toxicity or progression of the disease occurred. (LOE II, GOR C)
- Patients who have not treated with pemetrexed in first-line setting can take it as second-line. (LOE II, GOR A)
- After recurrence patients with objective response to first-line therapy may be treated with the same regimen (LOE II, GOR C), or gemcitabine or vinorelbine (LOE II, GOR C).
- Immunomodulating agents, targeted biotherapies and vaccines should not be used outside clinical trials (LOE I, GOR C).
**Response Evaluation**

Response evaluation should be done with modified RECIST criteria for mesothelioma\textsuperscript{17}. Assessment and follow up of MPM should be done by CT scan.

**Radiotherapy**

Radiotherapy can be used as palliative treatment to relief pain from tumor invasion to the chest wall or bone metastases, or as a part of multimodality approach after surgery or in conjunction to chemotherapy. However when a limited resection (pleurectomy or decortication) is done, the ability to fully cover all sites at risk is limited by the high needing doses to whole hemithorax which lead to severe lung toxicity\textsuperscript{18}. Adjuvant radiotherapy after EPP is reducing the local recurrence rate\textsuperscript{19}. The preferred technique and the total dose should be investigated in prospective studies. At the time, we know that a total dose of higher than 40 Gy might improve survival\textsuperscript{20}.

- **Radiotherapy should not be performed after pleurectomy or decortication** (LOE I, GOR A)
- **Adjuvant radiotherapy after EPP should be only proposed in clinical trials in specialized centers, as part of multimodality treatment** (LOE I, GOR A)
- **Further studies are needed to establish the role of radiotherapy. Recent studies have underlined the importance of radiotherapy technique in terms of local control and toxicity.** (Expert opinion)
- **The role of prophylactic radiotherapy along in drainage channels is questionable. If the procedure is decided, 21Gy in 3 consecutive days could be performed in the 4 weeks following thoracentesis or thoracoscopy** (LOE II, GOR C)
Surgery

The appropriateness of surgical treatment remains a controversial issue and is still under consideration, especially the EEP the most aggressive surgical treatment and is associated with low locoregional recurrence. We performed en block resection of the parietal and visceral pleura with ipsilateral lung, pericardium and/or diaphragm. EPP remains a surgical procedure with high 30day mortality (mortality rate 3.4% to 15%), even if performed by an experienced thoracic surgeon\textsuperscript{21,22}. Recently the mortality ranges around 5%, at experienced Thoracic Surgical Centers, while morbidity continues to be high, reaching levels around 50%. There is limited evidence for the efficacy of radical surgery (EPP) and the only long term survivors are those who undergo EPP, as part of a multimodality treatment. All specialists who are involved in the management of MPM agree that EPP should only be performed in clinical trials in specialized centers, always as part of a multimodality treatment (6 - 8).

Pleurectomy/Decortication (P/D) is the surgical procedure during which the parietal and visceral pleurae are removed. The term of Extended/D can be used for the resection of the parietal and visceral pleurae, with the intention to remove all gross tumor combined with the resection of the diaphragm and/or the pericardium. There is no randomized trial to support debulking surgery, while there are retrospective studies with low level evidence for debulking pleurectomy\textsuperscript{23}.

Selection criteria for the patients with MPM, who are candidates for surgical treatment, include good performance status, early stage disease provided that the cardio – respiratory reserves allow the performance of such operations. The inclusion of patients with N2 disease or sarcomatoid histological type is still controversial\textsuperscript{24}.

→ Pleurectomy/Decortication via open thoracotomy can be considered in patients with MPM in order to obtain symptoms control, especially in those patients who have entrapped lung syndrome and chest pain. (LOE II, GOR C).
→ **Pleurectomy/ Decortication performed by the implementation of VATS is preferred to open thoracotomy.** (LOE I, GOR C).

→ **EPP should only be performed in clinical trials in specialized centers, always as a part of multimodality treatment.** (LOE II, GOR A)

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### Flowchart for the management of Malignant Pleura Mesothelioma

**Pleural effusion and or pleura thickening (Suspicious for MPM)**

- CT chest
- Thoracentesis cytology
- Pleura biopsy
- Pleurodesis if required

**MPM**

- Chest/abdominal CT with contrast
- PET/CT
- Mediastinoscopy/EBUS (optional)
- Laparoscopy (optional)
- VATS (suspicion contralateral disease)
- Bone scan (if clinical suspicion)
- Brain CT/MRI (if clinical suspicion)

**Clinical stage I**

- PFTs
- V/Q
- Cardiac stress test

- If operable: Surgery
- If not operable: CTx

**Clinical stage II-III**

- PFTs
- V/Q
- Cardiac stress test

- If operable: *Surgery and adjuvant CTx and RT if EPP OR *Induction CTx and surgical exploration and RT if EPP
- If not operable: CTx

**Clinical stage IV**

- CTx
References


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6.10 MESOTHELIOMA

Kouloulias V, Trichas M.

Prophylactic irradiation of tracks

➔ Impossible to draw definitive conclusions regarding its efficacy (LOE II; GOR C)

Palliative radiotherapy

➔ Radiotherapy can be delivered locally in view of pain control or prevention of obstructive symptoms (LOE I; GOR VC)

PORT

➔ Caution must be exercised regarding the exposure of the contralateral lung to low-dose irradiation, especially when using IMRT (LOE III; GOR B)
7 ADVANCED LUNG CANCER DISEASE

Barbetakis N.

7.1 LUNG CANCER AND MALIGNANT PLEURAL EFFUSION

The discovery of malignant cells in pleural fluid and/or parietal pleura signifies disseminated or advanced disease and a reduced life expectancy in cancer patients. Median survival following diagnosis ranges from 3 to 12 months and is dependent on the stage and type of the underlying malignancy. The shortest survival time is observed in malignant effusions secondary to lung cancer.

Recommendations

➔ In lung cancer patients with symptomatic malignant pleural effusions, thoracentesis is recommended as the first drainage procedure for symptom relief. (LOE I; GOR C)
➔ In lung cancer patients with symptomatic pleural effusions that recur after thoracentesis, chest tube drainage and pleurodesis are recommended. (LOE I; GOR B)

7.1.2 Thoracentesis

- Observation is recommended if the patient is asymptomatic or there is no recurrence of symptoms after initial thoracentesis.
- Advice should be sought from the thoracic malignancy multidisciplinary team for symptomatic or recurrent malignant effusions.
- Repeat pleural aspiration is recommended for the palliation of breathlessness in patients with a very short life expectancy.
- Caution should be taken if removing more than 1.5 l on a single occasion.
- The recurrence rate at 1 month after pleural aspiration alone is close to 100%.
7.1.3 Chest tube drainage

- Intercostal tube drainage without pleurodesis is not recommended because of a high recurrence rate.
- Large pleural effusions should be drained in a controlled fashion to reduce the risk of re-expansion pulmonary oedema (RPO).
- Suction to aid pleural drainage before and after pleurodesis is usually unnecessary but, if applied, a high volume, low pressure system is recommended.
- In patients where only partial pleural apposition can be achieved, chemical pleurodesis should still be attempted and may provide symptomatic relief.
- Once effusion drainage and lung re-expansion have been radiographically confirmed, pleurodesis should not be delayed while the cessation of pleural fluid drainage is awaited.
- Analgesia and premedication: Lignocaine (3 mg/kg; maximum 250 mg) should be administered intrapleurally just prior to sclerosant administration. Premedication should be considered to alleviate anxiety and pain associated with pleurodesis.

7.1.4 Selecting a sclerosing agent

- Talc is the most effective sclerosant available for pleurodesis.
- A small number of patients (<1%) may develop acute respiratory failure following talc administration.
- Tetracycline is modestly effective, has few severe side effects, and is the preferred sclerosant to minimise adverse event rates.
- Bleomycin and mitoxantrone are alternative sclerosants with a modest efficacy rate but is expensive.
- Pleuritic chest pain and fever are the most common side effects of sclerosant administration.

7.1.5 Thoracoscopy and malignant pleural effusion

- Thoracoscopy should be considered for the diagnosis of suspected but unproven malignant pleural effusion.
- Thoracoscopy should be considered for the control of recurrent malignant pleural effusion.
- Thoracoscopy is a safe procedure with low complication rates\(^2\).
7.1.6 **Long term indwelling pleural catheter drainage**

- Chronic indwelling pleural catheters are effective in controlling recurrent and symptomatic malignant effusions in selected patients.

7.1.7 **Pleuroperitoneal shunting**

- Pleuroperitoneal shunts are an alternative and effective option in patients with a trapped lung or failed pleurodesis.

7.1.8 **Pleurectomy**

- Pleurectomy is an effective but invasive method for treating malignant pleural effusions. Complications may include empyema, haemorrhage, and cardiorespiratory failure (operative mortality rates of 10–13%).

7.2 **LUNG CANCER AND MALIGNANT PERICARDIAL EFFUSION**

Malignant involvement of the heart and/or pericardium is not uncommon in patients with advanced cancer (10%) and is involved in the mechanism of mortality in one third of cases.

**Recommendations**

- Subxiphoid pericardiocentesis and intrapericardial infusion of cytotoxic and/or sclerosing substances (cisplatin, bleomycin, mitoxantrone, thiotepa, mitomycin-C, vinblastine, tetracycline, interferon/interleukin-2, OK-432).

- **Surgical intervention** (Subxiphoid pericardial window, VATS pericardial window, Thoracotomy). Surgery has indication in undiagnosed cases and in refractory pericardial effusions. It is avoided in critically ill patients.
7.3 LUNG CANCER AND CENTRAL AIRWAY OBSTRUCTION

Approximately 20–30% of patients with lung cancer will develop airway obstruction and therefore the management of airway obstruction is a vital component of the services provided by an interventional program\(^5\). The three basic types of obstruction are endoluminal, extraluminal and a combination of both. A mainly endoluminal stenosis can be treated with various techniques. For an extraluminal compression the only option is placement of stents, which results in efficient palliation and may prolong survival.

**Recommendations**

**Endoluminal obstruction**

- electrocautery
- argon plasma coagulation
- cryotherapy
- laser therapy
- brachytherapy
- photodynamic therapy
- rotating tip microdebrider

**Extraluminal obstruction**

- stent insertion
- palliative brachytherapy
7.4 LUNG CANCER AND MASSIVE HEMOPTYSIS

In cases of massive hemoptysis patient's life is threatened and emergency admission in intensive care unit must be achieved. The threat lies in asphyxiation by flooding of the tracheobronchial tree. Before definitive treatment, the risk remains even after cessation of an episode of massive hemoptysis because relapses are unpredictable. It is a medical emergency associated with a 30–50% rate of mortality reported in the last 20 years.

**Recommendations**

- **Medical management** (rest in bed, insertion of a wide-bore intravenous cannula, monitoring of arterial blood gases, aerosoltherapy of adrenaline, adapted antibiotic therapy if needed, and correction of clotting disorder if associated). Isolation of the bleeding lung is possibly needed (double-lumen endotracheal tube).

- **Bronchoscopy** (Its objective is threefold: to see the cause of bleeding if possible; to localize the site of bleeding; and to carry out endobronchial control measures such as adrenaline lavage or YAG laser electrocautery).

- **Chest CT scan and CT angiography** (bleeding from pulmonary artery system or bronchial artery system).

- **Arterial embolization** (Seldinger technique through femoral access).

- **Emergency surgical treatment is applied when the site of bleeding is localized, the indication of pulmonary resection and the other means of treatment have failed.**
7.5 LUNG CANCER AND TRACHEOESOPHAGEAL FISTULA

Tracheoesophageal fistulae are rare complications of lung cancer and its treatment. Novel antiangiogenic agents in cancer treatment such as bevacizumab potentially impact wound healing and may contribute to tracheoesophageal fistula development.

7.5.1 Supportive therapy
Supportive therapy is recommended for patients who present late in the course of the fistula and already have pulmonary sepsis. The supportive measures include nasogastric drainage, tracheostomy, gastrostomy, and intravenous hydration and antibiotics.

7.5.2 Endoscopic interventions
Tissue glues and amino acid solutions have been instilled in small fistula with some success but they can cause obstruction of the respiratory tree due to their sealing effect. Conventional oesophageal prostheses are suitable for tracheoesophageal fistula with a stenotic tumour but often migrate and allow food to track into the fistula in a normal sized oesophagus. Covered self-expanding stents have been used to successfully treat malignant tracheoesophageal fistula but may prove to be unsuccessful in a dilated oesophagus.

7.5.3 Surgery
Burt reported that bypass therapy and radiation therapy were the only treatments that significantly prolonged survival compared to supportive care. With radiation therapy, TEFs initially heal but usually recur, leading to respiratory tract contamination. Esophageal bypass with gastric, colonic, or jejunal interposition would have significantly improved survival rates but has a high risk of immediate mortality.


Recommendations

For patients with malignant TEF or bronchoesophageal fistula, stenting of esophagus, airway, or both should be considered for symptomatic relief. Attempts at curative resection or esophageal bypass of the involved airway and/or the esophagus are not recommended. (LOE I; GOR C)

7.6 LUNG CANCER AND SUPERIOR VENA CAVA SYNDROME

Obstruction of the SVC is usually caused by malignancies, the majority of which are due to lung cancer. Typically, the lung cancer spreads by lymph node metastases into the right paratracheal or precarinal lymph nodes, although some cancers cause obstruction of the SVC by direct extension. SVC obstruction is present in 10% of patients with SCLC and 1.7% of patients with NSCLC.

Recommendations

In patients with SVC obstruction from suspected lung cancer, definitive diagnosis by histologic or cytologic methods is recommended before treatment is started. (LOE I, GOR C)

In patients with symptomatic SVC obstruction due to SCLC, chemotherapy is recommended. (LOE I, GOR C)

In patients with symptomatic SVC obstruction due to NSCLC, stent insertion and/or radiation therapy are recommended. Stents are also recommended for SCLC or NSCLC symptomatic patients with SVC obstruction who fail to respond to chemotherapy or radiation therapy. (LOE I, GOR C)
References


