Cancer of the lung, pleura and mediastinum

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According to the authors and editors, this report contains the most justified principles of diagnostic and therapeutic procedures prepared considering the scientific value of evidence and category of recommendations. These principles should always be interpreted in the context of an individual clinical situation. The recommendations do not always correspond to the current reimbursement rules in Poland. In case of doubt, the current possibilities of reimbursement of individual procedures should be established.

1. *The quality of scientific evidence*
   I — Scientific evidence obtained from well-designed and conducted randomized clinical trials or meta-analyses of randomized clinical trials
   II — Scientific evidence obtained from well-designed and conducted prospective observational studies (non-randomized cohort studies)
   III — Scientific evidence obtained from retrospective observational studies or case-control studies
   IV — Scientific evidence obtained from clinical experiences and/or experts, opinions
2. *Category of recommendations*
   A — Indications confirmed unambiguously and absolutely useful in clinical practice
   B — Indications probable and potentially useful indications in clinical practice
   C — Indications determined individually

Lung cancer

Epidemiology, aetiology, and prophylaxis

Lung cancer is the most frequent malignancy in Poland and the leading cause of cancer-related deaths [1]. It accounts for about 20% and 10% of all cancers in men and women, respectively (in recent years — about 15,000 and 7000 cases every year) and causes about 30% and 17% of all deaths caused by cancer (in recent years — annually around 16,000 and 7500 deaths, respectively). A higher number of deaths in relation to the number of cases indicates shortages in the registration of lung cancer cases. The incidence and mortality rate of lung cancer has been decreasing in recent years in men and at the same time increasing in women. Approximately 13.5% of patients with lung cancer in Poland survive for five or more years after diagnosis.

The risk of lung cancer morbidity depends primarily on exposure to the carcinogenic components of tobacco smoke (active and passive smoking) and, to a lesser extent, on certain physical and chemical environmental factors (e.g. radon, nickel, chromium, arsenic, asbestos, hydrocarbon compounds), as well as genetic factors (primarily polymorphisms of genes involved in the inactivation of harmful components of tobacco smoke and gene disorders responsible for the repair of DNA damage).

Previous attempts to pharmacologically prevent lung cancer and reduce mortality by using conventional X-ray screening (X-ray) and cytological sputum tests have been ineffective. Low-dose chest computed tomography (CT) is of higher value in the detection of neoplastic lesions in the lungs. National Lung Screening Trial (NLST) results showed a 20% reduction in lung cancer mortality among high-risk individuals (age 55–74 years and more than 30 pack-years smoking history) undergoing low-dose chest CT compared to the control group (X-ray examination) [2]. The results of the study became the basis for the development of early detection programs for lung cancer in the groups at highest risk in some countries. In 2017 and 2018, European [3, 4] and Polish [5] recommendations on screening were published, which have not been introduced in Europe so far (mainly due to difficulties in proving their effectiveness). Screening of people from the highest risk group has been financed since 2016 in the United States. Recently, the results of the NELSON study were presented — only in the form of a conference presentation — which after 10 years of observation showed a reduction in mortality from lung cancer (women — 39%, men — 26%) when low-dose

CT was performed in a risk group (eligibility criteria similar to NLST) [6].

Screening tests must be associated with — being of the highest importance — primary prevention (total elimination of exposure to tobacco smoke). They should also include the assessment of the occurrence of emphysema and cardiovascular risk by determining calcification in coronary vessels [3–5]. It is reasonable to carry out pilot early-detection programs to increase the possibility of radical treatment use (especially in regions with low detection of early-stage lung cancer). Early lung cancer detection programs should be carried out by highly specialised centres that have all the possibilities of recognising and treating patients with lung cancer and relevant experience.

Recommendations

— To reduce the lung cancer risk, exposure to tobacco smoke components should be eliminated (active and passive smoking) (I, A).
— In regions with low detectability of early lung cancer, it is reasonable to conduct early-detection programs using low-dose computed tomography to increase the possibility of radical treatment (III, B).

Pathomorphology and molecular biology

Primary lung cancer originates from epithelial cells. The most common are four histological types:
— adenocarcinoma (45% — increased frequency in the last period);
— squamous-cell carcinoma (30%);
— small-cell carcinoma (15%);
— large-cell carcinoma (10%).

Other histological types account for less than 1% of all primary lung tumours.

Lung cancer develops centrally — in the area of large bronchi (the so-called "perihilar" lesion) — or peripherally. Adenocarcinomas occur more frequently in the peripheral parts of the lungs. Metastases occur most frequently in regional lymph nodes (followed by liver, brain, second lung, bones, adrenal glands, subcutaneous tissue, and bone marrow). Metastases can also arise in distant organs without involvement of regional lymph nodes. Lung cancer can also spread locally by infiltrating the anatomic structures of the mediastinum and the diaphragm, pleura, and chest wall.

The 2015 World Health Organisation (WHO) classification of epithelial pulmonary carcinomas [7] (Table 1) introduced some changes in comparison with the previous version from 2011, of which the most significant are:
— new division of adenocarcinomas and squamous-cell carcinomas;
— the need to use immunohistochemistry (IHC) and genetic tests in pathomorphological diagnostics in order to individualise treatment;
— the recommendation to recognise large-cell carcinoma only in the postoperative material only;
— combining in one group cancers with features of neuroendocrine activity.

IHC tests should be performed using a panel typical for the differentiation of adenocarcinoma (TTF1, thyroid transcription factor) and squamous-cell carcinoma (p40 or p63).

Small-cell lung cancer (SCLC) differs from other histological types in terms of many biological and clinical features (high proliferation rate, short doubling of tumour mass, outstanding predisposition to produce early metastases, chemosensitivity, and relative radiosensitivity) [8], which justifies in practice the division into SCLC and non-small cell lung cancer (NSCLC).

In the case of ambiguous histological picture and the impossibility to determine the NSCLC type based on tumour morphology, IHC, and neuroendocrine indices, it is possible to diagnose not otherwise specified (NOS) cancer, which, however, should not account for more than 10% of all NSCLC diagnoses. The percentage of NOS diagnoses can be reduced due to the greater availability of tissue material, whose examination allows the determination of the full histological diagnosis [7].

The ambiguous histological picture and the IHC examination of the expression of glandular differentiation markers justify the diagnosis of NSCLC corresponding to adenocarcinoma (NSCLC — favours adenocarcinoma), and in the case of squamous cell immunophenotype, the diagnosis of NSCLC corresponding to squamous-cell carcinoma is allowed (NSCLC — favours squamous-cell carcinoma) [7].

Histological classification of NSCLC is supplemented by division according to differentiation (histological malignancy), which distinguishes four degrees (G, grade): GX — no possibility to determine differentiation, G1 — high differentiation, G2 — moderate differentiation, G3 — low differentiation, G4 — undifferentiated cancer. However, the degree of histological malignancy is of limited importance in the choice of treatment method [7].

In patients with advanced NSCLC, it is necessary to evaluate *EGFR* and *ALK* and *ROS1* genes status to detect mutations in *EGFR* gene and translocations in *ALK* and *ROS1* genes [9–11]. The presence of these disorders is a predictor of targeted therapy with EGFR (in Poland, currently — afatinib, erlotinib, gefitinib, and osimertinib) and ALK or ROS1 (in Poland, currently, crizotinib is reimbursed in lung cancers with *ALK* translocation) tyrosine kinase inhibitors (TKIs). It should be remembered that *EGFR* and *KRAS* mutations as well as *ALK* and *ROS1* translocations almost always exclude each other [12].

Genes can be evaluated using tissue material or — in the case of a confirmed sufficient number of cells in the sample — cytological examination (preferred mate-

Table 1. 2015 World Health Organisation pathomorphological classification of lung cancer [7]

Type	Subtype
Adenocarcinoma	Lepidic adenocarcinoma
	Acinar adenocarcinoma
	Papillary adenocarcinoma
	Micropapillary adenocarcinoma
	Solid adenocarcinoma
	Invasive mucinous adenocarcinoma with variants in the form of mixed mucinous and non-mucinous
	Colloid adenocarcinoma
	Foetal adenocarcinoma
	Enteric adenocarcinoma
	Minimally invasive adenocarcinoma with variants in the form of mucinous or non-mucinous
	Preinvasive lesions
	— atypical adenomatous hyperplasia
	— adenocarcinoma *in situ* mucinous or non-mucinous
Squamous-cell carcinoma	Keratinizing squamous-cell carcinoma
	Non-keratinizing squamous-cell carcinoma
	Squamous-cell carcinoma *in situ*
Neuroendocrine tumours	Small-cell carcinoma with variants in the form of combined small-cell carcinoma
	Large-cell carcinoma with variants in the form of combined large-cell carcinoma
	Typical and atypical carcinoids
	Preinvasive lesion — diffuse idiopathic pulmonary neuroendocrine hyperplasia
Large-cell carcinoma	
Adenosquamous carcinoma	
Sarcomatoid carcinoma	Pleomorphic sarcomatoid carcinoma
	Spindle-cell sarcomatoid carcinoma
	Giant-cell sarcomatoid carcinoma
	Carcinosarcoma
	Pulmonary blastoma
Salivary gland-type tumours	Mucoepidermoid carcinoma
	Adenoid-cystic carcinoma
Unclassified carcinomas	

rial is paraffin-embedded). If inhibitors of the immune checkpoints are to be used, the PD-L1 (programmed death ligand 1) protein expression should be evaluated in the tissue material or, in its absence, in the cytological material [9].

Prognosis in lung cancer patients depends primarily on the primary stage, while the age and gender of patients are of lesser importance. The new pathomorphological classification indicates a different clinical course in individual histological subtypes of adenocarcinoma (e.g. better prognosis — lepidic and papillary subtypes, worse prognosis — micropapillary and solid subtypes), but the differences does not affect the choice of treatment method. In patients with advanced cancer stage, prognosis depends mainly on performance status (PS) and the degree of weight loss in the period preceding the diagnosis. The prognostic significance of activating *EGFR* and *ALK* gene mutations has not been definitively confirmed, but the presence of these disorders (10–15% and 3–5% of Caucasian patients, respectively) is strongly correlated with the activity of appropriate molecularly targeted drugs. The prognosis in SCLC is generally worse than in NSCLC. In SCLC, in addition to tumour stage, the high activity of lactate dehydrogenase (LDH), which is associated with tumour mass, has an unfavourable prognostic value.

Recommendations

— An absolute prerequisite for commencing treatment is to determine the pathomorphological diagnosis of lung cancer based on the examination of tissue or cellular material (IV, A).
— Pathomorphological diagnosis of lung cancer should take into account the principles and criteria of the current WHO classification (III, A).
— Pathomorphological diagnosis should be supplemented by immunohistochemistry and — according to indications — genetic tests (I, A).
— The genetic-molecular assessment can be performed based on tissue material examination or — in the case of a sufficient number of tumour cells in the specimen — cytological examination (II, B).

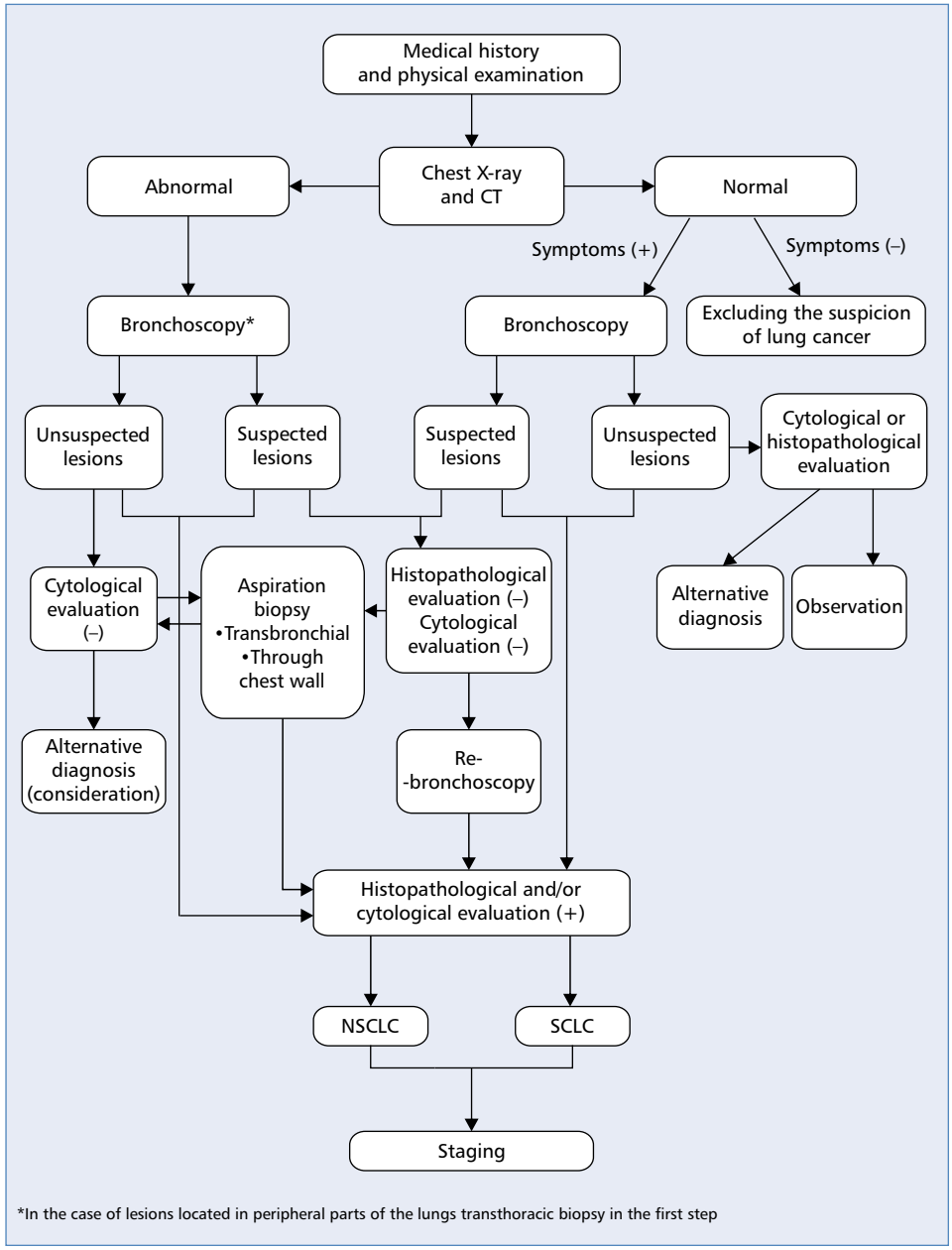


Figure 1. Principles of diagnostic procedures in lung cancer. CT — computed tomography; NSCLC — non-small cell lung cancer; SCLC — small cell lung cancer

— The diagnosis of NOS non-small cell lung cancer can only be made if it is not possible to obtain the appropriate material for the study (IV, A).
— The result of the pathomorphological postoperative examination should include the diagnosis of lung cancer (histological type and subtype and malignancy grade), the status of lymph nodes and blood and lymphatic vessels, and the assessment of surgical margins and tumour staging according to the current pathomorphological classification (IV, A).

Diagnostics

Diagnostic procedure includes determining the diagnosis and stage of lung cancer (Figure 1).

Medical history

Lung cancer is one of the malignancies in which the symptoms occur usually late. In the case of suspected lung cancer, medical history consists of an interview for symptoms (Table 2) and a careful assessment of active and passive exposure to tobacco smoke, familial

Table 2. Lung cancer symptoms

Symptoms associated with local tumour spread	General symptoms
Cough (especially a change in its character in smokers or non-smokers who are chronically coughing)	Arthralgia
Dyspnoea	General weakness
Haemoptysis	Weight loss
Pain in the chest	Increase in body temperature
Recurrent or prolonged pneumonia	Disorders of superficial sensation
Hoarseness	Thrombophlebitis
Swallowing disorders	Other symptoms of paraneoplastic syndromes
Pain in the shoulder	
Superior vena cava syndrome	
Horner's syndrome	

occurrence of tumours, and exposure to harmful environmental factors.

Physical examination

The occurrence of asymmetric symptoms in the physical examination of the respiratory system in a person burdened with an increased risk of lung cancer is an absolute indication for further diagnosis.

Physical examination of people with suspected lung cancer should particularly consider:

— symptoms associated with stricture or closure of bronchial lumen (asymmetry of thoracic tremor, percussion sound or alveolar murmur and weakening of alveolar murmur, suppression of percussion sound), localised (focal) wheezing over affected bronchi, bronchial murmur in the abnormal location;
— enlargement of peripheral lymph nodes (especially supraclavicular);
— symptoms of pleural effusion presence (suppression of percussion sound, weakening of alveolar murmur);
— symptoms of pericardial effusion presence and myocardial infiltration (enlargement of the heart silhouette, weakening of heart tones, jugular venous distension, liver enlargement, hepatojugular reflux, low blood pressure amplitude, arrhythmia);
— symptoms of superior vena cava *syndrome* (SVCS) (swelling of the face, increased dyspnoea, enlarged neck circumference, swelling of the upper limbs, widening of the jugular veins and on the chest wall, bruising of the face and mucous membranes);
— hepatomegaly;
— pain on pressure of the skeletal system and chest wall;
— paraneoplastic symptoms;
— symptoms from central and peripheral nervous system;
— body weight in relation to the expected value.

Performance status assessment

An essential element in lung cancer diagnosis is the assessment of performance status (PS), which should be carried out with use of WHO or Eastern Cooperative Oncology Group (ECOG) scale.

Imaging examinations

X-ray images of lung cancer can be very diverse. Suspicion of lung cancer should be made particularly by the finding in a conventional chest X-ray in posterior-anterior and lateral projections:

— well-rounded shadow (a completely solid or partially solid lesion or the image of so-called ground glass opacities);
— changes in hilar outline;
— air flow disturbances (asymmetry, atelectasis);
— infiltration change;
— pleural effusion.

Normal results of conventional X-ray does not exclude cancer located in areas with limited access (lung apex or mediastinum) or a small intrabronchial lesion. Therefore, all patients with suspected symptoms should have a chest CT scan with intravenously administered contrast agent (the test should additionally include the upper abdominal cavity with adrenal glands). In special situations, a magnetic resonance (MR) scan of the chest is performed, which can determine the state of the surrounding structures (e.g. lung apex, chest wall, diaphragm, or large vessels).

If a single nodule is present in lung parenchyma of undetermined character and up to 3 cm in diameter, the procedure proposed by the Fleischner Society [13] (Figure 2) is indicated, the main elements of which are determining the possibility of resection and the likelihood of malignant character of lesion (e.g. the character of ground glass opacities or microcalcifications with asymmetrical distribution, and especially marginal — the so-called *corona radiata*). Positron emission tomography (PET) in combination with CT (PET-CT) enables the differentiation of benign and malignant lesions and the determination of indications for other tests or follow-up.

PET-CT is helpful in assessing the tumour burden before planned surgical treatment and radical irradia-

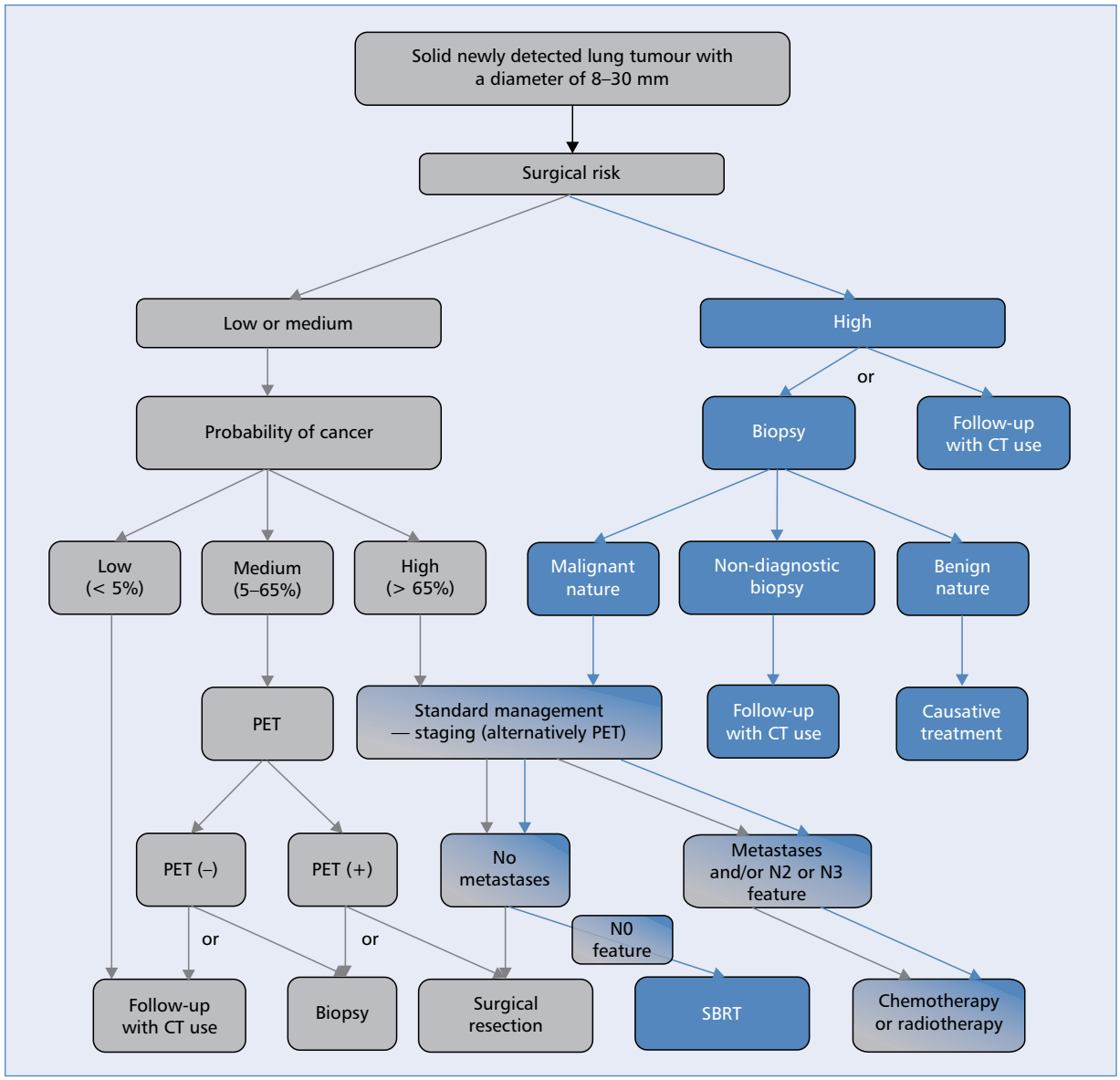


Figure 2. Guidelines for management in case of detection in chest CT scan a solid lung nodule with a diameter of 8–30 mm [13]. PET — positron emission tomography; CT — computed tomography; SBRT — stereotactic body radiation therapy

tion (the highest diagnostic accuracy in assessing the state of the mediastinal lymphatic system and detecting distant metastases) [14, 15] and should be performed in all patients qualified for surgical and radical radiotherapy (RT) or chemoradiotherapy (RCHT). The factor differentiating cancerous nature of lesions in PET-CT is the standardised uptake value (SUV), which depends on many variables (e.g. equipment parameters). For this reason, it is not always possible to draw final conclusions entirely on the basis of SUVs. It is advisable that each department performs analyses of the compliance of PET-CT results and pathomorphological post-operative reports regarding lymph nodes status. Due to the possibility of obtaining false positive or false negative results, PET-CT results should be treated with caution [15].

False positive results (especially in the lymph nodes) may occur in comorbidities with an inflammatory reaction (e.g. sarcoidosis, tuberculosis, or pneumoconiosis), while false negative results may in particular refer to adenocarcinomas. If PET-CT result is positive or borderline, a microscopic verification of possible neoplastic involvement of the lymph nodes using endobronchial ultrasonography (EBUS), oesophageal ultrasonography (EUS), or mediastinoscopy is necessary [15].

Brain imaging (preferably MR) is performed prior to planned radical treatment (patients in stages II and III before resection of pulmonary parenchyma and patients in grade III before combined radical RCHT; the remaining patients — only in the presence of suspicious symptoms). Evaluation of the bone system (scintigraphy

or X-ray) is indicated in patients with symptoms suggestive of metastases [15].

Endoscopic examinations

Bronchofiberoscopy is indicated in patients with suspected lung cancer because:
— is necessary when qualifying for surgical treatment (including radical);
— gives the possibility of obtaining cytological or histological sample;
— is helpful in cancer staging.

The diagnostic value of bronchofiberoscopy is significantly lower in peripheral changes. In the case of central lesions, at least five samples should be taken during endobronchial biopsy. It is recommended to perform a biopsy, a bronchial brushing, and a bronchoalveolar lavage (BAL) at the same time, since it may result in a sensitivity of cytological and histological evaluation of 80% [16].

Transbronchial needle biopsy — currently performed during EBUS or EUS procedures — is primarily used to determine the diagnosis and stage of lung cancer (sensitivity for NSCLC — 60–80%). It is performed using long (≥ 13 cm) cytological needles (usually 20–22 G) or histological needles (e.g. 19 G). It is recommended to take at least two samples from each location [17].

Laboratory tests

As part of the initial diagnosis it is necessary to perform a complete blood count (CBC) with a smear and clotting system parameters, biochemical tests (serum levels of glucose, creatinine, urea, sodium, potassium, calcium, bilirubin and transaminase, alkaline phosphatase, and LDH), and urinalysis. Other tests are carried out depending on individual indications. As part of the initial diagnosis and monitoring of the course of treatment, it is not recommended to assess serum markers, e.g. carcinoembryonic antigen (CEA) or fragments of cytokeratin 19 (CYFRA 21-1) [15].

Pathomorphological and molecular evaluation

The goals of pathomorphological evaluation in the diagnosis of lung cancer include determination of histological type and subtype as well as tumour range, differentiation of primary and secondary lesions, assessment of the so-called surgical margins, and detection of genetic disorders with significant importance for the choice of systemic treatment [7].

Primary tests in pathomorphological diagnostics of lung cancer include:
— histological evaluation tissue sample taken during bronchofiberoscopy;
— cytological evaluation of bronchial brushing or BAL;
— histological or cytological evaluation of the material obtained by means of a biopsy through the chest wall, bronchus, or oesophagus.

Pathomorphological evaluation should take into account the determination of neuroendocrine features on the basis of microscopic image, as well as IHC tests. The IHC test is necessary to determine the type and histological subtype of lung cancer and allows the differentiation of primary lung cancers and metastases of neoplasms with other sites, which in practice mainly concerns adenocarcinomas.

Histological examination should be performed (e.g. in the case of biopsy through the chest wall — with use a core needle), because obtaining tissue material often allows more accurate determination of the type and subtype of cancer and facilitates the extension of molecular tests (particularly important in the case of choice of systemic therapy preceding local treatment and in patients who are not eligible for pulmonary parenchyma resection). Good quality and properly protected cytological material also allows reliable determination of tumour type and subtype as well as molecular tests [7, 9].

If material for pathomorphological evaluation cannot be obtained using the aforementioned basic procedures, other methods may be used, such as:
— biopsy of mediastinal lymph nodes during EBUS or EUS;
— cytological sputum examination (low-sensitivity test and used only when bronchoscopy or biopsy through the chest wall cannot be performed);
— cytological evaluation of pleural effusion and/or pleural biopsy;
— biopsy of peripheral lymph nodes;
— mediastinoscopy;
— mediastinotomy;
— fluorescence bronchofiberoscopy with biopsy;
— cryobiopsy;
— thoracoscopy;
— biopsy of metastatic lesion;
— thoracotomy (after all other possibilities have been exhausted) [7, 15].

Before the planned treatment it is necessary to establish a pathomorphological diagnosis. In cases of justified difficulties in obtaining the material for examination, with simultaneous clinical and radiological features indicating a very high probability of cancer, a multidisciplinary team may decide to start treatment without pathological diagnosis.

Current diagnostics of lung cancer also includes molecular tests. Evaluation of biomarkers can be performed in tissue and cytological material (e.g. in an aspirate obtained by means of a fine-needle biopsy through the chest wall or bronchi). It is necessary to confirm a sufficient number of cells in preparation, and in the case of cytological material it is advisable to use methods of "embedding" cytological material in a paraffin block [9, 10]. An alternative to molecular testing using tissue or cytological material is the use of plasma free DNA circulating in the blood (cfDNA), so-called liquid biopsy [9].

When qualifying for the treatment with EGFR tyrosine kinase inhibitors in patients with adenocarcinoma and NOS NSCLC, the presence of clinically relevant primary *EGFR* gene mutations (activating and responsible for resistance) should be evaluated, which *de novo* occur in 10–15% and 1% of patients, respectively. Evaluation of the *EGFR* gene within exons 18–21 should be carried out using a method with high sensitivity and specificity (preferably using a certified test for clinical diagnosis). In the case of treatment failure with EGFR inhibitors I or II generation, re-biopsy is recommended to evaluate the presence of a secondary T790M mutation in *EGFR* gene (mutation connected to resistance to EGFR TKIs). Evaluation of *KRAS* gene status is not necessary because it does not affect the choice of systemic treatment [10].

In patients diagnosed with adenocarcinoma or unspecified NSCLC without activating mutations in *EGFR* gene, *ALK* and *ROS1* genes should be evaluated in order to detect rearrangements that occur in 3–5% and 1% of patients, respectively. The presence of rearrangements in both genes should be confirmed by fluorescence *in situ* hybridisation (FISH). However, it is advisable to pre-select patients based on the evaluation of the expression of ALK and ROS1 fusion proteins by IHC. The presence of rearrangement of the *ALK* or *ROS1* gene is an indication for the use of crizotinib or other ALK tyrosine kinase inhibitors [11]. Currently, the new generation sequencing (NGS) method is being introduced to the practice, which enables simultaneous assessment of the condition of many genes and shortens the time of molecular research. Complexity and interpretation difficulties mean that the NGS test should be performed only in laboratories with proven experience in this area.

The simultaneous assessment of clinically significant biomarkers based on one medical referral is optimal and recommended [10].

In the case of development of other molecular-targeted drugs and their reimbursement, the scope of tests should be extended (e.g. mutations in *BRAF*, *ERBB2 — HER2*, and *MET* genes). High reliability of pathomorphological diagnostics with the use of IHC and diagnostics with molecular biology methods can be provided only by laboratories with properly documented experience, having for all tests a valid certificate of European quality control program, regularly subjected to periodic external quality control, and ensuring comprehensive and simultaneous execution of analytical procedures.

Recommendations

— In each patient with suspected lung cancer, a medical history and physical examination, chest imaging (conventional radiography and computed tomography, in justified situations — magnetic resonance imaging), and bronchofiberoscopy should be performed (IV, A).
— In each patient qualified for resection of pulmonary parenchyma or radio (chemo) therapy with radical intention, positron emission tomography should be performed (II, A).
— Brain imaging is performed in patients with stage II and III before planned resection of the pulmonary parenchyma and with stage III before radical radio (chemo)therapy (II, B).
— Performing other tests (including positron emission tomography) should depend on the clinical situation and the planned treatment (IV, A).
— It is not recommended to perform serum marker tests as part of the diagnosis of lung cancer (II, A).
— In the case of the presence of a single nodule in parenchyma of undefined nature and a diameter of up to 3 cm, the probability of its malignancy and the possibility of resection using positron emission tomography should be determined (IV, A).
— The basic tests performed to obtain the material to determine the pathomorphological diagnosis and molecular characteristics of the lung cancer are bronchoscopy and biopsy through the chest wall, bronchus, or oesophagus (IV, A).
— The results of pathomorphological evaluation in lung cancer should include determination of tumour histological type and subtype, and in case of postoperative examination should also include the diagnosis of lung cancer (histological type and subtype and grade), assessment of lymph node status, as well as blood vessels and lymphatic vessels, assessment of surgical margins, and tumour staging according to the current disease pathomorphological classification (IV, A).
— Pathomorphological diagnosis of lung cancer should be supplemented by immunohistochemistry and — in the case of patients with advanced lung cancer — genetic tests to detect disorders that are important when deciding on systemic treatment (currently — *EGFR* and *ALK* genes) (I, A).
— In the case of treatment failure with I- or II-generation EGFR inhibitors, re-biopsy is recommended to assess the presence of secondary T790M mutation in the *EGFR* gene (I, A).
— In patients with advanced lung cancer qualifying for immunotherapy with immune checkpoint inhibitors the expression of PD-L1 protein should be determined (II, B).
— Diagnosis of NOS non-small cell lung cancer can be made only if it is not possible to obtain the appropriate material for evaluation (IV, A).

Table 3. Examinations used for lung cancer staging

Primary tumour assessment	Lymph node assessment	Distant metastasis assessment
— X-ray	— CT (less frequently MR)	— US or CT of abdominal cavity
— CT (less frequently MR)	— Bronchofiberoscopy	— Biopsy of single lesion in adrenal gland with suspicion of metastasis
— Bronchofiberoscopy	— Mediastinoscopy	— CT or MR of the brain (SCLC — always; NSCLC — before planned radical treatment [details in the text] and in case of clinical suspicions)
— Transbronchial biopsy ("blind", "semi-blind" transbronchial biopsy with the use of radial ultrasound transducer, EBUS, EUS)	— Parasternal mediastinotomy	— Bone scintigraphy (SCLC — planned combination treatment, NSCLC — clinical suspicion)
— Biopsy through the chest wall (peripheral changes)	— PET-CT*	— PET-CT*
— Cryobiopsy of peripheral lesions	— Physical examination	— FNA or surgical biopsy of suspected lesions
— Cytological examination of pleural or pericardial effusion	— FNA or surgical biopsy of suspected supraclavicular lymph nodes	
— Thoracoscopy	— Thoracoscopy	
— EUS	— EUS**	
	— EBUS**	

*In the assessment of the mediastinal lymphatic system in patients with potential indications for surgical treatment, PET-CT is a complementary method (negative PET-CT result with enlarged lymph nodes with > 10 mm in short axis size in the CT requires invasive mediastinal diagnostics, and in the case of smaller dimensions resignation from EBUS/EUS or mediastinoscopy is justified; positive PET-CT result does not mean the presence of metastases and in any case requires histological verification using mediastinoscopy or a US-guided biopsy). In addition, in patients with potential indications for surgical treatment, PET-CT allows more precise assessment of distant organs (especially metastases in the adrenal glands and bones). Suspicion of metastases in mediastinal lymph nodes or in other organs does not relieve the need for a biopsy. PET-CT examination is indicated in cancer staging before the planned surgical treatment and is useful in assessing the extent of disease and in planning radical RT or RCHT in patients with locally advanced NSCLC. PET-CT is an alternative to other imaging studies and bilateral bone marrow trepanobiopsy in the assessment of SCLC stage before planned treatment with a radical intention (I–III stage = LD form). Bone marrow evaluation in patients with SCLC is not necessary in the case of normal LDH activity, absence of bone metastases in scintigraphy, and thrombocytopaenia. MR examination may be helpful in case of diagnostic difficulties in patients with suspected bone metastases and inconclusive results of other imaging examinations.

**Invasive mediastinal assessment (EBUS/EUS) is also recommended in the case of a negative PET-CT or CT result in patients with perihilar or peripheral lung cancer, if one of the following features is present: (i) tumour with a diameter of more than 3 cm, (ii) no uptake or very low uptake in primary tumour, (iii) suspicion of ipsilateral involvement of hilar lymph nodes in PET-CT or CT [14].

CT — computed tomography; MR — magnetic resonance; FNA — fine-needle aspiration; EUS — oesophageal ultrasonography; US — ultrasonography; EBUS — endobronchial ultrasonography; PET — positron emission tomography; LDH — lactate dehydrogenase; RT — radiotherapy; RCHT — radiochemotherapy

Staging

Determination of lung cancer stage includes assessment of primary tumour (T feature), regional lymph nodes (N feature), and organs in which metastases may occur (M feature). In patients qualified for treatment with a radical intention, it is absolutely necessary to determine the size and location of the primary tumour and its relation to the surrounding anatomical structures (chest wall, pleura, diaphragm, heart, large vessels, and oesophagus) and the state of regional lymph nodes. The list of examinations used in the staging assessment is presented in Table 3. On the basis of the combined assessment of T, N, and M features (Table 4), the clinical stage of NSCLC is determined (Table 5). At the diagnosis of NSCLC, the proportion of patients in stages I–II, III, and IV is approximately 25%, 35%, and 40%, respectively.

In assessment of SCLC stage, a simplified classification has been applied so far, which distinguished the stage of limited disease (LD) or extensive disease (ED). The term of a limited disease was defined as a tumour that did not exceed one half of the chest, regardless of metastatic involvement of ipsilateral hilar lymph node and bilateral mediastinal and supraclavicular lymph nodes, not excluding ipsilateral malignant pleural tumour effusion. The presence of tumour lesions outside the mentioned area indicated the diagnosis of extensive disease. Currently, in SCLC — as in NSCLC — the TNM classification is recommended [18, 19].

The frequency of SCLC in I–III and IV stages according to TNM classification is approximately 35% and 65% at diagnosis.

In patients with lung cancer subjected to excision of pulmonary parenchyma and lymph nodes, the final stage is determined on the basis of pathomorphological examination of the surgical material. The "pathological" stage (pTNM) determined in this way is more accurate and reflects the prognosis of patients better than does the clinically defined stage (cTNM) [18].

Recommendations

— NSCLC staging should be made using the principles and criteria for the TNM classification (IV, A).
— If there are two lesions suspected to be primary cancer, they should be assessed separately (III, A).

Table 4. TNM classification of lung cancer (UICC, 2016) [19]

Feature	Characteristics
T	
TX	Primary tumour cannot be assessed or tumour proven by presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
T1	Tumour 3 cm in greatest dimension surrounded by lung or visceral pleura without invasion in the main bronchus
T1a(mi)	Minimally invasive adenocarcinoma — solitary adenocarcinoma ≤ 3 cm with a predominately lepidic pattern and ≤ 5 mm invasion in any one focus
T1a	Tumour ≤ 1 cm in greatest dimension (also uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus)
T1b	Tumour >1 cm but ≤ 2 cm in greatest dimension
T1c	Tumour > 2 cm but ≤ 3 cm in greatest dimension
T2	Tumour > 3 cm but ≤ 5 cm or tumour with any of the following features: — involves main bronchus regardless of distance from the carina but without involvement of the carina — invades visceral pleura — associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung
T2a	Tumour > 3 cm but ≤ 4 cm in greatest dimension
T2b	Tumour > 4 cm but ≤ 5 cm in greatest dimension
T3	Tumour > 5 cm but ≤ 7 cm in greatest dimension or a tumour of any size with infiltration of one of these areas: — chest wall (including the parietal pleura and superior sulcus tumours) — phrenic nerve — parietal pericardium or Associated with separate tumour nodule(s) in the same lobe as the primary tumour
T4	Tumour > 7 cm in greatest dimension or a tumour of any size with infiltration of one of these areas: — mediastinum — diaphragm — heart — great vessels — trachea — recurrent laryngeal nerve — oesophagus — vertebral body — carina or Tumour of any size associated with separate tumour nodule(s) in a different ipsilateral lobe than that of the primary tumour
N	
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	
MX	Distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present
M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion
M1b	Single extrathoracic metastasis
M1c	Multiple extrathoracic metastases in one or more organs

Table 5. Stages of lung cancer (UICC, 2016) [19]

Stage	Characteristics		
Occult carcinoma	TX	N0	M0
0	Tis	N0	M0
IA1	T1a(mi), T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a, T1b, T1c	N1	M0
	T2a, T2b	N1	M0
	T3	N0	M0
IIIA	T1a, T1b, T1c, T2a,	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T4	N0, N1	M0
IIIB	T3, T4	N2	M0
	T1a, T1b, T1c, T2a,	N3	M0
	T2b	N3	M0
IIIC	T3, T4	N3	M0
IVA	Any T	Any N	M1a, M1b
IVB	Any T	Any N	M1c

— In lung cancer patients with mediastinal lymph node involvement found on imaging examinations, while qualifying for possible resection of pulmonary parenchyma, pathomorphological confirmation of the nature of suspicious lesions should be obtained (IV, B).
— In patients before the planned radical treatment, it is advisable — if possible — to obtain a pathomorphological confirmation of the presence of cancer in the single suspected lesions detected in imaging studies in other organs (IV, A).
— In patients with lung cancer subjected to excision of pulmonary parenchyma and lymph nodes, the final stage is determined on the basis of pathomorphological examination of postoperative material (IV, A).

Respiratory and cardiovascular capacity assessment

Before the planned surgical treatment and radical RT or RCHT, assessment of respiratory and cardiovascular capacity, including gasometry (optimally — arterial blood or arteriovenous capillary blood), spirometry, and lung plethysmography should be performed. The tests also include the determination of forced expiratory volume — 1st second (FEV_1), vital capacity (VC), maximum voluntary ventilation (MVV), and diffusing lung carbon monoxide (DLCO), exercise tests (six-minute walk test and "second floor" test) and electrocardiography and echocardiography (in justified situations — exercise electrocardiography and coronary angiography). Before qualifying for surgical treatment, the expected post-operative values of FEV_1 ($poFEV_1$) and DLCO (poDLCO) should be calculated in order to assess the risk of perioperative and pulmonary-cardiac complications [19]. Patients with poFEV1 and poDLCO results higher than 60% of the due value, in the absence of concomitant serious chronic diseases, may be eligible for surgery without additional exercise testing. Management in patients with poFEV1 or poDLCO values of up to 60% of the due value is shown in Figure 3 [20].

Recommendations

— In lung cancer patients, cardiovascular and respiratory capacity assessment is necessary before planned treatment (III, A).
— In all lung cancer patients, comorbidity of other serious diseases should be taken into account before deciding on treatment (III, A).

Treatment

Treatment of patients with lung cancer (general principles — see Figure 4) should be planned by a multidisciplinary team (thoracic surgeon, radiation oncologist, medical oncologist, pneumonologist, specialist in radiodiagnostics, and patologist) and carried out in centres with full access to current diagnostic methods, surgical treatment, RT, and systemic treatment. Such centres should have appropriate experience and condi-

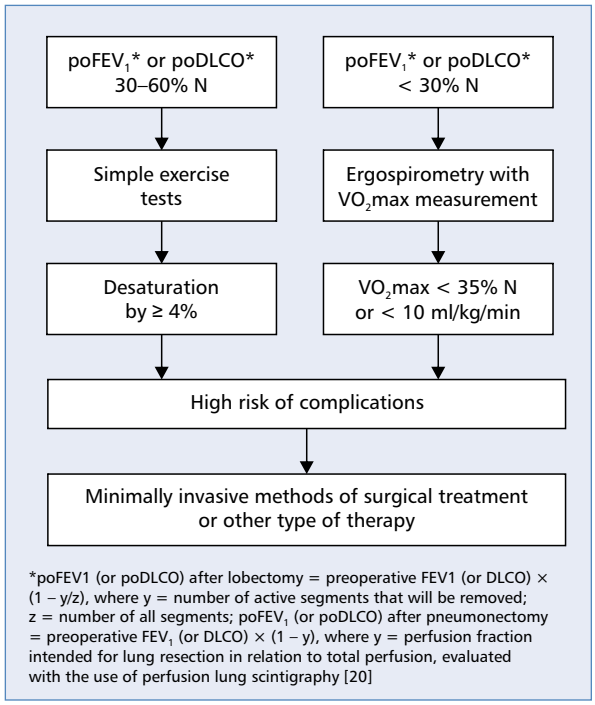


Figure 3. Management of patients with $poFEV_1$ or poDLCO values of up to 60% of the due value when qualifying for surgical treatment. $poFEV_1$ — expected post-operative forced expiratory volume — 1st second; poDLCO — expected post-operative diffusing lung carbon monoxide

tions for the use of combined treatment and appropriate management in cases of complications, which are often inevitable.

Non-small cell lung cancer — treatment in stages I–II and IIIA (potentially operable patients)

Surgical treatment

In patients with NSCLC in stages I and II and in selected patients with stage IIIA (without the N2 feature; in the case of N1 feature before eligibility for resection it is necessary to exclude the N2 feature using EBUS/EUS or mediastinoscopy) the treatment of choice is radical pulmonary parenchyma resection [21]. In patients with stage IIIA with the presence of the N2 feature, the results of primary surgical treatment are bad — resection of pulmonary parenchyma can be considered only in selected patients, provided use of neoadjuvant chemotherapy (CHT) and lymph node response is confirmed in PET-CT and mediastinoscopy [22, 23].

Lobectomy is the method of choice in patients who are eligible for resection. Pneumonectomy is performed only when the lobectomy is not likely to be radical. Both types of resection are routinely accompanied by removal of ipsilateral hilar lymph nodes and mediastinal nodes [21, 24]. The postoperative material should contain at least six lymph nodes from N1 (three lymph nodes) and N2 group (three lymph nodes; always lymph nodes below the tracheal bifurcation — group number 7). The influence of lymphadenectomy extent on the results of surgical treatment has not been definitively established, but a more extensive excision of the lymphatic system allows for a more complete determination of postoperative cancer stage and facilitates qualification for adjuvant treatment [21–23]. In patients with stage I and some patients with stage II lung cancer the recommended method of treatment is videothoracoscopic lobectomy [24–26]. Resection more limited than lobectomy is justified only in patients with significant limitation of respiratory reserves.

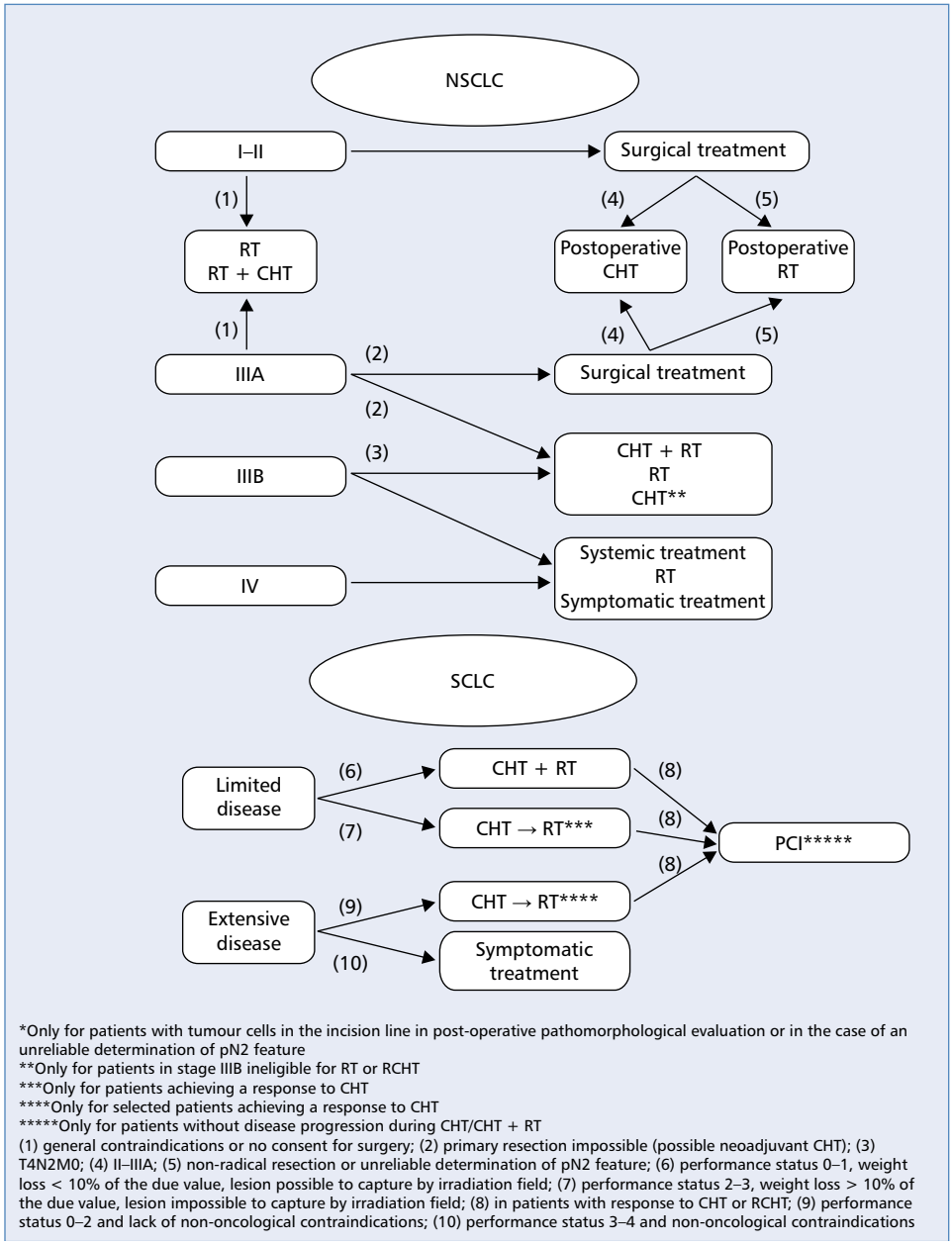
If resection is not possible due to significant medical contraindications or lack of patient's consent, the use of radical RT or RCHT should be considered with modern PET-CT-based planning techniques (dose intensity modulation, consideration of respiratory motion, irradiation based on current imaging) with total dose of 60–66 Gy (2.0 Gy per fraction). This treatment can be used in patients in good PS and without significant reduction of respiratory and circulatory capacity. In patients with small size (T1 or T2) peripheral tumour and without metastases in lymph nodes detected in imaging tests (PET-CT) who are not eligible for surgical treatment due to limited respiratory and/or cardiovascular capacity, management of choice is stereotactic RT, which allows a percentage of local cure to be obtained similar to that of surgical treatment. The role of stereotactic RT in perihilar tumours is still under investigation [27].

The value of ablation methods (thermoablation, cryoablation) in patients with reduced circulatory and cardiac capacity requires confirmation in prospective studies, and their routine use is unjustified.

Postoperative radiotherapy

The results of the meta-analysis of randomised clinical trials (RCTs) showed that in patients with pN0 and pN1 features post-operative RT may even worsen treatment outcomes, and in patients with pIIIA it reduces the risk of local recurrence and slightly prolongs overall survival [28]. The main limitations of this meta-analysis are suboptimal RT techniques used in previous clinical trials and inadequate patient selection. The results of the next meta-analysis of RCTs suggest a beneficial effect of modern post-operative RT in relation to local control and survival time in patients in pIII stage [29, 30], which, however, still needs to be confirmed in prospective studies.

Adjuvant RT is indicated when the presence of tumour cells is found in the cut line in post-operative histological examination, but it is not recommended after complete tumour resection (tumour-free surgical



*Only for patients with tumour cells in the incision line in post-operative pathomorphological evaluation or in the case of an unreliable determination of pN2 feature
**Only for patients in stage IIIB ineligible for RT or RCHT
***Only for patients achieving a response to CHT
****Only for selected patients achieving a response to CHT
*****Only for patients without disease progression during CHT/CHT + RT
(1) general contraindications or no consent for surgery; (2) primary resection impossible (possible neoadjuvant CHT); (3) T4N2M0; (4) II–IIIA; (5) non-radical resection or unreliable determination of pN2 feature; (6) performance status 0–1, weight loss < 10% of the due value, lesion possible to capture by irradiation field; (7) performance status 2–3, weight loss > 10% of the due value, lesion impossible to capture by irradiation field; (8) in patients with response to CHT or RCHT; (9) performance status 0–2 and lack of non-oncological contraindications; (10) performance status 3–4 and non-oncological contraindications

Figure 4. Principles of primary treatment of patients with lung cancer. NSCLC — non-small-cell lung cancer; SCLC — small-cell lung cancer; RT — radiotherapy; CHT — chemotherapy; CHT + RT — chemoradiotherapy; PCI — prophylactic cranial irradiation (elective brain irradiation in patients with response to RCHT or CHT)

margin — R0) and in the presence of pN0 or pN1 features, provided that the pN feature is reliably assessed. Adjuvant RT uses a dose of 60–66 Gy (fractional dose 2.0 Gy per day with conventional fractionation and using a 4–15 MeV megavoltage beam). Treatment should begin within six weeks of surgery.

Postoperative chemotherapy

The results of a meta-analysis of studies with random selection of patients indicate that the use of post-operative CHT improves the five-year survival by approximately 5% [31]. Significant benefits of supplementary CHT apply only to patients in II and IIIA stages (including patients undergoing post-operative RT), but they depend on gender and age of patients as well as histological type of cancer. In patients in stage I, adjuvant CHT does not improve prognosis.

Post-operative CHT should include 3–4 cycles of a regimen with cisplatin 80–100 mg/m^2 on day 1 in combination with vinorelbine at a dose of 25–30 mg/m^2 on days 1 and 8 (frequency every three weeks), whose efficacy is best documented [31]. Post-operative CHT

can be used only in patients in very good or good PS, with full recovery after surgery and without significant co-morbidities and medical contraindications. The risk of adverse reactions during post-operative CHT is higher in patients over 70 years of age and patients after pneumonectomy. In case of simultaneous indications for postoperative RT, it can be started at the same time as CHT. The usefulness of molecular prognostic and predictive factors assessment in the qualification to post-operative CHT has not yet been proven [10].

Preoperative treatment

In previous studies pre-operative CHT was mainly used in selected patients with stage IIIA and pN2 feature, but the optimal treatment strategy has not been definitively determined. In a meta-analysis of randomised controlled trials of 2385 patients in IB–IIIA stages a 13% reduction in relative risk of death was found, which corresponds to the absolute difference in five-year survival at 5% (statistically significant difference) in favour of pre-operative CHT compared with surgical treatment alone [32].

Pre-operative CHT may be considered in patients with pIIIA stage with feasible lobectomy (initial CHT in patients undergoing pneumonectomy does not prolong survival as compared to less aggressive resection), always based on multidisciplinary team decision after reliable determination of mediastinal lymph nodes (imaging and invasive tests — pN2 feature). Treatment includes 2–3 cycles of CHT using a cisplatin-based regimen in combination with vinorelbine, gemcitabine, paclitaxel, or docetaxel. It is necessary to carefully monitor the response and tolerance. Surgical treatment can be carried out after recovery from haematological toxicity during a three-week gap from the last CHT cycle. The condition for qualifying for resection is obtaining a histologically confirmed complete response in the mediastinal lymph nodes [32].

Preoperative RCHT does not improve outcomes, except for patients with superior sulcus tumour *(Pancoast tumour*), in whom simultaneous use of CHT (two cycles of cis-platinum in combination with the second drug) and RT (50–60 Gy) in most cases allows complete resection. Surgery should be performed 4–6 weeks after completion of RCHT [33].

Recommendations

— Resection of the pulmonary parenchyma with removal of hilar and mediastinal lymph nodes is the treatment of choice in patients with non-small-cell lung cancer in I–II and IIIA stages with N1 feature (I, A).
— Lobectomy is the preferred method of pulmonary resection. Pneumonectomy can only be performed if the lobectomy does not ensure complete resection (II, A).
— In patients with non-small-cell lung cancer in stage I and some patients in stage II, the recommended method is videothoracoscopic lobectomy (I, A).
— In patients with non-small-cell lung cancer with T1 or T2 feature and without metastases in lymph nodes, who are not eligible for surgical treatment due to respiratory or circulatory failure, stereotactic radiotherapy is the treatment of choice (II, A).
— In patients in I–IIIA stages, who are not eligible for resection and stereotaxic radiotherapy, radical radiotherapy or chemoradiotherapy should be used (II, A).
— Postoperative complementary radiotherapy in patients with non-small-cell lung cancer with pN0 and N1 features is not justified (I, A) except the patients after incomplete resection (III, B).
— The role of postoperative radiotherapy in patients with pN2 feature is not clearly defined (II, C).
— Postoperative radiotherapy should be started within six weeks of surgery; it can be started simultaneously with chemotherapy (III, B).
— Post-operative chemotherapy (cisplatin and vinorelbine — 3–4 cycles) in patients with non-small-cell lung cancer is recommended for pII and pIII stages (I, A).
— Pre-operative chemotherapy (regimens containing two drugs, including cisplatin) can be used in selected patients with non-small-cell lung cancer in stage IIIA with pN2 feature (I, B).
— Surgery may be offered for patients with non-small-cell lung cancer with the N2 feature only if complete response to chemotherapy, confirmed in positron emission tomography and mediastinoscopy, is achieved (II, B).
— In patients diagnosed with superior sulcus non-small cell lung cancer, potentially qualifying for surgery, pre-operative radiotherapy or chemoradiotherapy should be used (II, A).

Non-small cell lung cancer — treatment in IIIA (inoperable patients) and IIIB stages

Patients with stage IIIA NSCLC, in whom complete resection cannot be performed due to advanced stage of disease or other reasons, should receive RT or RCHT according to the rules referring to stage IIIB. The primary surgical treatment — based on the management principles in patients with stages II–IIIA — may be considered in selected patients with T4N0 or T4N1 stages, whereas patients with T1–3N3 and T4N2–N3 stages are not eligible for resection, and in this group RT or RCHT is the treatment of choice [33–35]. These differences in the procedure justify conducting full diagnostics in order to assess the status of lymph nodes classified as N2 and N3 features. The presence of pleural or pericardial effusion (confirmed by cytological examination of the material obtained by means of puncture or thoracos-

copy) currently qualifies the tumour to grade M1 and constitutes an indication for treatment in accordance with the rules in force in generalised disease.

The results of a meta-analysis of randomised clinical trials indicate that the combination of RT and CHT is more effective compared to the RT alone, and the simultaneous RCHT is more valuable than the sequential use of both methods, but at a higher risk of acute oesophagitis (as of pneumotoxicity and myelotoxicity, but to a lesser extent) [34, 36, 37]. Simultaneous RCHT can be used in specialised centres with available treatment of complications. Chemoradiotherapy — especially concurrent — can only be used in patients with good performance status, without significant (more than 10% of the due value) weight loss, with limited tumour mass and adequate respiratory capacity [34, 36, 37]. In some patients who do not qualify for concurrent RCHT (e.g. due to tumour burden), 2–4 pre-treatment CHT cycles may be considered, with the need to monitor the response to initial systemic therapy. In selected patients over 70 years of age in very good PS, with normal cardiorespiratory capacity and without serious comorbidities, sequential CHT and RT may be used [38]. Irradiation should begin within 2–3 weeks of CHT completion (longer interval reduces the effect of initial CHT). In the case of progression during CHT, it should be terminated and the radical RT should start immediately.

The use of CHT before or after concurrent RCHT (induction or consolidation therapy) does not increase the effectiveness of therapy but is associated with higher incidence of side effects and therefore is not recommended [33–38]. The results of the phase III study showed that the use of consolidation immunotherapy with durvalumab (monoclonal antibody blocking programmed death receptor 1 ligand, PD-L1) in patients with stage III NSCLC with objective response or stable disease following concomitant RCHT decreases by 49% the relative risk of disease progression or death compared to placebo (median duration of progression-free survival — 17 and 6 months, respectively) and has a significant effect on overall survival (reduction of death risk by 32%, median — not reached for durvalumab and 29 months for placebo); two-year survival — 66% and 56%, respectively). The incidence of severe adverse events was similar in both groups of patients [39].The drug is registered in the European Union, but in Poland it is currently not reimbursed.

In a radical RT (alone or in combination with CHT) a dose of 60–66 Gy is applied using a high-energy photon beam with conventional fractionation (1.8–2.0 Gy per day) and conformal planning [33, 34]. Increasing the dose above 66 Gy does not give any clinical benefit [35, 37]. The irradiated volume should cover the area of the primary tumour and involved hilar and mediastinal lymph nodes. It is recommended to use modern RT techniques (planning based on PET-CT, modulation of dose intensity, consideration of respiratory motion, irradiation based on real-time imaging). Irradiation of non-affected groups of lymph nodes, in particular of the opposite mediastinal and supraclavicular areas, does not improve efficacy and increases treatment toxicity.

Radical RT or RCHT are not indicated in patients with impaired performance status (grade 2 or higher according to the WHO scale), presence of pleural effusion, active infection, weight loss over 10% of the value due in the three months preceding the treatment commencement, and coexistence of other serious diseases (e.g. severe cardiovascular or respiratory failure, recent myocardial infarction or stroke, renal failure). In the aforementioned situations, palliative RT or CHT is used.

As part of the simultaneous RCHT (treatment of choice), cisplatin (75–80 mg/m^2 — day 1) is used in combination with etoposide (100–120 mg/m^2 — day 1, 2, and 3) or vinorelbine (30 mg/m^2 — day 1 and 8). In the case of sequential RCHT, regimens consisting of cisplatin and one of the above-mentioned drugs or taxoid (docetaxel 75 mg/m^2 — day 1 or paclitaxel 200 mg/m^2 — day 1) can be used. In patients with contraindications to cisplatin, carboplatin (AUC 6 — day 1) may be used in combination with the mentioned drugs. Subsequent cycles of CHT within the sequential and simultaneous RCHT should be repeated at 21-day intervals [33, 34].

In patients with contraindications to RCHT, only radical RT at a dose of 60–66 Gy (30–33 fractions) can be used. Use of hypofractionated RT in the regimen 66 Gy/22 fractions is also allowed [33]. However, a recent analysis of RCTs indicates that the conditions for the benefit from hypofractionated RT use in combination with CHT in patients who are not eligible for radical RT are good performance status and life expectancy of at least three months [40]. The decision regarding selection of the fractionation scheme should be made on the basis of individual assessment of post-radiation complication risk.

Recommendations

— Surgical treatment (primary or preceded by initial chemotherapy) can only be considered in selected patients with locally advanced non-small-cell lung cancer (II, B).
— The treatment of choice in patients with locally advanced non-small-cell lung cancer is radical chemoradiation or — in the case of contraindications to chemotherapy — radiotherapy alone (in both situations a dose of 60–66 Gy, including primary tumour and ipsilateral hilar and mediastinal lymph nodes) (I, A).
— Patients with locally advanced superior sulcus non-small-cell lung cancer undergo resection — depending on feasibility — followed by chemoradiotherapy or chemoradiation alone (III, A).

— In patients with locally advanced non-small-cell lung cancer, the treatment of choice is simultaneous radiotherapy and chemotherapy, while sequential therapy is acceptable only in the case of a clinically justified inability to conduct simultaneous chemoradiation (I, A).
— The chemotherapy regimens for combined chemoradiotherapy in patients with locally advanced non-small-cell lung cancer should include cisplatin (I, A).
— Consolidating chemotherapy after chemoradiotherapy is not justified (I, A).
— In patients undergoing radical simultaneous chemoradiation with PD-L1 expression on tumour cells, consolidation with durvalumab should be considered (I, A).

Non-small cell lung cancer — treatment in stage IV

Treatment of patients with disseminated NSCLC is of a palliative nature. Depending on the individual clinical situation, the use of CHT or EGFR, ALK, and ROS1 tyrosine kinase inhibitors, immunotherapy, palliative RT, or symptomatic treatment only may be considered. Currently, EGFR first- (erlotinib, gefitinib) or second-generation (afatinib) and third-generation (osimertinib) inhibitors, ALK inhibitor (crizotinib), and PD-1 inhibitors (nivolumab, pembrolizumab, atezolizumab) are available in Poland. The choice of systemic treatment method depends on the histological type (non-squamous- or squamous-cell carcinoma) and molecular features of the tumour. In patients with activating genetic disorders, the treatment of choice is molecularly targeted treatment. The choice of treatment should take into account the patient's age and PS as well as the presence of co-morbidities. In patients with non-squamous cell carcinoma, the possible presence of primary mutations (activating and responsible for resistance) should be determined in exons 18–21 of *EGFR* gene, followed by the presence of *ALK* and *ROS1* gene rearrangements. These tests are best performed within one medical order. Determination of PD-L1 expression using the validated IHC method to qualify patients with squamous- and non-squamous-cell carcinoma for immunotherapy can be carried out using tissue or cell material (in case of non-squamous-cell carcinoma it should be preceded by an assessment of *EGFR* and *ALK* genes status). If, in the case of tumour recurrence, it is not possible to perform a genetic test in archived tumour material, a re-biopsy is recommended. In patients with progression during treatment with EGFR tyrosine kinase inhibitors, it is necessary to re-sample the material for molecular testing in order to evaluate the mechanism of resistance (possible presence of T790M mutation). Firstly, it is recommended to evaluate for this mutation in circulating DNA (cfDNA, liquid biopsy), and if a negative result is obtained — re-biopsy or needle biopsy should be considered. When choosing the procedure, the patient's preferences should be taken into account. In selected patients with single adrenal or cerebral metastases — based on the decision of a multidisciplinary team — surgical treatment including excision of primary and metastatic lesions may be considered.

First-line systemic treatment

Chemotherapy

Numerous randomised clinical studies and meta-analyses showed survival prolongation and quality of life improvement in patients with advanced NSCLC receiving palliative CHT [41, 42].

Palliative CHT in patients with NSCLC in stage IV may be used, if:
— PS is very good or good (WHO category — 0 or 1);
— no body weight loss of no more than 10% is revealed within the three months before starting treatment;
— no serious comorbidities and/or sequelae of previous cancer treatment are found;
— adequate function of the haematopoietic system, liver, kidneys, and cardiovascular and respiratory system is confirmed;
— objective assessment of response to treatment according to RECIST (Response Evaluation Criteria in Solid Tumours) criteria, version 1.1. is possible.

Patients who do not meet all of the abovementioned conditions may receive best supportive care or palliative RT depending on the individual situation. Palliative RT, regardless of lesions in other organs, is the method of choice in patients with troublesome complaints associated with the spread of a tumour in the chest (symptoms of superior vena cava syndrome, obstructive dyspnoea, haemoptysis, dysphagia, pain). Irradiation is also useful in patients with painful or fracture-threatening bone metastases and secondary deposits in the central nervous system (CNS).

In advanced NSCLC, CHT is used according to the regimen containing cisplatin (75–80 mg/m^2 — day 1) in combination with one of the following drugs: etoposide (100–120 mg/m^2 — day 1, 2, and 3), vinorelbine (25–30 mg/m^2 intravenously — day 1 and 8 or 25–30 mg/m^2 intravenously — day 1 and 60–80 mg/m^2 orally — day 8 or 60–80 mg/m^2 orally — day 1 and 8), gemcitabine (1000–1250 mg/m^2 — day 1 and day 8), docetaxel (75 mg/m^2 — day 1), paclitaxel (200 mg/m^2 — day 1), or pemetrexed (500 mg/m^2 — day 1), wherein in combination with pemetrexed the recommended dose of cisplatin is 75 mg/m^2 (day 1 of the cycle). The results of meta-analyses of RCTs showed that the cisplatin-containing regimens compared with carboplatin (especially in combination with taxoids and gemcitabine) result in longer overall survival [43, 44]. The use of carboplatin (AUC 5–6 — day 1) in combination with these drugs may

only be considered in patients with contraindications to the use of cisplatin (gemcitabine and pemetrexed are registered only in combination with cisplatin).

In NSCLC patients with histology other than those with a predominance of squamous-cell carcinoma, the combination of cisplatin and pemetrexed is more effective than other CHT regimens [45].

Patients older than 70 years and in good PS (grades 0–1 in the WHO scale) can receive multi-drug CHT [46].

Regimens without platinum derivatives can be considered only in the case of contraindications to the use of this group of drugs [44]. In the case of absolute contraindications to the use of schemes containing two drugs including platinum derivatives, single-dose CHT (e.g. intravenous or oral vinorelbine) may be considered [47].

The duration of palliative CHT depends on its effectiveness and tolerance, which justifies the assessment of treatment effects not later than after the second cycle. Treatment should not exceed 3–4 cycles in general, but patients with progressive response may use an additional two cycles (a total of six cycles of CHT) [48].

The use of maintenance or consolidation therapy (in Poland not reimbursed) after obtaining an objective response after initial CHT may slightly prolong the overall survival (difference — 1–3 months compared with CHT without further maintenance treatment). In patients with very good or good PS (WHO grades 0–1) without persistent adverse effects after initial CHT and with non-squamous-cell carcinoma, the use of pemetrexed maintenance therapy prolongs time to progression [49]. It was also found that patients with *EGFR* gene mutation and without progression after CHT may benefit from erlotinib maintenance treatment [50]. So far, however, the criteria for selecting patients for the aforementioned procedure have not been defined and maintenance therapy is a subject of controversy.

Molecularly targeted treatment

Numerous RCTs and their meta-analyses indicate that in patients diagnosed with adenocarcinoma and the presence of activating mutations in *EGFR* gene, the use of one of the first- (erlotinib — 150 mg per day or gefitinib — 250 mg per day) or second-generation (afatinib — 40 mg per day) EGFR tyrosine kinase inhibitors may produce higher response rate and longer progression-free survival and is better tolerated compared to CHT [51, 52]. The use of EGFR tyrosine kinase inhibitors is the first choice in the treatment of patients with *EGFR*-activating mutations. These EGFR inhibitors have very similar efficacy, and the differences concern only side effects (e.g. more frequent occurrence of diarrhoea after application of afatinib or abnormalities in liver function during treatment with gefitinib). Previous RCTs showed no significant differences between the anti-EGFR drugs and CHT in terms of overall survival, because the majority of patients who progressed during or after CHT received EGFR inhibitors in the next treatment line. Only for afatinib — in the combined analysis of LUX-Lung 3 and 6 [53] — a significant increase in overall survival compared to CHT was observed in patients with *EGFR* exon 19 deletion (median for afatinib and chemotherapy in LUX-Lung 3 and 6 trials — 33 *vs.* 21 months and 31 *vs.* 18 months, respectively), which was not observed in patients with *EGFR* exon 21 substitution. Treatment with EGFR tyrosine kinase inhibitors should be continued to disease progression or serious side effects.

A phase III clinical trial conducted in an Asian population showed a significant prolongation of progression-free survival and overall survival after dacomitinib (second-generation EGFR tyrosine kinase inhibitor) compared to gefitinib (14.7 *vs*. 9.2 months and 34.1 *vs.* 26.8 months, respectively), with higher toxicity of dacomitinib [54]. This drug is currently being evaluated for registration in the first-line of treatment for patients with advanced NSCLC with the presence of activating *EGFR* mutations in exon 19 or 21.

The phase III study compared the efficacy of first-generation EGFR inhibitors (erlotinib or gefitinib) and osimertinib (a third-generation inhibitor, active in the presence of activating mutations in *EGFR* 19 or 21 exons and T790M resistance mutations in exon 20) in the first- line of treatment [55]. Significant prolongation of progression-free survival was found in osimertinib group (median — 19 and 10 months, respectively). Higher efficacy of osimertinib was found in patients with and without CNS involvement. The influence of osimertinib on overall survival has not yet been evaluated, but the drug is currently registered in the first-line treatment based on the extension of progression-free survival (in Poland so far only reimbursed in the second-line of treatment).

Phase III trial results show some benefits of bevacizumab — a monoclonal antibody directed against vascular endothelial growth factor (VEGF) — in combination with CHT. However, the study excluded patients with squamous-cell carcinoma, haemoptysis, and bleeding disorders or undergoing anticoagulant therapy, as well as metastases in the brain and pharmacologically uncontrolled hypertension. Irrespective of the careful selection of the study group, side effects in patients receiving bevacizumab were more frequent and more severe [56].

Attempts to combine cetuximab with CHT as part of first-line treatment yielded conflicting results (no effect in one study and a slight increase in overall survival in another) [57].

In patients diagnosed with adenocarcinoma and *ALK* gene rearrangement in a phase III trial, it was found that crizotinib (ALK tyrosine kinase inhibitor) used in

first-line treatment reduces the relative risk of tumour progression or death by 55% compared with CHT [58]. The use of crizotinib in the first-line is strongly justified, but currently the drug is reimbursed in Poland only in the second-line treatment. In randomised trials, significantly greater benefits were also found following the use of other ALK inhibitors (ceritinib and alectinib) compared to CHT (the use of crizotinib in first-line treatment and other ALK tyrosine kinase inhibitors is not yet reimbursed in Poland).

In a phase III clinical trial comparing alectinib (a second-generation ALK tyrosine kinase inhibitor) with crizotinib, significant differences were found in favour of alectinib (reduction in the relative risk of disease progression or death by 53%) with better tolerance [59]. The differences concerned the whole population and patients with CNS metastases, which results from better penetration of alectinib across the blood-brain barrier.

The use of crizotinib is also justified in first-line treatment of patients with *ROS1* gene rearrangement [60].

In selected patients with oligopression and with simultaneous response of other lesions during tyrosine kinase inhibitor treatment, their further use after local treatment may be considered (excision or RT — especially stereotactic, provided it can be used).

Immunotherapy

Among immune checkpoint inhibitors, pembrolizumab (PD-1 inhibitor) is of proven value in the first-line treatment. In a phase III clinical trial, a significant prolongation of progression-free survival time and overall survival after pembrolizumab treatment compared to CHT (platinum-derived patterns) was demonstrated in patients with PD-L1 expression in at least 50% of tumour cells (median — 10 *vs.* 6 months and 30 *vs*. 14 months, respectively) [61]. Benefits were reported by patients with both squamous- and non-squamous-cell carcinoma. In the case of another PD-1 inhibitor — nivolumab — no significant benefits have been demonstrated during first-line treatment [62].

Atezolizumab (PD-L1 inhibitor) was evaluated in IMpower-150 trial [63] in first-line treatment in patients with non-squamous-cell carcinoma. This study analysed the value of chemotherapy (carboplatin and pemetrexed) used in combination with bevacizumab with or without atezolizumab (with maintenance treatment in both arms with bevacizumab alone or bevacizumab and atezolizumab). In the group of patients receiving atezolizumab, a significantly better overall survival rate after 12 and 24 months (67% and 43% and 61% and 34%, respectively), and a longer progression-free survival (median of 8.3 and 6.8 months, respectively) was obtained. Severe adverse events were more common in patients treated with atezolizumab (58% *vs*. 50%). The reduction in the risk of death depended on PD-L1 expression.

In a phase III clinical study, the addition of CHT (two-drug regimen) to pembrolizumab in patients with non-squamous-cell carcinoma resulted in a higher 12-month survival rate compared to CHT alone (69% *vs*. 49%) [64]. The benefits of adding CHT to pembrolizumab were independent of PD-L1 expression, but the greatest reduction in the risk of death (58%) was in patients with high expression (50% or more cells). The addition of CHT did not significantly increase the frequency of serious adverse reactions. The combined use of immunotherapy and CHT in first-line treatment is not yet reimbursed in Poland.

Immunotherapy with the use of anti-PD-1 drugs (e.g. pembrolizumab and nivolumab) or anti-PD-L1 (e.g. atezolizumab) may cause side effects (most commonly rash, diarrhoea, liver dysfunction and hypopituitarism, or hypothyroidism). Side effects of immunotherapy usually appear after 2–6 weeks of treatment. Early diagnosis and appropriate management allow most patients to continue treatment [65, 66].

Second-line systemic treatment

Chemotherapy

In selected patients without *EGFR*, *ALK* and *ROS1* gene disorders and with progression after prior palliative CHT, leading to objective response lasting at least three months, the use of docetaxel or pemetrexed in the second-line treatment may be considered [67]. The superiority of multiple-drug CHT over monotherapy in second-line treatment was not demonstrated in RCTs [68]. The effectiveness of other cytotoxic drugs, except docetaxel and pemetrexed, in second-line treatment has not been proven. Second-line treatment can only be used in patients who are in good PS and without persistent complications of previous CHT. Pemetrexed in second-line treatment is slightly more effective than docetaxel in patients with non-squamous-cell carcinoma [67].

Molecularly targeted treatment

The use of EGFR tyrosine kinase inhibitors in second-line treatment after previous CHT is justified only in patients with *EGFR* gene mutation. In the case of patients with *ALK* and *ROS1* gene rearrangement, it is justified to use crizotinib. Molecular disorders should be determined on the basis of reliable tests (optimally simultaneously within one medical order). The duration of treatment should depend on its tolerance and outcomes.

In patients with *EGFR* gene mutation, in whom one of the EGFR tyrosine kinase inhibitors (afatinib, erlotinib or gefitinib) was used as first-line treatment, and the disease progressed after remission, the T790 mutation in exon 20 of *EGFR* gene should be tested (liquid biopsy or re-sampling of tissue material) [69]. Phase III clinical trial in patients with this mutation, showed superiority of osimertinib compared to chemotherapy — median dura-

tion of progression-free survival was 10 and 4 months, respectively (reduction of relative risk by 70%) [70].

In patients with *ALK* gene rearrangement, ALK tyrosine kinase inhibitors are the treatment of choice (this therapy is currently not reimbursed in Poland in the first line).

In patients with *ALK* gene rearrangement and disease progression during the first line of CHT, the use of crizotinib allows prolongation of progression-free survival by five months and a reduction in relative risk of disease progression or death by 51% compared to docetaxel or pemetrexed [71]. In phase III study, crizotinib was compared to brigatinib (ALK tyrosine kinase inhibitor second generation) in patients who had not previously received anti-ALK therapy (27% of patients had previously received CHT). In the group of patients who were previously treated with CHT, the risk of disease progression or death was 65% lower after brigatinib treatment [72]. Brigatinib is registered in the second line treatment for patients with *ALK* gene rearrangement (in Poland this indication is not covered by reimbursement).

In the case of failure of first-line treatment using crizotinib, ceritinib is highly effective [73] (this treatment is currently not reimbursed in Poland).

The efficacy of dabrafenib (BRAF kinase inhibitor) and trametinib (MEK kinase inhibitor) was assessed in phase II study in patients with NSCLC with *BRAF V600E* mutation after failure of previous systemic treatment. The median progression-free survival and objective responses rate were 9.7 months and 63.2%, respectively. Treatment with dabrafenib and trametinib in patients with *BRAF V600E* mutation is currently not reimbursed in Poland [74].

The use of docetaxel in combination with nintedanib (an anti-angiogenic drug) in patients with advanced adenocarcinoma with progression after previous multi-drug CHT with the use of platinum derivatives reduced the risk of death by 25% in comparison with docetaxel monotherapy [75]. The benefits associated with the use of nintedanib and docetaxel were related to patients with so-called early chemoresistance (disease progression on treatment and during the first three months from the end or nine months from the start of CHT).

Immunotherapy

Phase III clinical trial results showed that anti-PD-1 drugs (nivolumab and pembrolizumab) and anti-PD-L1 (atezolizumab) used in second-line treatment for NSCLC patients (both squamous- and non-squamous-cell carcinoma) are more effective than docetaxel. In the case of squamous-cell carcinoma, the use of nivolumab compared to CHT was associated with a 41% reduction in the relative risk of death, regardless of PD-L1 expression [76]. In patients with non-squamous-cell carcinoma, the decrease of relative risk of death compared with docetaxel was 27% with nivolumab [77] and atezolizumab [78] and 33% with pembrolizumab (the difference in favour of pembrolizumab was highest in patients with PD-L1 expression on at least 50% of cancer cells — 47%) [79].

Radiotherapy

In patients with advanced NSCLC and signs and symptoms in chest indicate a good results after palliative RT, which can be used in various regimens (e.g. 20 Gy in five fractions in five days, 30 Gy in 10 fractions in 12 days or 16 Gy in two fractions of 8 Gy with one-week interval).

The indications for palliative RT are also symptomatic metastases in the CNS or bones. In selected cases of airway obstruction due to endobronchial tumour growth, valuable palliative treatment may be endobronchial brachytherapy, resection of the obliterating mass with the use of laser or insertion of endobronchial prosthesis (stent), which can also be used in the case of bronchial outside pressure.

Anti-osteolytic treatment

Bone metastases occur in 30–40% of patients with NSCLC. The results of the phase III trials showed that the use of zoledronic acid [80] or denosumab [81] in patients with advanced NSCLC with bone metastases may prevent or delay bone complications. Analysis of subgroups in a study using denosumab in various cancers, in addition to the anti-osteolytic effect, also showed an increase in survival in a subset of NSCLC patients [81].

Pleurodesis

In patients with recurrent pleural effusion, a good palliative effect gives the use of pleurodesis (especially with the use of talc).

Treatment of patients with a single metastasis

In the case of primary cancer diagnosed together with a single metastasis, treatment with a radical intention may be considered, but it is necessary to carry out a detailed assessment of the extent of the disease using PET-CT.

In patients with a single adrenal metastasis, in whom complete excision of the primary lesion is possible, adrenalectomy may be considered, followed by pulmonary resection (in the case of localisation of lung cancer and adrenal metastasis on the left side, simultaneous excision of both lesions from transdiaphragmal approach during thoracotomy could be performed). Treatment of primary chest changes should be carried out according to the previously presented principles [82].

A similar procedure (excision of metastasis with irradiation of the postoperative area and pulmonary resection in the second stage) may be considered in

patients with a single brain metastasis. If CNS metastasis excision or radical treatment of primary tumour in the chest is not feasible, RT of metastasis (if possible stereotactic irradiation) is indicated in the first step, followed by treatment of the primary lesion according to the previously presented principles [82].

The presence of a single cancer lesion in the second lung (so-called synchronous cancer) — depending on the location and other factors — is not a contraindication to radical treatment (primarily resection).

Recommendations

— In patients with disseminated non-small-cell lung cancer, the choice of treatment method depends on clinical and pathomorphological and molecular characteristics (I, A).
— Patients with disseminated non-small-cell lung cancer with EGFR mutations should receive one of the EGFR tyrosine kinase inhibitors as part of the first-line treatment (I, A).
— Patients with non-small-cell lung cancer with ALK gene rearrangement should receive one of the ALK tyrosine kinase inhibitors in the first-line treatment (I, A).
— Patients with disseminated non-small-cell lung cancer with the presence of PD-L1 expression at 50% or more of the percentage of cells should receive pembrolizumab in the first-line treatment (I, A).
— Patients with metastatic non-small-cell lung cancer without *EGFR* mutation and with PD-L1 expression less than 50% should receive chemotherapy in the first line (regimens containing two drugs including cisplatin or — in justified situations — carboplatin, and monotherapy may be considered only in selected clinical situations) (I, A).
— Patients with metastatic non-small-cell lung cancer the use of bevacizumab or cetuximab in combination with chemotherapy is not justified (I, A).
— The second-line treatment of patients with disseminated non-small-cell lung cancer depends on the clinical-pathomorphological characteristics, the effects of earlier systemic therapy and molecular characteristics. In this group the following therapy modalities should be considered: chemotherapy (docetaxel or pemetrexed), docetaxel in combination with nintedanib, first- or second-generation EGFR inhibitors in patients who have not received these drugs in first line, or osimertinib in patients previously treated with the first- or second-generation EGFR inhibitors, ALK inhibitors (crizotinib in case of *ALK* gene rearrangement), immunotherapy (nivolumab or pembrolizumab), palliative radiotherapy, or symptomatic treatment (I, A).
— In selected patients with non-small-cell lung cancer with a single metastasis, treatment with a radical intention may be considered (III, B).
— In the case of progression in a single area with simultaneous response in other tumour lesions during the treatment with EGFR or ALK inhibitors, continuation of current systemic therapy in combination with local management (resection or radiotherapy) should be considered) (III, B).
— In patients with metastatic non-small-cell lung cancer with bone metastases, zoledronic acid is recommended (I, B).
— In patients with disseminated non-small-cell lung cancer and with chest problems or signs and symptoms related to metastases, palliative radiotherapy should always be considered (I, A).
— In patients with non-small-cell lung cancer with recurrent pleural effusion, it is advisable to perform pleurodesis with talc (II, A).

Small cell lung cancer — primary treatment

Chemotherapy

Chemotherapy is the essential method of treatment for patients with SCLC. The regimen of choice is a combination of cisplatin with etoposide (PE scheme) in various modifications (e.g. cisplatin 80 mg/m^2 — day 1 or 30 mg/m^2 — day 1, 2, and 3 and etoposide 100 mg/m^2 — day 1, 2, and 3, every 21 days) [83]. The limitation for the use of the PE regimen is the coexistence of renal dysfunction — then cisplatin can be replaced with carboplatin (in a dose calculated according to Calvert's formula for AUC 6) [83]. The less effective and currently rarely used regimen is a combination of cyclophosphamide, doxorubicin and vincristine or etoposide (CAV or CAE scheme: cyclophosphamide 1000 mg/m^2 — day 1, doxorubicin 45 mg/m^2 — day 1, vincristine 2 mg — day 1) or etoposide 80 mg/m^2 — day 1–3, every 21 days). Anthracyclin-containing chemotherapy is contraindicated in patients with significant cardiovascular disorders and cannot be used simultaneously with chest X-ray [84, 85].

Standard treatment includes 4–6 cycles of CHT. Unjustified dose reduction and prolonged intervals between cycles should be avoided. There is no justification for the alternate use of different CHT regimens, maintenance therapy, and treatment intensification [85].

The phase III IMpower133 trial compared first-line chemotherapy with carboplatin and etoposide with or without atezolizumab in patients with stage IV SCLC — the overall survival time was two months longer (median — 12.3 and 10.3 months) in the case of treatment with a PD-L1 inhibitor [86]. Atezolizumab in combination with CHT in patients with SCLC is not yet reimbursed.

Radiochemotherapy

In patients with a localised SCLC (stages I–III according to TNM classification), determined on the basis of correctly performed initial diagnosis, it is advisable to use simultaneous CHT (the combination of cisplatin and etoposide is a regimen of choice) and chest irradiation. Simultaneous RCHT compared to the sequential use of both methods increases the chance of cure or long-term remission with prolonged survival, but at the expense of severe acute radiation reactions [87]. If CHT and RT cannot be started simultaneously, it should be attempted to start RT no later than simultaneously with the second cycle of CHT [88]. The use of simultaneous RCHT should not reduce the due intensity of CHT [88, 90].

Only patients in good condition and without other factors that increase the risk of serious complications are eligible for RCHT. Chemo-radiotherapy is not used in patients with pulmonary lymphangiosis and/or pleural effusion and in situations when the lesion could not be encompassed by RT because of its significant dimensions.

The irradiated area includes primary lesion and metastatic local lymph nodes as well as the area of adjacent unchanged lymph nodes. Currently, RT conventionally fractionated at a dose of 60–66 Gy — 30–33 fractions or hyperfractionated (45 Gy in two fractions of 1.5 Gy per day for three weeks, minimum interval between fractions — six hours) is recommended. It is also recommended to use modern RT techniques (similar to NSCLC) [87].

The results of the phase III study show that the use of chest irradiation (30 Gy — 10 fractions) after achieving an objective response to CHT in patients with stage IV SCLC increases the time to disease progression and two-year survival rate (13% *vs*. 3%) [89]. Benefits are observed primarily in patients with cancer dissemination limited to the chest organs. These observations justify the consideration of chest irradiation also in patients with stage IV SCLC after achieving a response to CHT.

In patients with localised (stage I–III) and extensive (stage IV) cancer, who have responded to RCHT or CHT, elective cranial irradiation allows a reduction in the risk of brain metastases and extension of the survival time [90, 91].

Surgical treatment

Surgical treatment in SCLC is used very seldom — it can only be considered in patients with T1N0M0 and in some patients with T2N0M0 cancer (less than 5% of all SCLC patients). Surgical treatment is preceded by a full assessment of tumour burden (including mediastinoscopy). If the diagnosis of SCLC is established intraoperatively and there is a possibility of radical excision of the lesion, the lobe is removed and a radical lymphadenectomy is performed (pneumonectomy is not recommended because extensive surgery make subsequent CHT difficult to use). Surgical treatment should always be completed with full CHT (4–6 cycles), and in the presence of metastases in the lymph nodes, additional RT should be considered. In all cases, elective cranial irradiation is used [92].

Surgical treatment (excision of persistent lesions after a partial response following CHT) is also used in selected patients with a mixed form (SCLC and NSCLC) [92].

Small cell lung cancer — treatment at relapse

The treatment of patients with recurrent SCLC after previous CHT or RCHT depends on the effectiveness of the first-line therapy and performance status.

In patients with relapse of SCLC after at least three months after completion of CHT with objective response, an attempt can be made to re-use the original regimen. In patients who did not respond to first-line treatment or in whom remission lasted less than three months, the chance of achieving a response after second-line treatment (e.g. CAE or CAV regimen after prior use of the cisplatin and etoposide regimen) is low. In patients with good performance status, topotecan monotherapy can be used (1.5 mg/m^2 intravenously — day 1–5, every 21 days) [85].

In case of progression limited to the brain, the choice of treatment method (CHT or RT) depends on the patient's condition, previous treatment, and the intensity of neurological symptoms.

The number of second-line CHT cycles depends on the tolerance of the treatment and the objective benefits obtained. In selected cases palliative RT is used.

Recommendations

— In the majority of patients with small-cell lung cancer in stage I–III, concomitant chemoradiation should be used, or, in the case of contraindications, chemotherapy and radiotherapy should be administered consecutively (I, A).
— In patients with small-cell lung cancer, a chemotherapy regimen consisting of cisplatin and etoposide should be used (I, A).
— Surgical treatment of patients with small-cell lung cancer can only be considered in stage T1–2 N0 (III, A).
— In patients with small-cell lung cancer in stage I–III with response to chemoradiotherapy or chemotherapy, elective central nervous system irradiation should be used (at a dose of 25 Gy in 10 factions, treatment should be started within 2–5 weeks after completion of radiochemotherapy or chemotherapy) (I, A).
— In patients with stage IV small-cell lung cancer, chemotherapy should be used, and if response is achieved, elective irradiation of central nervous system (I, A) and — in selected patients — chest irradiation should be considered (I, B).

— Before the irradiation of the central nervous system, magnetic resonance imaging of the brain is advisable (II, B).
— The management of relapsed small-cell lung cancer patients depends on the clinical characteristics and benefits obtained during the initial treatment (options — second-line chemotherapy, palliative radiotherapy, or symptomatic care) (II, A).

Follow-up after treatment

The aim of observation in patients with lung cancer treated with radical intention is early detection of relapse, complications of treatment, and independent primary cancer. The results of a prospective, randomized study showed no differences in terms of overall survival in patients who after pulmonary resection in stages I–III were monitored using CT scans performed at 3-, 6- and 12-month intervals [93]. There is no indication for active search for asymptomatic metastases in other organs (abdominal cavity, brain, bones) [94]. The schedule of control tests in palliative patients should take into account the individual clinical situation. An interesting solution, potentially increasing the effectiveness of control tests compared to their traditional form, is the electronic reporting of symptoms by patients [95].

Recommendations
— In patients with lung cancer treated with radical intention in the first 24 months after radical treatment, it is recommended to perform a chest CT scan every six months and every 12 months for the following three years (I, B).
— In the remaining patients, the control test schedule should be individualised (III, C).

Malignant pleural mesothelioma

Epidemiological and pathomorphological characteristics

Malignant pleural mesothelioma is the most common primary malignancy originating from submesothelial cells that line the pleura and pericardium. Due to significant diagnostic problems, especially in differentiation, until recently it was difficult to determine the actual incidence of this cancer. Currently the progress of pathomorphological diagnostics (especially the introduction of IHC methods) allows us to establish the diagnosis with greater certainty [97]. Diagnosis and treatment of patients with mesothelioma should be carried out in centres with extensive experience in this field. In recent years pleural mesothelioma has been the cause of approximately 250 deaths in Poland per year [1]. The average age of onset is about 60 years.

Since the introduction of more precise diagnostic criteria, there has been an increase in morbidity (previously, a large proportion of pleural mesotheliomas were considered to be pleural metastases of adenocarcinoma with an undetermined primary lesion location). This tendency also results from the actual increase in incidence, caused by the high exposure to asbestos until now (in the past extensively used in the construction, textile, shipbuilding, and car industries). Direct contact with asbestos can be proven in approximately 70–80% of patients with malignant pleural mesothelioma. The greatest risk concerns people employed in asbestos mines and their families living near mineral deposits, as well as people directly exposed to asbestos during many years of work in the shipbuilding industry [97].

In the histological pattern epithelial and sarcoma components are present. The most common type is epithelioid (about 55%), in which the prognosis is slightly better than in the others. The biphasic type is diagnosed less frequently (about 30%), and the least common (about 15%) is the sarcomatoid type, characterised by an especially aggressive course [98].

Diagnostics

Diagnostics include recognition of pleural lesions, confirmation of their malignant character, differentiation with metastases of another cancer, and burden assessment. For this purpose, close co-operation of the pathologist, radiologist, and clinician is necessary. An appropriate volume of material sample should also be obtained for IHC studies (Figure 5). In the majority of patients, mesothelioma is diagnosed at the local and regional stage (metastases in distant organs are relatively rare).

Medical history

Medical history includes an interview for exposure to asbestos and symptoms associated with the localisa-

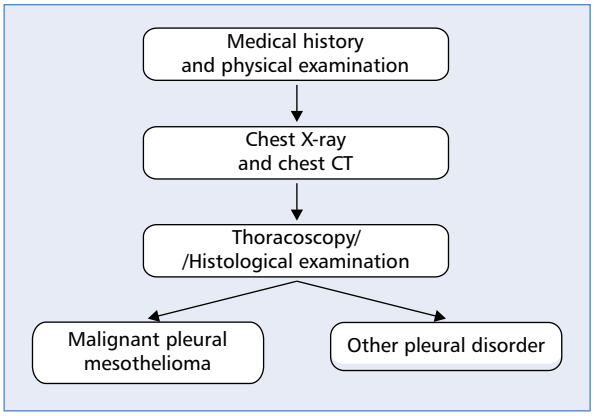


Figure 5. Principles of diagnostic procedures in malignant pleural mesothelioma. CT — computed tomography

tion of primary lesion and local spread along the pleural surface (chest wall pain, dyspnoea, signs of threatening cardiac tamponade).

Physical examination

Physical examination consists in a typical assessment of respiratory system and chest condition.

Imaging examinations

The result of a conventional chest X-ray can only be the basis for mesothelioma suspicion. An absolutely essential method of mesothelioma imaging (especially in the assessment of its extent and degree of chest wall, pericardium, and diaphragm infiltration) is CT scan. In a few patients who potentially qualify for surgery with radical intention, MR may be helpful. The PET-CT examination is not applicable except in situations where treatment with radical intention is considered [98]. Performing earlier pleurodesis significantly hinders the interpretation of the results of the PET-CT examination.

The most common radiographic symptoms include:
— pleural thickening;
— nodular mass on pleural surface;
— pleural effusion;
— infiltration of chest wall;
— pericardium infiltration;
— diaphragm infiltration.

Pathomorphological evaluation

In pathomorphological diagnosis, it is essential to distinguish malignant mesothelioma from benign mesothelial and other malignant tumours, as well as to determine its histological type (epithelioid, biphasic, or sarcomatoid). Diagnosis is based on histological evaluation and IHC assays (assessment of specific protein in mesothelioma cells — calretinin, vimentin, cytokeratin, mesothelin, thrombomodulin, osteopontin), including clinical data [96, 99]. The material for histopathological examination is most often obtained by means of thoracoscopy; during the procedure a lot of excisions from suspicious pleural lesions should be taken. Pleural mesothelioma should not be recognised solely on the basis of cytological examination of pleural effusion or material obtained with fine-needle aspiration [96, 97].

Staging

In the assessment of malignant pleural mesothelioma, the UICC classification from 2017 applies (Table 6, 7) [19].

Treatment

Patients with malignant pleural mesothelioma should be treated only in specialised centres with ex-

Table 6. Staging of malignant pleural mesothelioma (UICC, 2016) [19]

Feature	Characteristics
Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour limited to the ipsilateral parietal pleura with or without mediastinal pleura and with or without diaphragmatic pleural involvement
T2	Tumour involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: — involvement of the diaphragmatic muscle — extension of tumour from the visceral pleura into the underlying pulmonary parenchyma
T3	Locally advanced but potentially resectable tumour; tumour involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: — involvement of the endothoracic fascia — extension into the mediastinal fat — solitary, completely resectable focus of tumour extending into the soft tissue of the chest wall — non-transmural involvement of the pericardium
T4	Locally advanced, technically unresectable tumour; tumour involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: — diffuse extension or multifocal masses of tumour in the chest wall, with or without associated rib destruction — infiltration of the rib — direct diaphragmatic extension of the tumour to the peritoneum — direct extension of the tumour to the contralateral pleura — direct extension of the tumour to a mediastinal organ — direct extension of the tumour into the spine — tumour extending through to the internal surface of the pericardium with infiltration of full thickness of the pericardium, with cancer cells in a pericardial effusion or tumour involving the myocardium — infiltration of brachial plexus
Lymph nodes	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastases
N1	Metastases present in one or more ipsilateral intrapulmonary, hilar, or mediastinal lymph nodes
N2	Metastases in the contralateral lymph nodes, ipsilateral or contralateral supraclavicular, and/or area of oblique muscles lymph nodes
Metastases	
M0	No distant metastasis
M1	Distant metastasis present

Table 7. Stages of malignant pleural mesothelioma (UICC, 2016) [19]

Stage	T	N	M
IA	T1	N0	M0
IB	T2, T3	N0	M0
II	T1, T2	N1	M0
IIIA	T3	N1	M0
IIIB	T1, T2, T3	N2	M0
	T4	Any	M0
IV	Any	Any	M1

tensive experience in this field and the possibility of using all methods of diagnosis and treatment (surgery, RT, and CHT).

Radical surgical treatment is possible only in the epithelioid histological type in stages I, II, and III (without N2 feature), after careful qualification including the assessment of performance status, tumour burden, and the coexistence of other diseases (especially cardiovascular diseases). Before qualification for radical treatment, mediastinoscopy is necessary [100, 101]. Radical resection can be achieved with extrapleural pneumonectomy (excision of the lung and pulmonary and parietal pleura) and removal of half of the diaphragm and pericardium with their reconstruction. An alternative procedure is pleurectomy and decortication (resection with lung sparing — removal of the pleura with or without partial excision of diaphragm and pericardium). In both cases, dissection of mediastinal lymph nodes is most often performed. The choice of surgical treatment method is a subject of controversy - extrapleural pneumonectomy seems more justified in patients with lower risk of relapse and with very good or good performance status and absence of other diseases of clinical significance, but it is much more burdensome [101]. In some patients undergoing radical resection, complementary CHT and RT are used, but the value of these methods has not yet been unequivocally verified.

Palliative treatment methods to prevent the accumulation of neoplastic effusion include pleurectomy or pleurodesis (preferably with talc). The results of randomised study showed better local control of pleural effusion with the use of videothoracoscopic pleurectomy, but this procedure has no effect on overall survival [102].

In some patients (particularly with epithelioid type) who are not eligible for resection, moderate prolongation of survival and periodic symptoms alleviation can be achieved after use of palliative CHT. Only patients in good performance status with feasible objective response assessment are eligible for treatment.

The highest efficacy in mesothelioma is demonstrated by some antimetabolites (pemetrexed, gemcitabine, and raltitrexed) and cisplatin, doxorubicin, and vinorelbine. The most effective one is a regimen composed of cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) — both drugs on the first day of the cycle repeated every three weeks [103]. Assessment of CHT effectiveness requires the use of modified RECIST criteria, which results from the plane character of changes in the mesothelioma and the frequent coexistence of pleural effusion. Selected patients (good performance status, lack of persistent effects of earlier treatment) may have a short-term benefit from the second-line CHT (e.g. vinorelbine, doxorubicin, gemcitabine) [104].

The results of randomised trials indicate that the addition of anti-angiogenic drugs — bevacizumab [105] or nintedanib [106] — increases the effectiveness of CHT with the use of cisplatin and pemetrexed. Neither drug is reimbursed in Poland for the treatment of patients with pleural mesothelioma.

Radiotherapy in mesothelioma is used:
— as post-operative treatment in patients in stages I–III (postoperative RT), but in some patients in combination with CHT;
— as palliative treatment to reduce the symptoms associated with locally advanced tumour.

The development of RT techniques, in particular the introduction of intensity modulated radiation therapy (IMRT), increased the precision and safety of treatment and enabled the use of higher doses. As a result, this led to a reduction in the risk of local tumour recurrence after surgery and a slight improvement in survival rates. The use of modern RT can be considered as part of combined treatment (postoperative RT and CHT) [107].

In patients who are not eligible for CHT, symptomatic management is warranted.

Follow-up after treatment

Depending on treatment assumption, observation of patients includes medical history and physical examination and — due to the risk of local recurrence — chest CT scan.

Recommendations
— Standard imaging study for suspected malignant pleural mesothelioma is chest computed tomography (IV, A).
— The basis for diagnosis of malignant pleural mesothelioma should be the result of histological examination of the material (numerous sections) sampled during thoracoscopy and immunohistochemical assays of markers specific for mesothelioma (IV, A).
— If malignant mesothelioma is diagnosed, it is necessary to determine the histological type (IV, A).
— In patients with malignant pleural mesothelioma in stages I–III, after exclusion of N2 feature, the possibility of complete resection should be considered.

If this is not feasible, the surgical procedure should be aimed to control the accumulation of pleural effusion (pleurodesis or decortication) (II, B).
— In patients with advanced mesothelioma, chemotherapy should be considered (a regimen containing cisplatin and pemetrexed) (I, A).
— In selected patients with advanced mesothelioma, the use of second-line chemotherapy may be considered (II, B).
— In patients with malignant pleural mesothelioma, radiotherapy should be considered as part of combined treatment involving surgery and chemotherapy. Radiotherapy can also be considered in palliative treatment (II, B).

Mediastinal malignant tumours

Epidemiological characteristics

Mediastinal tumours are rare (less than 1.5% of all cancers) [1]. In adults, thymoma and thymic carcinomas are most common, and in children the neoplasms of neural origin. The organ origin of mediastinal tumours determines their location (adults — most often in anterior part; children — in posterior part).

Mediastinal lymphomas are discussed in detail in the part of the diagnostic-therapeutic guidelines dedicated to lymphomas.

Many lesions located in the mediastinum are benign, and among malignant tumours more often are metastases from other locations. It is always necessary to carry out detailed diagnostics (histological evaluation and staging).

Primary thymic tumours

Primary thymic tumours originate from epithelial cells and are characterised by T-lymphocyte proliferation of different intensity. Thymic tumours — in contrast to lymphomas and germ-cell tumours — are usually characterised by relatively slow development. Approximately half of the patients have general symptoms (usually paraneoplastic syndromes) [108]. The most common is myasthenia gravis (about 30% of patients), less frequently aplastic anaemia, neuropathy, and disorders of the immune system. Thymomas with symptoms of myasthaenia are characterised by a better prognosis (probably due to earlier diagnosis) [109, 110].

Thymic tumours show a tendency to infiltrate adjacent structures (lung, pleura), while metastases in distant organs are rare.

Diagnostics

Diagnostic goals include establishing the diagnosis and determining the extent of the disease. The complexity of mediastinal tumours makes it necessary to cooperate with many specialists (specialist in radiodiagnostics, pathomorphologist, pneumonologist, thoracic surgeon, oncologist, and — in the case of myasthenia gravis — a neurologist).

In addition to medical history and physical examination (including assessment for paraneoplastic symptoms), CT scan should be performed (radiographs of anterior mediastinum usually show a circular or oval opacity with clear borders). In addition, serum markers (AFP — alpha-fetoprotein and beta-HCG — the beta subunit of human placental gonadotropin) should be assessed to differentiate from embryonal tumours. Due to the low incidence of metastases in distant organs, PET-CT scan are of limited usefulness [110].

Pathomorphological diagnosis

The need to perform a biopsy depends on the results of imaging tests and clinical status (e.g. characteristic changes in CT scan qualifying for radical excision in patients with myasthaenia do not require a preliminary biopsy; in other cases the material should be sampled) [111].

The current WHO classification includes thymic epithelial cell morphology and the number of T lymphocytes, and distinguishes six types of thymomas with different prognoses [112]:
— A — thymoma with no nuclear atypia, and accompanied by few, if any, non-neoplastic lymphocytes;
— AB —type A thymoma admixed with foci rich in non-neoplastic lymphocytes;
— B1 — thymoma with features of functional thymus with large numbers of cells that have an appearance almost indistinguishable from normal thymic cortex;
— B2 — thymoma with scattered plump cells with vesicular nuclei and distinct nucleoli among a heavy population of non-neoplastic lymphocytes;
— B3 — thymoma predominantly composed of epithelial cells that have a round or polygonal shape and that exhibit no or mild atypia;
— C — thymic carcinoma.

The prognosis for patients with type A, AB, and B1 thymomas is significantly better compared to the other types, with radical excision being the decisive factor in all types.

Staging

The most frequently used classification of thymic cancer includes the degree of infiltration and the presence of metastases (Table 8–10) [112].

Treatment

Treatment of patients with thymic tumours should be carried out in specialized centres with documented experience and all therapeutic options available. The primary method of treatment in stages I and II is

a complete resection, which in selected patients can be supplemented with RT and/or CHT [113]. In patients with myasthenia before surgery, the neurological status should be assessed (the risk of myasthenic crisis).

Surgical treatment consists of complete macroscopic and microscopic excision of the thymus and adipose tissue of the anterior mediastinum via sternotomy approach and cervical incision (less invasive methods — e.g. videothoracoscopy — are less effective). Patients after complete resection of the thymomas in stage I do not require additional RT or CHT. Postoperative RT should be considered in thymomas in stage IIB and histological type B2 or B3 (other patients in II stage do not require RT). Post-operative RT is routine management in thymomas in advanced stage III and IVA and in the case of non-radical resection. The total dose of RT is 45–50 Gy after complete excision and 50–54 Gy after incomplete excision, with dose escalation (boost) up to 60–66 Gy in the area with probable presence of persistent cancer. The irradiated area should include a thymic lodge with an appropriate margin. In thymic carcinoma complementary RT (50–54 Gy with boost up to 60–66 Gy in the area at risk of recurrence) is used in stages II–IVA [113, 114]. It is recommended that modern RT techniques be used — similar to those in lung cancer.

At the locally advanced stage (stages III and IVA) combined treatment is recommended, including initial CHT, resection (then possible in 50–70% of patients), and post-operative RT [113, 115]. In patients who do not qualify for a complete resection, RCHT is used [115].

Table 8. The Masaoka-Koga Stage Classification for Thymic Malignancies [112]

Stage	Characteristics
I	No capsular invasion
IIA	Microscopic capsular and fatty tissue invasion
IIB	Macroscopic capsular invasion
III	Macroscopic invasion of neighbouring organs
IVA	Pleural or pericardial dissemination
IVB	Distant metastases outside chest

Table 10. Stages of thymic tumours (UICC, 2016) [19]

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IVA	Any	N1	M0
	Any	N0, N1	M1a
IVB	Any	N2	M0, M1a
	Any	Any	M1b

Table 9. TNM classification of thymic tumours (UICC, 2016) [18]

Feature	Characteristics
Primary tumour	
T1	Encapsulated tumour or extending into the anterior mediastinal fat; possible infiltration of mediastinal pleura
T1a	Tumour with no infiltration of mediastinal pleura
T1b	Tumour with infiltration of mediastinal pleura
T2	Invasion to the pericardium (both parietal and full pericardial thickness)
T3	Tumour infiltrating at least one of the following structures: lung, brachiocephalic vein, superior vena cava, diaphragmatic nerve, chest wall, extrapericardial pulmonary veins, or pulmonary artery
T4	A tumour infiltrating at least one of the following structures: aorta, aortic arch vessels, intrapericardial pulmonary veins, or pulmonary artery
Lymph nodes	
NX	Metastases in lymph nodes cannot be assessed
N0	No metastases in lymph nodes
N1	Metastases in anterior (perithymic) lymph nodes
N2	Metastases in deep intrathoracic or cervical lymph nodes
Metastases	
M0	No distant, pleural, or pericardial metastases
M1	Distant or pleural or pericardial metastases
M1a	Pleural or pericardial metastases
M1b	Distant metastases (including lungs)

Thymomas show relatively high chemosensitivity (70–100% of objective responses) — CHT is used in combination with local treatment or alone [116]. The following regimens are most often used:

— CAP — cisplatin 50 mg/m^2 IV — day 1
doxorubicin 50 mg/m^2 IV — day 1
cyclophosphamide 500 mg/m^2 IV — day 1
cycles every 21 days
— ADOC — cisplatin 50 mg/m^2 IV — day 1
doxorubicin 40 mg/m^2 IV — day 1
vincristine 0.6 mg/m^2 IV — day 3
cyclophosphamide 700 mg/m^2 IV — day 4
cycles every 21 days
— PE — cisplatin 60 mg/m^2 IV — day 1
etoposide 120 mg/m^2 per day IV — day 1, 2, and 3
cycles every 21 days

Follow-up after treatment

In patients undergoing radical treatment (resection with or without adjuvant therapy) for stage I or II thymic tumour, the first CT scan should be performed after three months, followed by every 12 months for the first five years and then every two years. For patients treated for stage III or IVA thymomas and for thymic cancer, CT scans should be repeated every six months for two years and then every 12 months. Observation is recommended for at least 10 years [113].

Other mediastinal tumours

Germinal neoplasms of the mediastinum in 90% concern men, and they are divided into seminomas and non-seminomas (in women germinomatous and non-germinomatous germ-cell tumours, respectively). Most often they are located in anterior mediastinum (this is the most common — apart from the gonads — localisation of germ-cell tumours). Symptoms of germinal tumours of the mediastinum occur earlier than in thymomas. Prognosis of patients with germ-cell mediastinal tumours is worse than in the same tumours located in the gonads. The treatment of choice is CHT (regimens with cisplatin) and resection of persistent lesions; in some patients diagnosed with seminoma RT is also used [118, 119].

Neoplasms of nervous system origin occur primarily in the posterior mediastinum and most often come from peripheral nerves and ganglia of the vegetative system (malignant nature in 20–30% of cases). Management is based on surgical treatment (RT and CHT are of limited use).

The primary treatment method of mediastinal mesenchymal tumours is also surgical resection [119].

Recommendations

— The standard imaging test for suspected mediastinal neoplasm is chest CT scan (IV, A).
— The basis for diagnosis in mediastinal tumours is a histological examination of material taken through core needle biopsy supplemented with immunohistochemical tests (IV, A).
— The management of thymic tumours depends on the possibility of complete resection (IV, A).
— The indication for postoperative radiotherapy in thymic tumours is clinical stage IIB and histopathological type B2 and B3, as well as stage III and IVA and non-radical resection (IV, A).
— The indication for postoperative radiotherapy in thymic cancer is stage II or higher (IV, A).
— In locally advanced thymic tumours, pre-operative chemotherapy or chemotherapy in combination with radiotherapy should be considered (IV, A).
— Chemotherapy is used for generalised thymic tumours and mediastinal germ-cell tumours (IV, A).
— The management of mediastinal germ-cell tumours consists of the use of chemotherapy and resection of persistent lesions (radiotherapy in some cases should also be considered) (IV, A).

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