Non-small-cell lung cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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On behalf of the ESMO Guidelines Working Group*

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incidence

The crude incidence of lung cancer in the EU is 52.5/100 000/year, the mortality 48.7/100 000/year. Among men the rates are 82.5 and 77.0/100 000/year, among women 23.9 and 22.3/100 000/year, respectively. NSCLC accounts for 80% of all cases. About 90% of lung cancer mortality among men (and 80% among women) is attributable to smoking.

diagnosis

Pathological diagnosis should be made according to the WHO classification from a biopsy or fine needle aspiration. EGFR mutation analysis may be performed if feasible and the use of EGFR tyrosine-kinase inhibitors (TKIs) is being considered.

staging and risk assessment

- Complete history and physical examination, CT scan of the chest and upper abdomen.
- MRI of the brain if abnormal neurologic history or examination (to be substituted by CT scan if MRI not available).
- Bone scintigraphy in the presence of bone pain, elevated serum calcium level or elevated alkaline phosphatase level.

patients with potentially curative treatment

- Whole-body FDG–PET scan if available. In case of pathological mediastinal lymph node uptake, biopsy of an abnormal node is recommended (required if positivity would rule out curative treatment).
- If FDG–PET not available or result inconclusive (i.e. primary tumor without pathological uptake): biopsy of mediastinal lymph nodes ≥1 cm in short axis.

- MRI of the brain for clinical stage III (to be substituted by CT scan if MRI not available) planned for definitive local treatment.
- Biopsy to rule out metastatic disease in otherwise potentially resectable patients with an isolated extra thoracic lesion. Cytology of pleural/pericardial effusions in patients otherwise resectable.

Patients with NSCLC should be staged according to the TNM 2002 system and be grouped into the stages shown in Table 1.

treatment of local disease

- Surgery of resectable NSCLC in functionally fit patients (lobectomy/pneumonectomy plus mediastinal lymph node dissection should be standard procedure).
- Cisplatin-based adjuvant combination chemotherapy is recommended in stages II and IIIA [I, A], and can be considered in stage IB (T > 4 cm).
- Preoperative cisplatin-based combination chemotherapy can be considered in patients with stage IIIA N2 disease [II, B]. For restaging, a CT scan of the chest and upper abdomen should be performed and minimally invasive techniques providing mediastinal cytohistological diagnosis may be

Table 1.

<table>
<thead>
<tr>
<th>Occult carcinoma</th>
<th>Tx N0 M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis N0 M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1 N0 M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2 N0 M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T1 N1 M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T2 N1 M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T3 N0 M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T1, T2 N2 M0</td>
</tr>
<tr>
<td></td>
<td>T3 N1, N2 M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T N3 M0</td>
</tr>
<tr>
<td></td>
<td>T4 Any N M0</td>
</tr>
</tbody>
</table>

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considered. Surgery is questionable in those patients with persistent N2 disease after chemotherapy.

- Postoperative radiotherapy can be considered in patients not radically resected.
- Postoperative radiotherapy is not recommended for patients with radically resected stage I and II disease [I, A] and should only be considered for patients with resected stage IIIA disease/mediastinal node involvement.
- Curative conformal radiotherapy as a single modality or less-than-standard surgical resections (i.e. sublobar resection) are to be considered in patients unfit for standard surgery.
- Concurrent chemotherapy and thoracic radiotherapy should be considered the treatment of choice for fit patients with locally advanced, unresectable stage III NSCLC.

### treatment of stage IV disease

- Two-drug, platinum-based chemotherapy combined with vinorelbine, gemcitabine or a taxane prolongs survival, improves quality of life and controls symptoms in patients with good performance status [I, A]. Non-platinum combination chemotherapy can be considered in patients who are not fit to receive platinum agents. In first-line metastatic EGFR-mutated patients EGFR TKIs treatment may be contemplated.
- In elderly patients and patients with performance status 2, single-agent chemotherapy is recommended [II, B]. However, some elderly patients without comorbidity and performance status 0–1 can be treated in the same way as younger patients.
- Timing and duration of palliative first-line treatment: chemotherapy should be initiated while the patient is in good performance status. Treatment should be stopped after no more than four cycles in patients not responding to therapy; in responding patients no more than six cycles are recommended [II, B].
- Resection of single metastases can be considered in selected cases [III, B].

### second-line chemotherapy

Second-line systemic treatment (docetaxel, pemetrexed, erlotinib) improves disease-related symptoms and improves survival [I, A]. Erlotinib response rates are higher in non-smokers, women, adenocarcinomas, Asians and patients with EGFR mutations [II, A].

### response evaluation of stage IV disease

Response evaluation is mandatory after two or three cycles of chemotherapy by repetition of the initial radiographic tests showing tumor lesions. Clinical benefit can be used in certain groups of patients.

### follow-up

The optimal approach to post-treatment management of patients with thoracic malignancies, including the role of radiologic evaluation, is controversial. For patients with potentially curative re-treatment, a history and physical examination should be performed every 3–6 months during the first 2 years, and every 6–12 months thereafter and radiologic evaluations should be considered at these time points.

### 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