

## Diagnosis

- Bronchoscopy is a technique ideally suited to central lesions and can be used with bronchial washing, brushing, bronchial and transbronchial biopsy
- EBUS and/or EUS allows evaluation of regional lymph nodes
- Transthoracic fine needle aspiration and/or core biopsy, passing a needle through the parenchyma under imaging guidance (typically CT), is indicated in case of mid to peripheral lesions
- In presence of a pleural effusion, thoracentesis could represent both a diagnostic tool and a palliative treatment
- More invasive, surgical approaches (mediastinoscopy, mediastinotomy, thoracoscopy etc.) in the diagnostic workup can be considered when the previously described techniques cannot allow for an accurate diagnosis
- With systematic collaboration and constant communication between pathologists and procedure performers, diagnostic yields will be significantly greater than with blind biopsies

## Pathology/molecular biology

- Adequate tissue material for histological diagnosis and molecular testing should be obtained to allow for individual treatment decisions
- Pathological diagnosis should be made according to the 2015 WHO classification of lung tumours
- Specific subtyping of all NSCLCs is necessary for therapeutic decision making and should be carried out wherever possible. IHC stains should be used to reduce the NSCLC-NOS rate to fewer than 10% of cases diagnosed [IV, A]
- EGFR mutation status should be systematically analysed in advanced NSCC [I, A]. Test methodology should have adequate coverage of mutations in exons 18-21, including those associated with resistance to some therapies [III, B]. At a minimum, when resources or material are limited, the most common activating mutations (exon 19 deletion, exon 21 L858R point mutation) should be determined [I, A]
- The availability of TKIs effective against T790M-mutant recurrent disease makes T790M testing on disease relapse mandatory [I, A]
- All patients with a negative cfDNA blood test still require tissue biopsy [II, A]
- Testing for ALK rearrangement should be systematically carried out in advanced non-squamous NSCLC [I, A]
- Detection of the ALK translocation by FISH remains a standard, but IHC with high-performance ALK antibodies and validated assays may be used for screening [III, A] and have recently been accepted as an equivalent alternative to FISH for ALK testing
- Testing for ROS1 rearrangement should be systematically carried out in advanced NSCLC [III, A]. Detection of the ROS1 translocation by FISH remains a standard; IHC may be used as a screening approach [IV, A]
- BRAF V600 mutation status should be systematically analysed in advanced NSCLC for the prescription of BRAF/MEK inhibitors [II, A]
- Molecular EGFR and ALK testing are not recommended in patients with a confident diagnosis of SCC, except in unusual cases, e.g. never/former light smokers or long-time ex-smokers [IV, A]
- If available, multiplex platforms (NGS) for molecular testing are preferable [III, A]. Whatever testing modality is used, it is mandatory that adequate internal validation and quality control measures are in place and that laboratories participate in, and perform adequately in, external quality assurance schemes for each biomarker test [III, A]
- PD-L1 IHC should be systematically determined in advanced NSCLC [I, A]
- Testing is required for pembrolizumab therapy but may also be informative when nivolumab or atezolizumab are used [I, A]