incidence and epidemiology

Non-small-cell lung cancer (NSCLC) accounts for 80%–85% of all lung cancer cases. Approximately 90% of lung cancers among men and 80% among women are related to smoking. The majority of patients present with advanced disease. The incidence differs considerably across different countries in Europe. The rates vary from 22 to 63 per 100 000 and from 5 to 33/100 000 per year in men and women, respectively. In most European countries, the incidence continues to rise in women but decreases in men. This trend seems to occur later in Southern and Eastern Europe than in the Northern regions.

Five-year age- and area-adjusted relative survival of all lung cancer patients in Europe continues to be low at 11%. Central European countries show slightly higher survival compared with other regions. Trends in lung cancer mortality in men have tended to decrease in many European countries during the last two decades, particularly in North and Western Europe. Among women, mortality rates are still increasing in many countries.

The major histopathological subtypes are adenocarcinoma, squamous cell carcinoma and large cell carcinoma. Again there are variations across different regions mainly reflecting different smoking behaviours. The proportion of adenocarcinoma has been increasing over time possibly due to the shift to low-tar filter cigarettes, which are inhaled more deeply into the periphery of the lung and also contain a higher amount of nitrosureas. On the other hand, the incidence of squamous cell carcinoma is decreasing. A subset of NSCLC tumour specimens are also categorized as NSCLC not otherwise specified (NOS), either due to small specimen size or poorly differentiated histology.

diagnosis

Pathological diagnosis should be made according to the WHO classification. Histological or cytological specimens can be obtained from the primary tumour, lymph node or distant metastases or from a malignant effusion. In general, the least invasive procedure should be used; however, quality and quantity of the sampling should allow for distinction of histological subtypes and for epidermal growth factor receptor (EGFR) mutation analysis. Histological specimens are preferred.

Use of predictive markers for treatment

Activating EGFR mutations (Exons 19, 21) are predictive for response and progression-free survival to the tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib based on several trials. The incidence of EGFR mutations in a Caucasian population is 10%. Higher rates are observed in never-smokers, in East-Asians, in patients with adenocarcinoma subtype and in women. Further prognostic and predictive molecular markers have been described but not prospectively validated.

staging and risk assessment

- Complete history including smoking history, past medical history including significant comorbidities, weight loss, performance status and physical examination.
- Blood counts and standard serum chemistry including renal function tests.
- CT scan of the chest and upper abdomen (including i.v.-contrast examination of liver and adrenals).
- MRI of the brain in the case of abnormal neurological findings (MRI preferred to CT scan due to higher sensitivity).
- Bone scan in the presence of bone pain, elevated serum calcium or elevated alkaline phosphatase levels.
• In the presence of a single metastatic lesion on imaging studies, biopsy of this lesion should be pursued to prove metastatic disease if otherwise curable (does not apply to solitary brain metastases).
• Pleural/pericardial effusions should be confirmed by a cytology or tissue specimen in patients otherwise curable.
• In the case of a solitary metastasis in brain, lung or adrenal gland; brain imaging and PET should be performed followed by further mediastinal staging if appropriate.
• The staging system for lung cancer has recently been revised through the International Association for Study of Lung Cancer (IASLC) and will be adopted by the UICC. Patients with NSCLC shall now be staged according to the UICC system (7th edition) and be grouped into the stage categories shown in Tables 1 and 2.

treatment of stage IV NSCLC

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 tumour-board or conference involving different specialists (medical and radiation oncologist, pneumologist, thoracic surgeon, radiologist and pathologist). 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 the different treatments.

In any stage of NSCLC, smoking cessation should be highly encouraged because smoking cessation may increase efficacy of treatment and decrease the risk of complications.

first-line treatment

• Platinum-based combination chemotherapy prolongs survival, improves quality of life, and controls symptoms in patients with a good performance status (PS) [I, A]. Recommended third-generation agents include vinorelbine, gemcitabine, taxanes, irinotecan and pemetrexed (non-squamous histology only).
• Pemetrexed is preferred to gemcitabine in patients with non-squamous histology according to a survival benefit demonstrated in a pre-planned subgroup analysis of one large randomized clinical trial [II, B].
• According to results of several meta-analyses, non-platinum-based combination chemotherapy of third-generation agents can be considered if platinum therapy is contraindicated. Most trials show lower response rates for non-platinum combinations but similar survival rates [I, A].
• Several meta-analyses showed higher response rates for cisplatin combinations when compared with carboplatin combinations. Overall survival was significantly superior for cisplatin in the subgroup of non-squamous histologies treated with third-generation regimens in one meta-analysis [I, A].
• According to two randomized clinical trials, bevacizumab may be added to a combination regimen of paclitaxel–carboplatin or gemcitabine–cisplatin in patients with tumours of non-squamous histology and PS0–1. Prolongation of survival has only been demonstrated for the

Table 1. TNM classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>T1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>≤3 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1b</td>
<td>≤2 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>&gt;2–3 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>&gt;3–5 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2b</td>
<td>&gt;5–7 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>≥7 cm; chest, diaphragm, pericardium, mediastinal pleura, main bronchus, &lt;2 cm from carina, total atelectasis, separate nodule(s) in same lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Mediastinum, heart, great vessels, carina, trachea, oesophagus, vertebra; separate tumour nodule(s) in a different ipsilateral lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>Ipsilateral peribronchial, ipsilateral hilar</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>Subcarinal, ipsilateral mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>Contralateral mediastinal or hilar, scalene or supraclavicular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1a</td>
<td>Separate tumour nodule(s) in a contralateral lobe; pleural nodules or malignant pleural or pericardial effusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1b</td>
<td>Distant metastasis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Stage grouping

<table>
<thead>
<tr>
<th>Stage grouping</th>
<th>Occult carcinoma</th>
<th>TX</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td></td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td></td>
<td>T1a,b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td></td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td></td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td></td>
<td>T1a,b, T2a,b</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIIB</td>
<td></td>
<td>T3</td>
<td>N1, N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T4</td>
<td>N0, N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td></td>
<td>Any T</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any N</td>
<td>M1</td>
<td></td>
</tr>
</tbody>
</table>
role of surgery and endoscopy

In certain situations surgery and endoscopic techniques should be considered with palliative intention. These situations include:

- recurrent pleural effusions where talc pleurodesis represents the standard of care; other sclerosing agents, e.g. bleomycin or tetracycline, are less effective [II, B];
- uncontrolled intrapulmonary infection which precludes the application of systemic antitumour therapy;
- significant local problems of a tumour (or metastasis) in a particular location (i.e. spinal cord compression, pathologic bone fracture);
- major airway stenosis with dyspnea or post-obstructive infection, where endoscopic debulking by Nd-YAG laser, cryotherapy or stent placement may be helpful;
- resection of a single metastasis in selected fit patients.

role of radiotherapy

Radiotherapy can provide rapid symptom control. Indications are:

- pain due to chest mass, bone metastases or neural compression;
- haemoptysis;
- cough and dyspnoea due to local obstruction of airways;
- superior vena cava syndrome;
- spinal cord compression;
- pathologic bone fractures (or risk of bone fractures) should be considered for postoperative radiotherapy after stabilizing.

patients with solitary metastases (brain, adrenal, lung)

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 [III, C].

isolated adrenal metastasis

Systemic chemotherapy is recommended. In selected fit patients adrenalectomy can be considered, if lung disease is resectable as well.

lung

Solitary lesions in the contralateral lung should be considered as secondary primary and treated with curative intention if both tumours are potentially curable.

second-line/third-line therapies

Second-line treatment improves disease-related symptoms and survival in patients with PS0–2 [docetaxel, pemetrexed (non-squamous histology only), gefitinib]; the same is true for erlotinib in second-line patients who cannot tolerate chemotherapy and third-line patients with PS0–3 [I, A].

Second-line combination regimens have demonstrated higher response and progression-free survival but no improvement of overall survival compared with single-agent treatments in a recent meta-analysis [I, A].

response evaluation

Response evaluation is recommended after two to three cycles of chemotherapy by repetition of the initial radiographic tests showing tumour lesions.
follow-up

The optimal approach to post-treatment management of patients with NSCLC, including the role of radiological evaluation, is controversial. Due to the often aggressive nature of the disease, generally close follow-up is advised. Modalities, i.e. radiographic evaluations, should also depend on individual retreatment options.

note

Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty.

literature