Thoracic neoplasms

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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 the 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 the case of doubt, the current possibilities for reimbursement of individual procedures should be determined.

1. *The quality of scientific evidence*
   I — Scientific evidence obtained from well-designed and properly conducted randomised clinical trials or meta-analyses of randomised clinical trials
   II — Scientific evidence obtained from well-designed and properly conducted prospective observational studies (non-randomised 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 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]. In 2018, it accounted for 16.1% — both in men and women — of all cancer cases (respectively — 13 425 and 7 801 cases annually) and was the cause of 28.2% and 17.6% of all cancer deaths, respectively (15 619 and 8 076). A higher number of deaths in relation to the number of cases indicates shortcomings in the registration of lung cancer cases. The incidence and mortality rates of lung cancer have been decreasing in recent years in men and increasing in women at the same time. Approximately 14.5% of patients with lung cancer in Poland survive 5 or more years after diagnosis. The 5-year and 10-year prevalences in Poland are 49 662 and 61 267 (30 449 and 19 213 as well as 37 274 and 23 993 in men and women).

The most common cause of lung cancer (about 85–90% of cases) is active or second-hand smoking. Reducing exposure to tobacco smoke is the only way to significantly reduce morbidity and mortality. European Commission recommendations indicate that reducing the risks of lung cancer can be achieved through the following:

— legislative action on tobacco products (e.g. packaging, labelling, and ingredients);
— cessation of tobacco product advertising;
— creating smoke-free spaces;
— appropriate tax policy and prevention of illegal trade.

It is also vital to help smokers overcome smoking habits and to take anti-tobacco measures aimed at young people, because over 90% of smokers enter addiction before the age of 26 [2].

The other causes of lung cancer include physical and chemical environmental and occupational factors (e.g. radon, nickel, chromium, arsenic, asbestos, hydrocarbon compounds), as well as inherited genetic factors (most of all polymorphisms of genes involved in the inactivation of harmful components of tobacco smoke and gene disorders responsible for the repair of DNA damage).

Pharmacological prophylaxis of lung cancer and screening with conventional chest X-ray examinations and sputum cytology do not reduce mortality. Low-dose chest computed tomography (CT) is of higher value as a screening test. 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) [3]. The results of the NLST study became the basis for the development of early-detection programmes for lung cancer in the groups at highest risk in some countries. In 2017 and 2018, European [4, 5] and Polish [6] recommendations on screening were published, although these recommendations have not been introduced in the majority of European countries so far (mainly due to difficulties in proving their effectiveness and low specificity, resulting in the need to perform invasive diagnostics, but also for other reasons) [7]. Screening of people from the highest risk group has been financed since 2016 in the United States. Recently, the results of the phase III NELSON study were presented a reduction in mortality from lung cancer (women — 39%, men — 26%) was shown after 10 years of observation when low-dose CT was performed in a risk group (eligibility criteria similar to NLST) [8]. Croatia has introduced a population-based, fully reimbursed screening test, and in Poland, the UK and Hungary, early-detection programme studies started in 2020.

Screening examinations must be associated with — being of the highest importance — primary prevention (total elimination of exposure to tobacco smoke). They should also include an assessment of the occurrence of emphysema and cardiovascular risk by determining calcification in coronary vessels [4–6]. It is reasonable to carry out early-detection programmes to increase the possibility of radical treatment use (especially in regions with low detection of early-stage lung cancer). Early lung cancer detection programmes should be carried out by highly specialised centres that have all diagnostic and therapeutic possibilities in patients with lung cancer and relevant experience (the above-mentioned conditions are adopted in Poland).

Recommendations

— Multidirectional measures should be taken to reduce exposure to tobacco smoke components (active and passive smoking) (I, A).
— It is warranted to continue early-detection programmes using low-dose CT to increase the possibility of radical treatment (I, A).

Pathology and molecular biology

Primary lung cancer originates from epithelial cells. The most common (approximately 85% of all cases) are non-small-cell lung cancers (NSCLC). The majority of NSCLC are adenocarcinomas-and squamous-cell carcinomas (the incidence of adenocarcinoma has increased recently). The incidence of large-cell lung cancer has decreased to about 2% since the introduction of immunohistochemistry (IHC). Small-cell lung cancer (SCLC) currently accounts for approximately 13% of all primary lung tumours and differs from other histological types in many biological and clinical features (rapid proliferation rate, short tumour doubling time, outstanding early metastasis tendency, chemosensitivity, and relative radiosensitivity) [9]. 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 the liver, brain, second lung, bones, adrenal glands, subcutaneous tissue, and bone marrow). Metastases can also arise in distant organs without the involvement of regional lymph nodes. Lung cancer can also spread locally by infiltrating the structures of the mediastinum and the diaphragm, pleura, and chest wall and filling the surrounding air spaces.

The 2015 World Health Organization (WHO) classification of epithelial pulmonary carcinomas [10] (Tab. 1) introduced some changes in comparison with the previous version from 2011, of which the most important is the introduction of the following:

— rules of handling small samples and cytological material (especially — in advanced forms of NSCLC);
— new classification of adenocarcinomas-and squamous-cell carcinomas;
— the need to use immunohistochemistry (IHC) and genetic tests in pathological diagnostics to treat individualisation;
— diagnosis of large-cell carcinoma and other rarely found NSCLC types only in postoperative material;
— classification into one group of cancers with features of neuroendocrine activity. The classification published this year [10] additionally presents new principles for determining the degree of differentia-

Table 1. 2015 World Health Organisation (WHO) pathological classification of lung cancer [10]

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 Fetal 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	Keratinising squamous-cell carcinoma Non-keratinising 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	

tion of lung adenocarcinomas (Grading), and in the group of neuroendocrine tumors, carcinoids were classified as neuroendocrine tumors, while small cell and large cell neuroendocrine carcinomas were classified as neuroendocrine carcinomas.

The scope of the procedures used in pathological diagnosis depends on the histological type of the cancer and the disease stage.

The handling of the preoperative specimen, as well as small and cytological specimens (cytoblocks), in patients with inoperable NSCLC requires the determination of cancer type and, in certain cases, the assessment of the predictive factors that enable making an appropriate therapeutic decision. The close cooperation between pathologists and clinicians who order the examination and plan treatment is crucial, as well as the rational use of the material sampled for pathological examination. Determination of NSCLC type is based on morphological criteria found in standard hematoxylin and eosin staining, additional histochemical tests for the presence of mucus in cancer cells and IHC, using a panel typical for the differentiation of adenocarcinoma (TTF1, thyroid transcription factor) and squamous-cell carcinoma (p40). In the case of an ambiguous histological picture and the impossibility of determining the NSCLC type based on tumour morphology, IHC, and neuroendocrine markers, it is possible to diagnose not otherwise specified (NOS) cancer. However, the proportion of such diagnoses should not exceed 10% of all NSCLC diagnoses. The percentage of NOS diagnoses can be reduced due to the greater availability of tissue material, which allows the establishment of a complete histological diagnosis [10].

The equivocal 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) [10].

Determination of neuroendocrine markers (NEMs) is indicated only in the case of morphological features suggesting neuroendocrine differentiation (routine use is not recommended because 10–20% of all NSCLCs express one of the NEMs with no impact on management) [10].

Pathological diagnosis of postoperative material requires the determination of cancer type, subtype and grade, presence of prognostic factors (e.g. blood or lymph vessels tumour emboli, nerve fibres, pleural and surrounding air spaces infiltration, the extent of necrosis), resection completeness and pathological disease stage (pTNM). For adenocarcinomas it is necessary to determine each type of morphological change found in the tumour [11].

Histological classification of NSCLC is supplemented by division according to differentiation (histological malignancy), which distinguishes 4 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 [10].

In patients with advanced NSCLC, it is necessary to evaluate *EGFR, ALK,* and *ROS1* gene status to detect their disorders [12–14]. The presence of mutations in the *EGFR* gene and translocations in the *ALK* and *ROS1* genes is a predictor of benefit from targeted therapy with epidermal growth factor receptor (EGFR) and ALK or ROS1 tyrosine kinase inhibitors (TKIs). Mutations within the *EGFR*/*KRAS* genes and *ALK*/*ROS1* translocations almost always exclude each other [12]. The extension of predictive marker panels to include *BRAF, MET, RET, NTRK, HER2,* and *KRAS* gene disorders will be associated with the introduction of new drugs targeting the above-mentioned molecular targets. The assessment of predictive biomarkers is currently also recommended in patients with squamous-cell carcinoma, which especially applies to young non-smokers, patients with diagnosis established based on scanty biopsy specimens, and patients with mixed NSCLC [13, 14].

Genes can be evaluated using tissue material or — in the case of a confirmed sufficient number of cells in the sample — cytological examination (the preferred material 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 (cytoblock) [10, 12].

'Liquid' biopsy (most often testing of blood plasma) is a reliable source of tumour circulating free DNA (cfDNA) and, more specifically, the fractions of circulating tumour DNA (ctDNA). Free DNA testing is a recommended alternative to examination of cellular or tissue samples in detecting resistance to first-or second-generation EGFR TKIs (presence of Thr790Met variant in *EGFR* gene, commonly referred to as T790M mutation) prior to the second-line targeted therapy. The assessment of predictive biomarkers based on circulating DNA analysis before first-line treatment is allowed only in the absence or limited availability of tissue or cellular material [13].

Prognosis in lung cancer patients depends primarily on the mainly stage, while the age and gender of the patients are of lesser importance. The new pathological 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 do not affect the choice of treatment method. In patients with advanced cancer stages, the 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 aberrations 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 addition to the tumour stage in SCLC, 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 pathological diagnosis of lung cancer based on the examination of tissue or cellular material (IV, A).
- Pathological diagnosis of lung cancer should take into account the principles and criteria of the current WHO classification (III, A).
- Pathological diagnosis should be supplemented by immunohistochemistry and — according to indications — genetic tests (I, A).
- The genetic and 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).
- Circulating DNA plasma testing can be performed to detect mutations driving resistance to anti-EGFR treatment and in the case of unavailability of tissue or tissue material (II, B).
- The diagnosis of not otherwise specified in non-small-cell lung cancer patients can only be made if it is not possible to obtain the appropriate material for testing (IV, A).
- The result of the pathological 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 pathological classification (IV, A).

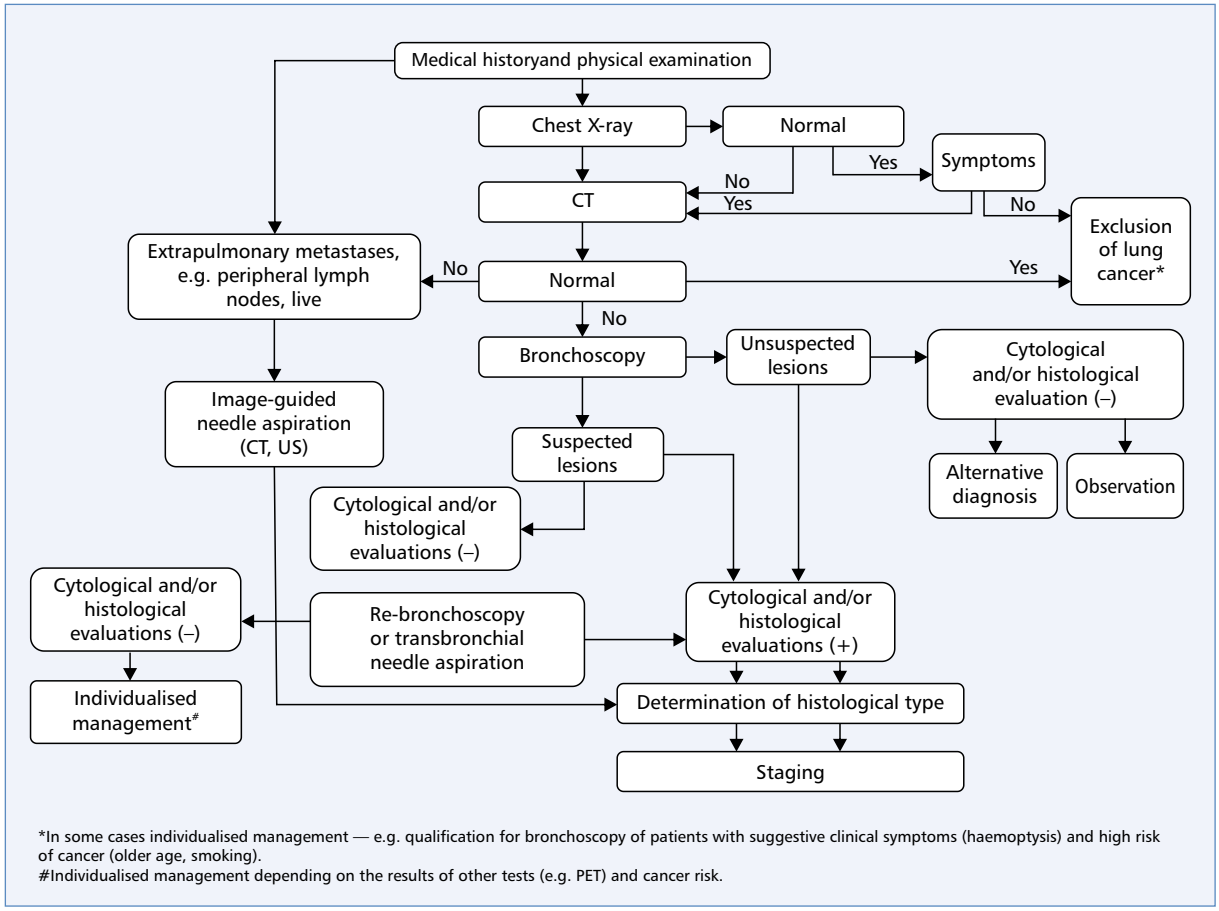


Figure 1. Diagnostic algorithm in lung cancer; CT — computed tomography; PET — positron emission tomography; US — ultrasonography

Diagnostics

The diagnostic procedure included determination of the diagnosis and stage of lung cancer (Fig. 1).

Medical history

Lung cancer is one of the malignancies in which the symptoms occur usually late. The vigilance of primary healthcare physicians and specialists is vital, expressed primarily by directing special attention to symptoms that may be underestimated by patients. These symptoms include, in particular, chronic cough (especially in people with long-term exposure to tobacco smoke or other carcinogens) and recurrent respiratory tract inflammation. In the case of suspected lung cancer, medical history consists of an interview for symptoms (Tab. 2) and a careful assessment of active and passive exposure to tobacco smoke, familial occurrence of neoplasms, and exposure to harmful environmental factors.

Physical examination

The presence 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 the following:

— 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 outline, weakening of heart tones, jugular venous distension, liver enlargement, hepatojugular reflux, low blood pressure amplitude, arrhythmia);
— symptoms of superior vena cava syndrome (swelling of the face, increased dyspnoea, enlarged neck circumference, swelling of the upper limbs, widening

Table 2. Lung cancer symptoms

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

of the jugular veins and on the chest wall, bruising of the face and mucous membranes);
— hepatomegaly;
— pain on the 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 (PS) assessment

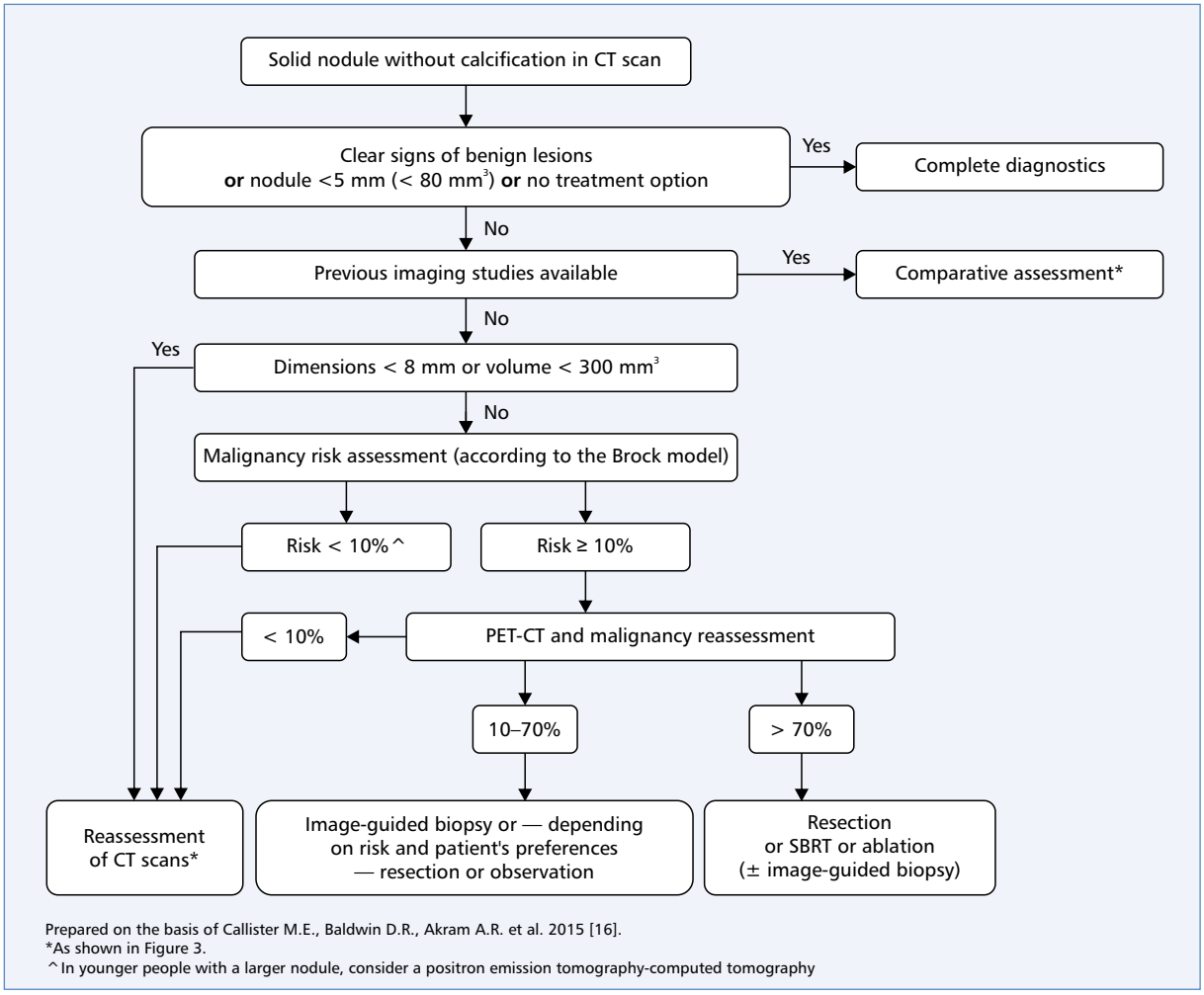
An essential element in lung cancer diagnosis is the assessment of PS, which should be carried out with the use of the WHO or Eastern Cooperative Oncology Group scale.

Imaging examinations

X-ray images of lung cancer can be very diverse. Suspicion of lung cancer should be made, particularly by the findings in a conventional chest X-ray in posterior-anterior and lateral projections:
— well-rounded shadow [completely solid or partially solid lesion or the image of so-called ground glass opacities (GGO)];
— changes in hilar outline;
— air flow disturbances (asymmetry, atelectasis);
— infiltrating lesion;
— pleural effusion.

Normal results of conventional chest X-rays do 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 chest CT scans with intravenously administered contrast agents (the test should also 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).

An important diagnostic problem is the management of patients with a single nodule in the lung parenchyma of an unspecified character and a diameter of up to 3 cm. These changes are often found on chest CT performed as part of screening tests or for other indications. In recent years, the recommendations of various scientific societies have been published that describe in detail the principles of diagnosing a single nodule in the lung, including the American College of Chest Physicians (ACCP) [15], the British Thoracic Society (BTS) [16], and the Fleischner Society recommendations [17]. The main goal of the recommendations is to assess the likelihood of the malignant character of the lesion, which determines further management. For the purposes of this study, the guidelines developed by the BTS [16] (Fig. 2–4) were used. Clinical data (e.g. age and tobacco smoke exposure) and features of the nodule in CT scan (size, radiological structure, and margins characteristics) play a key role in assessing the likelihood of a nodule malignant character. CT examination allows for the identification of solid and non-solid nodules (GGO with or without a solid component) and the assessment of the presence and characteristics of elements that may be helpful in assessing the likelihood of malignancy. The malignant features may be suggested by, for example, the presence of GGO (especially with a visible solid part), the presence of diffuse microcalcifications, and irregular outlines of the nodule margins (the so-called corona radiata). Contrary to this, total — or central — calcification and 'popcorn-like' calcifications are rather typical for benign nodules. In some cases, it is also advisable to perform positron emission tomography (PET) in combination with CT (PET-CT), which plays an important role in the differentiation of benign and malignant lesions and in determining indications for other tests or further observation. Malignancy risk calculators (models) are an important method for the diagnosis of a single lung nodule. Several such models have been developed that use different clinical and radiological data. The best known are the Mayo Clinic [18, 19] and Brock University models [20]. The latter was used to assess the risk of the malignant nature of pulmonary lesions in the BTS recommendations. In



Prepared on the basis of Callister M.E., Baldwin D.R., Akram A.R. et al. 2015 [16].
*As shown in Figure 3.
^ In younger people with a larger nodule, consider a positron emission tomography-computed tomography

Figure 2. Initial diagnostic procedures in patients with a single solid pulmonary nodule according to [16]; CT — computed tomography; PET — positron emission tomography; SBRT — stereotactic body radiation therapy

patients with additional PET-CT, a calculator that takes into account its results is used [21].

PET-CT is helpful in assessing the tumour burden before planned surgical treatment and radical irradiation (the highest diagnostic accuracy in assessing the state of the mediastinal lymphatic system and detecting distant metastases) [22, 23] and should be performed in all patients qualified for surgical and radical radiotherapy (RT) or chemoradiotherapy (RCHT). The factor differentiating the 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 perform analyses of the compliance of PET-CT results and pathomorphological postoperative 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.

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 the PET-CT result is positive or borderline, microscopic verification of possible neoplastic involvement of the lymph nodes using endobronchial ultrasonography (EBUS), oesophageal ultrasonography (EUS), or mediastinoscopy is necessary [22].

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 [23].

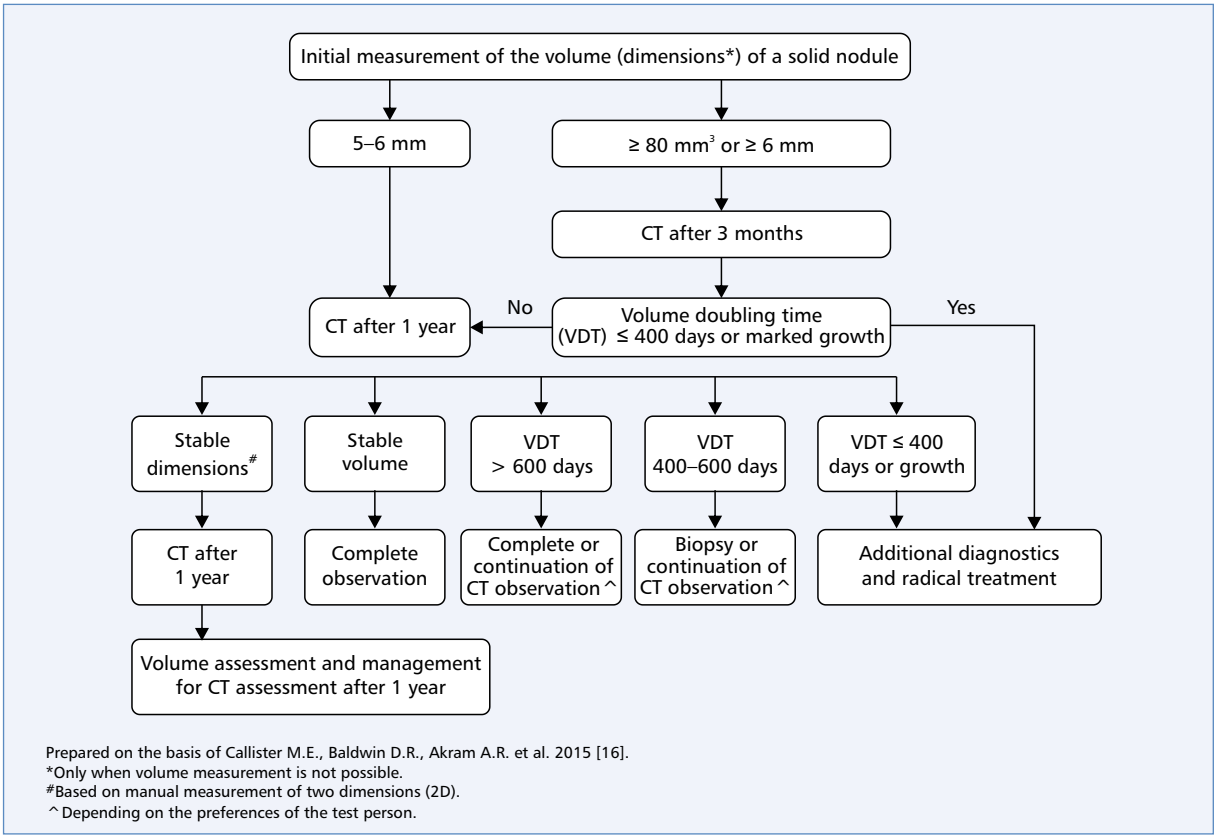


Figure 3. Recommendations for the assessment of changes in nodule size and choice of further treatment according to [16]; CT — computed tomography; VDT — volume doubling time

Endoscopic examinations

Bronchofiberoscopy is indicated in patients with suspected lung cancer because:

— is necessary when qualifying for surgical treatment;
— gives an opportunity to obtain cytological or histological sample;
— is helpful in cancer staging.

In patients with lesions visible in the bronchial lumen, at least 5 samples should be taken. The use of a brush biopsy and the collection of bronchoalveolar lavage fluid specimens can increase the diagnostic value of a forceps biopsy, which is a standard procedure in bronchoscopic tissue sampling. A very important aspect of endoscopic examinations is the adequacy of pulmonary lesion assessment and biopsy effectiveness. In the case of endobronchial lesions, the sensitivity of cancer diagnosis based on the collected biopsies should be at least 80–85% [24]. The use of EBUS enables an effective and safe needle biopsy of various stations of the mediastinal lymph nodes and central extrabronchial tumours. Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) is performed using cytological needles (usually 20–22 G) or — less often histological needles (e.g. 19 G). It is recommended to take at least 2 samples from each location [24, 25]. The sensitivity of EBUS-TBNA in detecting cancer infiltration of mediastinal lymph nodes is approximately 80–85%. Oesophageal ultrasound guided fine-needle aspiration (EUS-FNA) shows a slightly lower sensitivity, but the combination of EBUS-TBNA and EUS-FNA allows for a diagnostic sensitivity of 86–95% [25–27].

The diagnostic value of bronchofiberoscopy is significantly lower in peripheral lesions. However, the use of modern navigation techniques — e.g. electromagnetic navigation bronchoscopy and endobronchosonography with radial mini-probe — allows us to obtain a diagnostic sensitivity of 70% [28]. Transthoracic needle aspiration (TTNA) is slightly more sensitive (65–90%), but this technique is associated with a significantly higher risk of complications in the form of pneumothorax [28, 29].

Laboratory tests

As part of the initial diagnosis, it is necessary to perform a complete blood count with smear and coagulation system parameters, biochemical tests (serum levels of glucose, creatinine, urea, sodium, potassium, calcium, bilirubin and transaminase, alkaline phosphatase, and

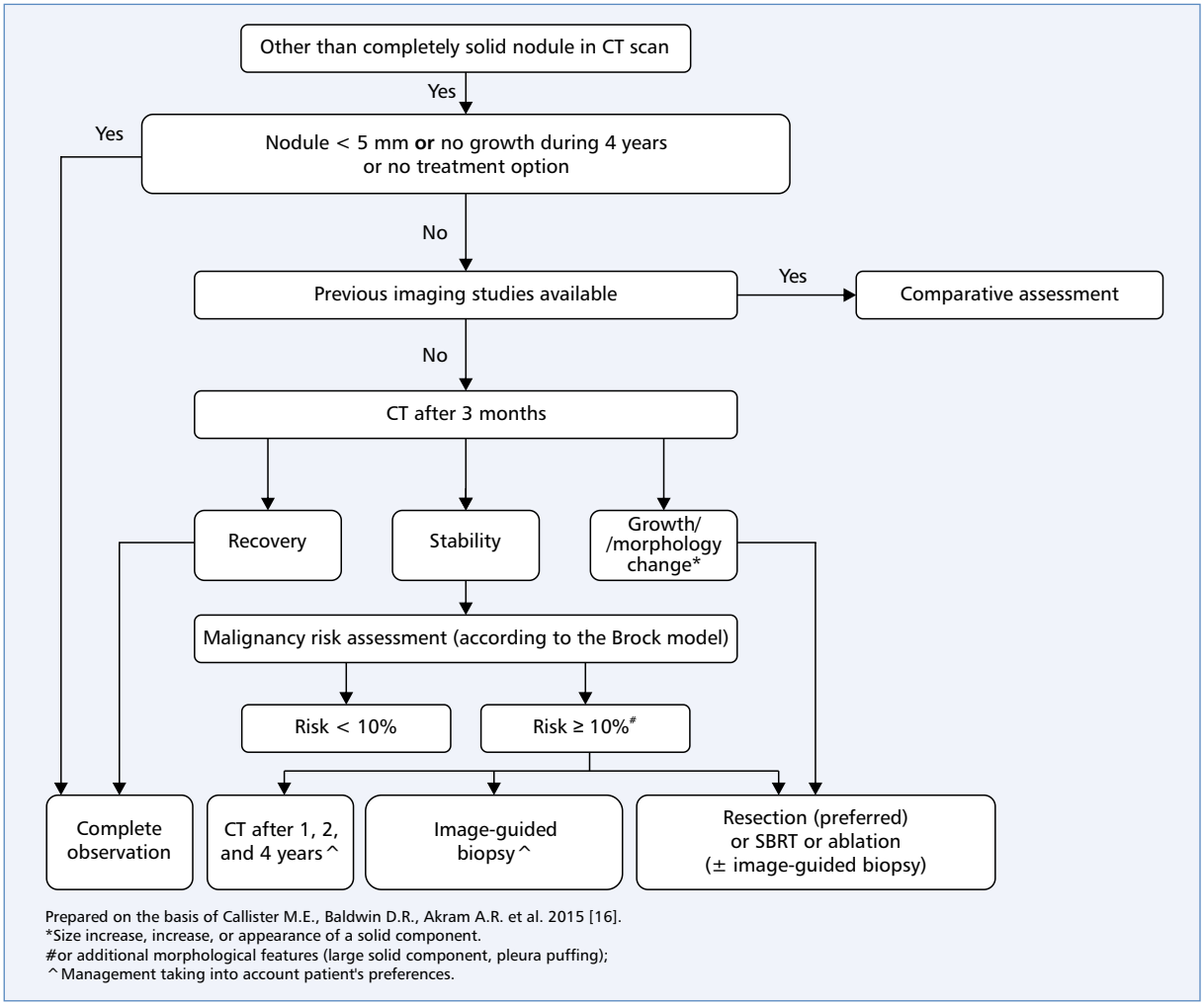


Figure 4. Management algorithm for non-solid nodules according to [16]; CT — computed tomography; SBRT — stereotactic body radiation therapy

LDH), and urinalysis. Other tests were 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 or fragments of cytokeratin 19 [14, 23].

Pathological and molecular evaluation

The goals of pathological evaluation in the diagnosis of lung cancer include determination of histologic 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 [10].

Primary examinations in pathological diagnostics of lung cancer include the following:

— histological evaluation of tissue samples taken during bronchofiberoscopy;
— cytological evaluation of bronchial brushing or bronchoalveolar lavage (BAL);
— histological or cytological evaluation of the material obtained with a biopsy through the chest wall, bronchus, or oesophagus.

Pathological evaluation should include IHC tests to determine the type and histological subtype of lung cancer and to differentiate the primary lung cancers and metastases in different localisations (in practice mainly adenocarcinomas). NEM determination is indicated only when morphological features of neuroendocrine differentiation are detected [10].

A histological examination of the tissue samples is desirable because it allows for the accurate determination of cancer type and subtype and facilitates the extension of the scope of molecular tests (particularly important in the case of choosing systemic treatment prior to local treatment and in patients not qualified for pulmonary parenchyma resection). Material of appropriate

quality for histological examination includes bronchial specimens (collected with forceps or cryoprobes), samples obtained through percutaneous transthoracic core needle biopsy, and, in the case of using thicker needles, samples collected by EBUS-TBNA. Adequate amounts of good-quality and properly protected cytological material also allow reliable determination of tumour type and subtype, as well as performing molecular tests [10, 12].

Depending on the clinical situation and the location of cancer lesions, other methods of obtaining materials for histological and cytological examinations are also used, such as the following:

— cytological evaluation of pleural effusion and/or pleural needle biopsy;
— needle or surgical biopsy of peripheral lymph nodes;
— needle biopsy of metastatic lesions;
— mediastinoscopy;
— mediastinotomy;
— thoracoscopy;
— thoracotomy (after all other options have been exhausted)
— cytological sputum examination (low-sensitivity test, used only when the material for microscopic examination cannot be obtained by another method) [14, 23].

Before starting treatment, it is necessary to establish a pathological diagnosis. If there are reasonable 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 a 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 with a fine-needle biopsy through the chest wall or bronchi). It is necessary to confirm a sufficient number of cells in preparation (neoplastic tissue should account for at least 20%), and in the case of cytological material, it is advisable to use methods of 'embedding' cytological material in a paraffin block [10, 12, 13]. An alternative to molecular testing using tissue or cytological material is the use for the assessment of somatic mutations' plasma cfDNA from dead cancer cells (so-called liquid biopsy). A negative result of cfDNA analysis is not conclusive, and re-biopsy is recommended [12, 13].

When qualifying for treatment with EGFR TKIs in patients with adenocarcinoma and NOS NSCLC, the presence of clinically relevant primary *EGFR* gene mutations (activating and responsible for resistance) should be evaluated, with *de novo* occurring in 10–15% and 1% of patients. Assessment 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). The test must detect *EGFR* gene mutations that occur with a frequency of at least 1% among known *EGFR* disorders. It is advisable that laboratories performing genetic testing for lung cancer patients have 2 alternative methods of identifying genetic disorders. In the case of treatment failure with EGFR inhibitor generations I or II, re-biopsy is recommended to evaluate the presence of a secondary T790M mutation in the *EGFR* gene (mutation associated with resistance to EGFR TKIs) [12, 13].

In patients diagnosed with adenocarcinoma or unspecified NSCLC without activating mutations in the *EGFR* gene, *ALK,* and *ROS1* genes should be assessed to detect rearrangements that occur in 3–5% and 1% of patients, respectively. The presence of *ALK* gene rearrangements can be found directly by fluorescence *in situ* hybridisation (FISH) and new generation sequencing (NGS) or indirectly by assessing membrane expression of ALK fusion protein with the use of IHC. In the assessment of *ROS1* gene rearrangement, the FISH or NGS method is recommended with the possibility of preselection based on ROS1 fusion protein expression by IHC. The presence of rearrangement of both genes or the presence of respective fusion proteins is an indication of the use of ALK/ROS1 TKIs. NGS method enables simultaneous assessment of the condition of many genes, shortens the time needed to perform the full range of molecular tests, and significantly reduces the consumption of tissue material. Complexity and interpretation difficulties mean that the NGS test should be performed only in laboratories with proven experience in this area [13].

Simultaneous evaluation of clinically relevant biomarkers based on one referral is recommended [14].

In the case of the development of other molecular-targeted drugs and their reimbursement, the scope of tests should be extended (e.g. mutations in *BRAF* and *HER2* genes and rearrangements in *MET, RET,* and *NTRK* genes) [14]. 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 a valid certificate of European quality control programme for all tests, regularly subjected to periodic external quality control, and ensuring comprehensive and simultaneous execution of analytical procedures.

Recommendations

— The diagnosis of lung cancer in Poland takes far too long. The condition for the improvement of the situation is the creation of specialised centres for comprehensive diagnostics and treatment.
— In each patient with suspected lung cancer, a medical history and physical examination, chest imaging (conventional radiography and CT, in justified situations — MR imaging), and bronchofiberoscopy should be performed (IV, A).

— Every patient qualified for resection of pulmonary parenchyma or radio(chemo)therapy with radical intention should be examined with the use of PET (II, A).
— Brain imaging should be performed in patients with stages II and III before planned pulmonary parenchyma resection and with stage III before radical radio(chemo)therapy (II, B).
— Performing other tests (including PET) 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 an undefined nature and a diameter of up to 3 cm, the probability of malignancy and resection using PET should be determined. Further invasive diagnostics should be based on malignancy risk, individual circumstances and treatment plan (IV, A).
— The basic tests performed to obtain the material to determine the pathomorphological diagnosis and molecular characteristics of lung cancer are bronchoscopy and biopsy through the chest wall, bronchus, or oesophagus (IV, A).
— The results of pathological 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 pathological classification (IV, A).
— Pathological 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, ALK, and ROS1 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 immunotherap`y with immune checkpoint inhibitors, the expression of the PD-L1 protein should be determined (II, B).
— Diagnosis of not otherwise specufied non-small-cell lung cancer can be made only if it is not possible to obtain the appropriate material for evaluation (IV, A).

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 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 applied in the staging assessment is presented in Table 3. On the basis of the combined assessment of T, N, and M features (Tab. 4), the clinical stage of NSCLC is determined (Tab. 5). At the diagnosis of NSCLC, the proportion of patients in stages I–II, III, and IV was approximately 25%, 35%, and 40%.

In the assessment of the SCLC stage, a simplified classification has been applied so far, which distinguishes the stage of limited disease (LD) or extensive disease (ED). The term of a LD was defined as a tumour that did not exceed one-half of the chest, regardless of metastatic involvement of the 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 ED. Currently, in SCLC — as in NSCLC — the TNM classification is recommended [14].

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

In patients with lung cancer subjected to excision of the pulmonary parenchyma and lymph nodes, the final stage is determined on the basis of a pathological examination of the surgical material. The 'pathological' stage (pTNM) determined in this way is more accurate and reflects the prognosis of patients better than the clinically defined stage (cTNM) [30, 31].

Recommendations

— Non-small-cell lung cancer staging should be performed using the principles and criteria for the TNM classification (IV, A).
— If two lesions are suspected to be primary cancers, they should be classified separately (III, A).
— In lung cancer patients with mediastinal lymph node involvement found on imaging examinations, while qualifying for possible resection of pulmonary parenchyma, pathological 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 pathological 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 the pulmonary parenchyma and lymph nodes, the final stage is determined on the basis of pathological examination of the postoperative material (IV, A).

Table 3. Examinations used for lung cancer staging

Primary tumour assessment	Lymph node assessment	Distant metastasis assessment
— X-ray	— CT (less frequent MR)	— US or CT of the abdomen
— CT (less frequent 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	
	— 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 for a 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 the 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 the SCLC stage before planned treatment with a radical intention (I–III stage = limited disease 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 thrombocytopenia. MR examination may be helpful in cases of diagnostic difficulties in patients with suspected bone metastases and inconclusive results from 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; EBUS — endobronchial ultrasonography; EUS — oesophageal ultrasonography; FNA — fine-needle aspiration; LDH — lactate dehydrogenase; MR — magnetic resonance; NSCLC — non-small-cell lung cancer; PET — positron emission tomography; RCHT — radiochemotherapy; RT — radiotherapy; SCLC — small-cell lung cancer; US — ultrasonography

Respiratory and cardiovascular capacity assessments

Before the planned surgical treatment and radical RT or RCHT, the risk of cardiovascular complications should be assessed, and the efficiency of lung ventilation and gas exchange should be determined. Medical history, physical examination, electrocardiography, and (if indicated) echocardiography, exercise electrocardiography, and coronary angiography play important roles in assessing the risk of cardiovascular complications. The test that assesses lung ventilation is spirometry, and the most important indicator used in qualifying for surgery is forced expiratory volume 1st second (FEV_1). The recommended method of assessing gas exchange efficiency is the measurement of the lung transfer factor for carbon monoxide (TLCO), also known as the diffusion lung capacity for carbon monoxide (DLCO). The above-mentioned examinations should be performed on each patient before surgical treatment is planned, because they are crucial for further treatment planning. The results of FEV_1 and DLCO can be assessed using the percentage of predicted value or predicted postoperative value expressed as the percentage of predicted value [32]. Patients with FEV_1 and TLCO results above 80% of the predicted value or an estimated postoperative value higher than 60% of the predicted value have a low risk of perioperative complications and can be qualified for surgery without additional tests. In patients with lower values, it is necessary to perform an additional functional assessment using simple exercise tests (stair climb test or pendulum test) or a full cardiopulmonary exercise test with VO_{2max} measurement. In the case of the stair climb test, climbing a height above 22 metres allows us to conclude that there is a low risk of postoperative complications, and climbing below 10 metres indicates a high risk and absolutely requires a full cardiopulmonary exercise test [33]. Figure 5 presents the recommended algorithm according to ACCP [35].

Recommendations

— In lung cancer patients, cardiovascular, and respiratory capacity assessment is necessary before planned treatment (III, A).

— In all lung cancer patients, the co-occurence of other serious diseases should be taken into account before deciding on treatment (III, A).

Table 4. TNM classification of lung cancer (UICC, 2016) [30]

Features	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 tumour with co-occuring satelliate lesion(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 co-occuring with satellite lesion(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 metastases
N1	Metastases in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastases in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastases in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M	
MX	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases present
M1a	Satelliate lesion(s) in a contralateral lobe; tumour with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion
M1b	Single extrathoracic metastases
M1c	Multiple extrathoracic metastases in one or more organs

Table 5. Stages of lung cancer (UICC, 2016) [30]

Stages	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

Treatment

Treatment of patients with lung cancer (general principles — see Fig. 6) should be planned by a multidisciplinary team (thoracic surgeon, radiation oncologist, medical oncologist, pneumonologist, specialist in radiodiagnostics, and pathologist) 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 capabilities for the use of combined treatment and appropriate management in cases of complications, which are often inevitable.

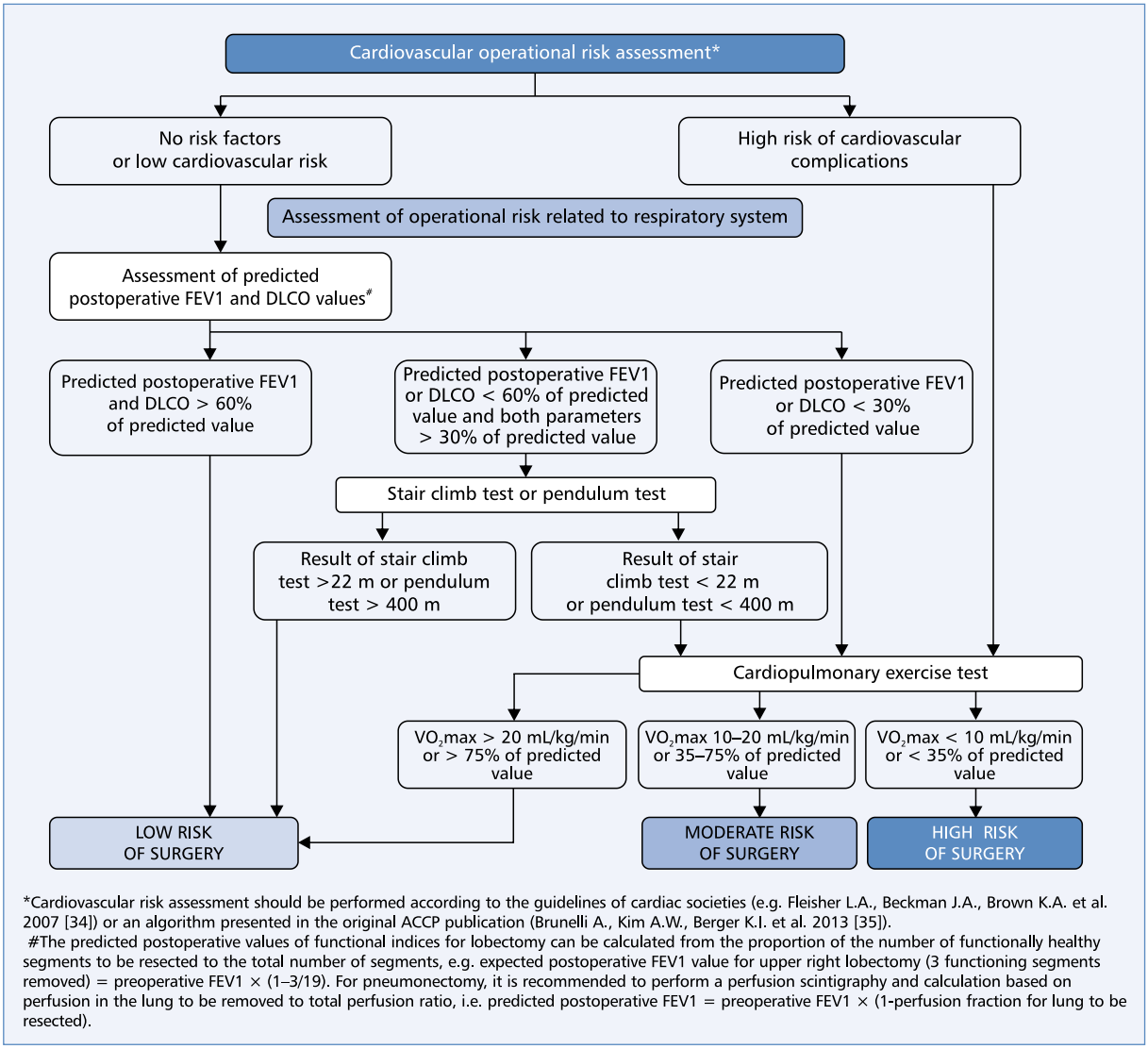
Non-small-cell lung cancer — treatment in stages I–II and IIIA (patients with potentially resectable disease)

Surgical treatment

In patients with NSCLC in stages I and II and in selected patients with stage IIIA (without the N2 feature), the treatment of choice is radical resection of the pulmonary parenchyma [36]. In the case of the N1 feature, before assessment of eligibility for resection, it is necessary to exclude the N2 feature using EBUS/EUS or mediastinoscopy. 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 complete response within lymph nodes following neoadjuvant chemotherapy (CHT) is confirmed in PET-CT and mediastinoscopy [37, 38].

Lobectomy is the method of choice for patients who are eligible for resection. Pneumonectomy is performed only when the lobectomy is not likely to be radical. Both types of resections are routinely accompanied by the removal of ipsilateral hilar lymph nodes and mediastinal nodes [36, 39]. The postoperative material should contain at least 6 lymph nodes from the N1 (3 lymph nodes) and N2 groups (3 lymph nodes; always lymph nodes below the tracheal bifurcation — group number 7). The influence of the extent of lymphadenectomy 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 postoperative determination of the disease stage and facilitates qualification for adjuvant treatment [36, 38, 39]. In patients with stage I and some patients with stage II lung cancer, the recommended method of treatment is a videothoracoscopic lobectomy [40, 41]. More limited resection (anatomical segmentectomy) is justified only in patients with significant limitation of respiratory reserves and in the case of *in situ* or minimally invasive adenocarcinoma [42].

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



*Cardiovascular risk assessment should be performed according to the guidelines of cardiac societies (e.g. Fleisher L.A., Beckman J.A., Brown K.A. et al. 2007 [34]) or an algorithm presented in the original ACCP publication (Brunelli A., Kim A.W., Berger K.I. et al. 2013 [35]).

#The predicted postoperative values of functional indices for lobectomy can be calculated from the proportion of the number of functionally healthy segments to be resected to the total number of segments, e.g. expected postoperative FEV1 value for upper right lobectomy (3 functioning segments removed) = preoperative FEV1 × (1–3/19). For pneumonectomy, it is recommended to perform a perfusion scintigraphy and calculation based on perfusion in the lung to be removed to total perfusion ratio, i.e. predicted postoperative FEV1 = preoperative FEV1 × (1-perfusion fraction for lung to be resected).

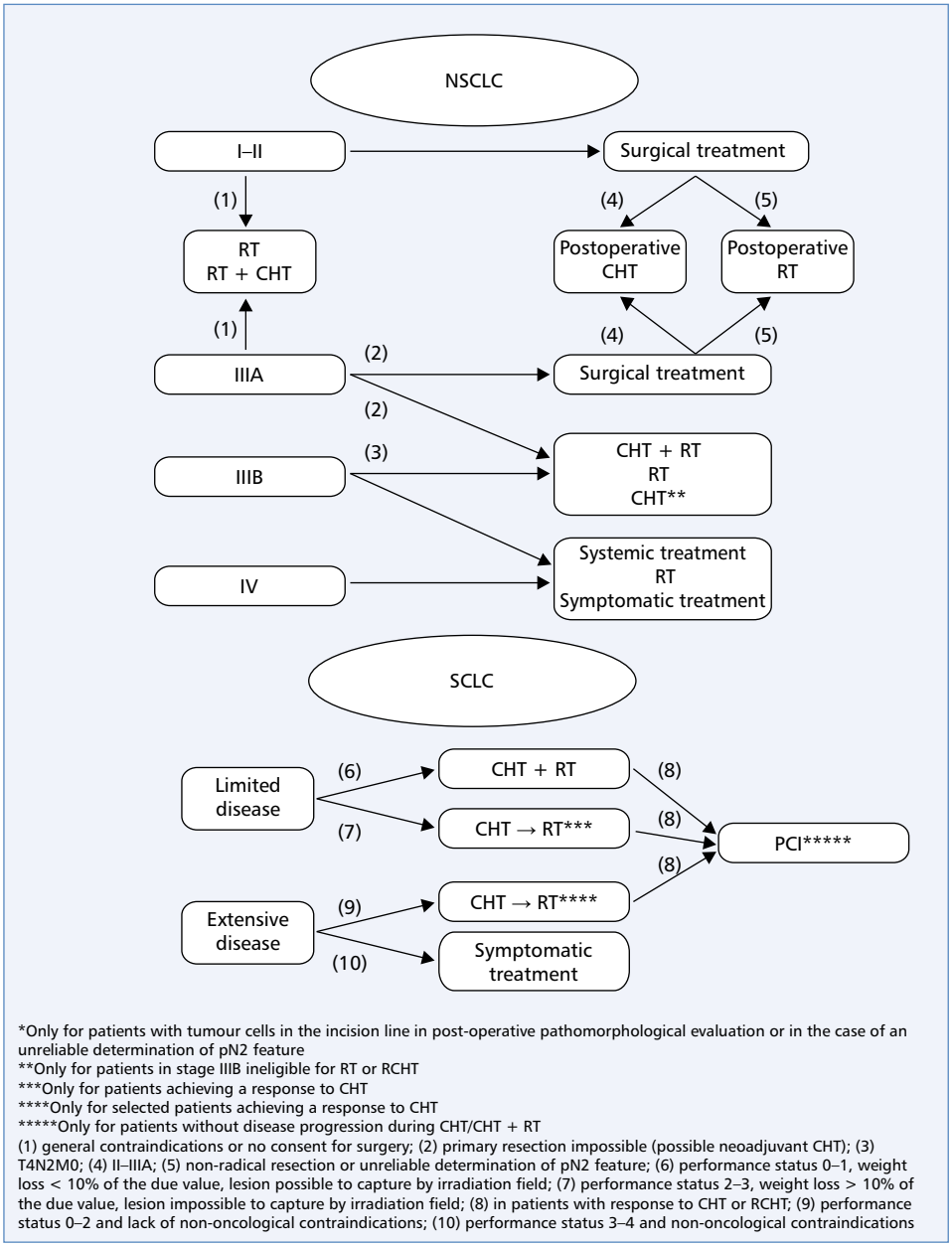
Figure 5. Algorithm for functional assessment, risk stratification, and qualification for resection procedures in lung cancer according to the American College of Chest Physicians (ACCP) — modified; DLCO — diffusion lung capacity for carbon monoxide; VO_2max — maximum oxygen uptake

intensity modulation, consideration of respiratory motion, irradiation based on current imaging) with a total dose of 60–66 Gy (2.0 Gy per fraction). This treatment can be used in patients with good PS and without a significant reduction of respiratory and circulatory capacity. In patients with small size (T1 or T2) peripheral tumours 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 function, management of choice is stereotactic RT, which allows a percentage of local cure to be obtained like that of surgical treatment. The role of stereotactic RT in perihilar tumours is still under investigation [43].

The ablation methods (e.g. thermoablation or cryoablation) in patients with limited respiratory and circulatory capacity can be considered only after excluding the possibility of surgical treatment and radiotherapy.

Postoperative radiotherapy

The results of the meta-analysis of randomised clinical trials showed that in patients with pN0 and pN1 features, postoperative RT may even worsen treatment outcomes, and in patients with pIIIA, it reduces the risk of local recurrence and slightly prolongs overall survival [44]. The main limitations of this meta-analysis are the suboptimal RT techniques used in previous clinical trials and inadequate patient selection. While the results



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

of the next meta-analysis of RCTs suggest a beneficial effect of modern postoperative RT in relation to local control and survival time in patients in the pIII stage [45, 46], the results of the LungART study indicate that postoperative RT in patients with stage pIIIA and pN2 features is not justified [47].

Adjuvant RT is indicated when the presence of malignant cells is confirmed in the cutting during in postoperative histological examination, but it is not recommended after complete tumour resection (tumour-free surgical 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 a 4–15 MeV megavoltage beam). Treatment should be initiated within 6 weeks of surgery [42].

Postoperative chemotherapy

The results of a meta-analysis of studies with random selection of patients indicate that the use of postoperative

CHT improves 5-year survival by approximately 5% [48]. Significant benefits of adjuvant CHT apply only to patients in stages II and IIIA (including patients undergoing postoperative RT), but advantage is independent from gender and age of patients as well as the histological type of cancer. For patients in stage I, adjuvant CHT does not improve their outcome.

Postoperative 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 one and 8 (frequency every 3 weeks) [48]. Postoperative CHT can be used only in patients with excellent or good PS, with full recovery after surgery, and without significant comorbidities and medical contraindications. The risk of adverse reactions during postoperative CHT is more pronounced in patients over 70 years of age and after pneumonectomy. In the case of simultaneous indications for postoperative RT, irradiation may be started at the same time as CHT. The usefulness of molecular prognostic and predictive factor assessment in the qualification of postoperative CHT has not yet been proven [12].

The phase III ADAURA study compared the value of postoperative treatment with osimertinib for 3 years versus a placebo in patients with stages IB–IIIA NSCLC with activating *EGFR* gene mutations (exon 19 deletion or exon 21 substitutions) who had undergone pulmonary resection (60% of patients received CHT). Patients with stages II and IIIA showed a 60% reduction in the relative risk of death. The relative risk of progression or death in patients with stages II and IIIA using osimertinib was lower by 83%, while in the entire study population (IB–IIIA stage) by 80%. The benefits were not related to the use of adjuvant chemotherapy. Adverse effects in the group of patients receiving osimertinib were slightly more frequent, with no adverse impact on quality of life [49]. In the case of a positive registration decision, the results of the ADAURA study will justify testing the *EGFR* gene status in patients undergoing parenchymal resection.

Postoperative rehabilitation

Postoperative rehabilitation improve physical capacity, muscle strength and alleviates the symptoms of fatigue, shortness of breath and depression in patients after lung parenchyma resection. It is a safe procedure that shortens length of hospital stay and reduces the incidence of pulmonary postoperative complications [50, 51].

The postoperative rehabilitation program should include chest physiotherapy, aerobic and resistance exercises, as well as inspiratory muscle training and breathing exercises. Aerobic exercise — performed 3 times a week at 50–70% of the heart rate reserve (difference between maximum exercise heart rate and resting heart rate) — supplemented with resistance exercises is safe and contributes to increased fitness and reduced premature death risk. Further research is needed regarding patients qualification and program, duration and frequency of postoperative rehabilitation, as well as its impact on the incidence of complications and deaths in the postoperative period [50].

Preoperative treatment

In previous studies, preoperative CHT was mainly used in selected patients with stage IIIA and pN2 features, 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 5% absolute difference in 5-year survival (statistically significant difference) in favour of preoperative CHT compared with surgical treatment alone [52].

Preoperative 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 regimen with cisplatin in combination with vinorelbine, gemcitabine, paclitaxel, docetaxel, or pemetrexed. It is necessary to carefully monitor the response and tolerance of preoperative treatment. Surgical treatment can be carried out after recovery from haematological toxicity during a 3-week gap from the last CHT cycle. The condition for qualifying for resection is to obtain a confirmed complete response in the mediastinal lymph nodes, either histologically or in PET-CT scan [42, 52].

Preoperative RCHT does not improve outcomes. The use of RCHT is only justified in patients with superior sulcus tumour (Pancoast tumour), in whom simultaneous use of CHT (2 cycles of cisplatin in combination with the second drug) and RT (50–60 Gy) in most cases allows to achieve complete resection. Surgery should be performed 4–6 weeks after completion of RCHT [4, 53].

Preoperative rehabilitation

Preoperative rehabilitation (especially in patients with concomitant chronic obstructive pulmonary disease) is important in reducing the risk of postoperative complications and shortening length of hospital stay in lung cancer patients, as it improves fitness and physical capacity of patients qualified for pulmonary resection [54].

Pre-operative rehabilitation should include chest physiotherapy, inspiratory muscle training, and moderate to high intensity aerobic and resistance

exercises. The most often recommended is a 4-week rehabilitation program, which includes 10 to 45 minutes trainings performed 3–5 times a week. Further research is needed regarding patients qualification and program, duration and frequency of preoperative rehabilitation, as well as its impact on the incidence of complications and deaths in the postoperative period [55, 56].

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 stages I–II and IIIA with N1 features (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 stage I non-small-cell lung cancer I and some stage II patients, the recommended method is a videothoracoscopic lobectomy (I, A).
- Rehabilitation is necessary in lung cancer patients before the planned surgical treatment (II, A).
- Early rehabilitation is essential in patients after lung parenchyma resection (II, A).
- In patients with non-small-cell lung cancer with T1 or T2 features 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 the I–IIIA stages, who are not eligible for resection and stereotactic radiotherapy, radical radiotherapy or chemoradiotherapy should be used (II, A).
- Postoperative adjuvant radiotherapy in patients with pN0, pN1, and pN2 features is not justified (I, A), except in patients after incomplete resection (III, B).
- Postoperative radiotherapy should be started within 6 weeks of surgery; it can be started simultaneously with chemotherapy (III, B).
- Postoperative chemotherapy (cisplatin and vinorelbine — 3–4 cycles) in patients with non-small-cell lung cancer is recommended for pII and pIII stages (I, A).
- Preoperative chemotherapy (regimens containing 2 drugs, including cisplatin) can be used in selected patients with non-small-cell lung cancer in stage IIIA with a pN2 feature (I, B).
- Surgery may be offered for patients with non-small-cell lung cancer with the N2 feature only if a complete response to chemotherapy, confirmed by PET and mediastinoscopy, is achieved (II, B).
- In patients diagnosed with superior sulcus non-small-cell lung cancer, potentially qualifying for surgery, preoperative radiotherapy or chemoradiotherapy should be used (II, A).

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

Patients with stage IIIA NSCLC, in whom complete resection cannot be performed due to advanced stage of disease or other reasons, as well as stage IIIB patients, should receive RT or RCHT. 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 RT or RCHT is the treatment of choice in this group [42, 53, 57]. The differences in the management that are mentioned above justify conducting full diagnostics 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 with puncture or thoracoscopy) currently qualifies the tumour as grade M1 and constitutes an indication for treatment under 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 RT alone, and the simultaneous RCHT is of more value than the sequential use of both methods, but at a higher risk of acute oesophagitis and, to a lesser extent, pneumotoxicity and myelotoxicity [58]. Simultaneous RCHT can be used in specialised centres with the availability to manage posttreatment complications. Chemoradiotherapy — especially concurrent therapy — can only be considered in patients with good PS, without significant (more than 10% of the predicted value) weight loss, with limited tumour mass and adequate respiratory capacity [42, 57]. In some patients who do not qualify for concurrent RCHT (e.g. due to tumour burden), 2–4 cycles of induction CHT may be considered, with the necessity to monitor the response to initial systemic therapy. In selected patients over 70 years of age in excellent PS, with normal cardiorespiratory capacity and without serious comorbidities, sequential CHT and RT may be used [59]. Irradiation should begin within 2–3 weeks of CHT completion (longer intervals reduce the effect of initial CHT). In the case of progression during CHT, it should be terminated, and RT should start immediately.

The use of CHT before or after concurrent RCHT (induction or consolidation therapy) does not improve treatment outcomes but is associated with a higher incidence of side effects and is therefore not recommended [42, 53, 57]. The results of the phase III PACIFIC study showed that the use of consolidation immunotherapy with durvalumab (monoclonal antibody blocking PD-L1) in patients with stage III NSCLC with objective response or stable disease following concomitant RCHT decreases the relative risk of disease progression or death by 48% compared to the placebo (median dura-

tion of progression-free survival — 17 and 6 months) and significantly increases overall survival (reduction of relative risk of death by 29%, medians — 47 months for durvalumab and 29 months for placebo; 4-year survival — 50% and 36%). The incidence of severe adverse events was similar in both groups [60].

In 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 (2.0 Gy per day) and conformal planning [53, 57]. Increasing the dose above 66 Gy does not add any clinical benefit [57]. The irradiated volume should cover the area of the primary tumour and involve the 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, particularly of the opposite mediastinal and supraclavicular areas, does not improve efficacy or increase treatment toxicity.

Contraindications for radical RT or RCHT include impaired PS (grade 2 or higher according to the WHO scale), presence of pleural effusion, active infection, weight loss over 10% of the normal value in the 3 months preceding the treatment initiation, 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 [42, 57].

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 (25 mg/m^2 — day 1 and 8), and in patients with non-squamous-cell carcinoma cisplatin (75 mg/m^2 — day 1) in combination with pemetrexed (500 mg/m^2 — day 1). In the case of sequential RCHT, regimens consisting of cisplatin and one of the above-mentioned drugs or taxoids (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 drugs listed above. Subsequent cycles of CHT within the sequential and simultaneous RCHT should be repeated at 21-day intervals [42, 53, 57].

In patients with contraindications to RCHT, only radical RT at a dose of 60–66 Gy (30–33 fractions) may be used. The use of hypofractionated RT (66 Gy/22 fractions) is also allowed [42, 53]. 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 PS and a life expectancy of at least 3 months [61]. The decision regarding the selection of the fractionation scheme should be made on the basis of an 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).
— In patients with locally advanced superior sulcus, non-small-cell lung cancer resection should be preceded by radiochemotherapy, and if resection is impossible, they should receive radiochemotherapy 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 (NSCLC) — treatment in stage IV

The 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 TKIs, immunotherapy or immunochemotherapy, palliative RT, or symptomatic treatment alone may be considered. Currently, EGFR inhibitors (afatinib, erlotinib, gefitinib, dakomitinib and osimertinib), ALK (alectinib, brigatinib, ceritinib, lorlatinib and crizotinib), ROS1 inhibitors (crizotinib), and PD-1 (nivolumab, pembrolizumab) or PD-L1 inhibitors (atezolizumab) are available in Poland for the treatment of patients with metastatic lung cancer. The choice of systemic treatment method depends on the histological type (non-squamous or squamous-cell carcinoma), molecular features of the tumour, and registered indications. In patients with activating genetic abnormalities, the treatment of choice is a molecularly targeted treatment. The choice of treatment should take into account the patient's age and PS, as well as the presence of comorbidities. In patients with non-squamous-cell carcinoma, the possible presence of primary mutations (activating and

responsible for resistance) in exons 18–21 of the *EGFR* gene and *ALK* and *ROS1* gene rearrangements should be determined. These tests are best performed within one medical referral. 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 cellular material (in case of non-squamous-cell carcinoma, it should be preceded by an assessment of *EGFR*, *ALK,* and *ROS1* genes status). If, in the case of tumour relapse, 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 TKIs, it is necessary to resample the material for molecular testing 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 — excision or needle re-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 have shown survival prolongation and quality of life improvement in patients with advanced NSCLC receiving palliative CHT [62, 63].

Palliative CHT in patients with stage IV NSCLC may be used if:

— PS is excellent or good (WHO category — 0 or 1);
— no body weight loss of no more than 10% is revealed within the 3 months before starting treatment;
— no serious comorbidities and/or sequelae of previous anticancer treatment were 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 the above-mentioned conditions may receive the 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 symptoms 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 regimens contain cisplatin (75–80 mg/m^2 intravenously— day 1) in combination with one of the following drugs: etoposide (100–120 mg/m^2 intravenously — day 1, 2, and 3), vinorelbine (30 mg/m^2 intravenously — day 1 and 8 or 30 mg/m^2 intravenously — day 1 and 60 mg/m^2 orally — day 8 or 60 mg/m^2 orally — day 1 and 8), gemcitabine (1000 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 cisplatin-containing regimens, compared with carboplatin (especially in combination with taxoids and gemcitabine), result in longer overall survival [64, 65]. 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 predominant squamous-cell carcinoma, the combination of cisplatin and pemetrexed is more effective than other CHT regimens [66].

Patients older than 70 years and in good PS (grades 0–1 on the WHO scale) can receive multidrug CHT [67].

Regimens without platinum derivatives can be considered only in the case of contraindications to the use of this group of drugs [65]. In the case of absolute contraindications to the use of regimens containing 2 drugs, (including platinum derivatives) single-agent CHT (e.g. intravenous or oral vinorelbine) may be considered [68].

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 evidence of increasing response may use an additional 2 cycles (a total of 6 cycles of CHT) [69].

The use of maintenance therapy with pemetrexed (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 excellent 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 the time to progression [70].

Molecularly targeted treatment

Numerous RCTs and their meta-analyses indicate that in patients diagnosed with adenocarcinoma and the presence of activating mutations in the *EGFR* gene,

the use of one of the EGFR TKIs may produce a higher response rate and longer progression-free survival and is better tolerated compared to CHT [71]. The use of EGFR TKIs is the first choice in the treatment of patients with *EGFR*-activating mutations. First-generation EGFR inhibitors have analogous 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 [72]. Only for afatinib — in the preplanned pooled analysis of LUX-Lung 3 and 6 studies [73] — a significant increase in overall survival compared to CHT was observed in patients with EGFR exon 19 deletions (median for afatinib and chemotherapy in LUX-Lung 3 and 6 trials — 33 *vs.* 21 months and 31 *vs.* 18 months). This benefit was not observed in patients with *EGFR* exon 21 substitution. Treatment with EGFR TKIs should be continued until disease progression or severe side effects occur.

A phase III clinical trial conducted in an Asian population showed a significant prolongation of progression-free survival and overall survival after dacomitinib (a second-generation EGFR TKI) compared to gefitinib (14.7 *vs.* 9.2 months and 34.1 *vs.* 26.8 months), with a higher toxicity of dacomitinib [74].

The phase III FLAURA 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. Progression-free survival and overall survival were significantly longer among patients treated with osimertinib (medians — 19 months *vs.* 10 months and 39 months *vs.* 32 months). Higher efficacy of osimertinib was found in patients with and without CNS involvement. Treatment with osimertinib was better tolerated (the incidence of serious adverse events was 42% and 47%) [75].

The use of the above-mentioned EGFR TKIs is reimbursed in Poland.

In phase III studies of patients diagnosed with adenocarcinoma and *ALK* gene rearrangement, significantly better survival rates were found after the use of ALK inhibitors compared to CHT. For crizotinib and ceritinib, the risk of death was reduced by 24% and 27%, respective [76, 77]. Phase III study comparing alectinib with crizotinib showed a median progression-free survival of 35 and 11 months, and reduced relative risk of disease progression or death by 57% in patients receiving alectinib with better treatment tolerance. The differences were found in the total entire and in patients with metastases in the CNS, which results from the better penetration of alectinib through the blood–brain barrier [78]. Brigatinib and lorlatinib also showed greater efficacy than crizotinib in phase III trials (significantly reduced the risk of disease progression or death by 51% and 72%; significant superiority of both drugs in patients with brain metastases) [79, 80]. In Poland, crizotinib, alectinib, ceritinib and brigatinib are reimbursed in the first line of treatment (loralatinib — in the second-line treatment).

The use of crizotinib is also justified (and reimbursed) in the first-line treatment of NSCLC patients with *ROS1* gene rearrangement (median overall survival in the PROFILE 1001 studies, 51 months) [81]. The pooled analysis of the results of phase II studies with entrectinib used in NSCLC patients with *ROS1* gene rearrangement confirmed the value of the drug (objective response rate 67%, 12-month progression-free survival and overall survival rates 55% and 81%) [82].

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

The value of drugs targeting other molecules (e.g. *RET*, *MET*, *BRAF*, *HER2*, *NTRK* and *KRAS* gene abnormalities) is currently being evaluated in clinical trials. Some of these drugs have been issued with a marketing authorization but are not currently reimbursed in Poland.

Phase III trial results show some benefits of bevacizumab — a monoclonal antibody directed against vascular endothelial growth factor — 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 [83].

Attempts to combine cetuximab with CHT as part of the first-line treatment yielded conflicting results (no effect in one study and a slight increase in overall survival in another) [84].

Immunotherapy

The results of phase III studies proved the value of the following immune checkpoint inhibitors in first-line treatment:

— pembrolizumab (PD-1 inhibitor) used either in monotherapy or with CHT;
— atezolizumab (PD-L1 inhibitor) used either in monotherapy or in combination with CHT or with bevacizumab and CHT;
— nivolumab (PD-1 inhibitor) used in combination with ipilimumab [CTLA4 (cytotoxic T lymphocyte antigen 4) inhibitor] and CHT;
— cemiplimab (PD-1 inhibitor) used as monotherapy.

The phase III study KEYNOTE-024 showed a significant increase in disease progression-free and overall survival with pembrolizumab compared to CHT (platinum-based regimens) in patients with PD-L1 expression in at least 50% of tumour cells (progression-free and overall survival 10 *vs.* 6 months and 32 *vs.* 16 months). The benefits were consistent in patients diagnosed with squamous-cell carcinoma and non-squamous-cell carcinoma. The incidence of serious adverse events was significantly lower in patients receiving pembrolizumab [80]. Monotherapy with pembrolizumab in NSCLC patients (squamous-and non-squamous-cell carcinoma) with PD-L1 expression in at least 50% of cells is reimbursed in Poland.

For another PD-1 inhibitor, nivolumab, no significant benefit over first-line CHT has been demonstrated [86].

The results of the phase III EMPOWER-Lung1 study [87], which assumed the randomization of patients with PD-L1 expression greater than or equal to 50% to treatment with cemiplimab (PD-1 inhibitor) or standard platinum-based chemotherapy, showed a significant reduction in progression and death risk after immunotherapy compared to chemotherapy (by 46% and 43%, respectively). Cemiplimab monotherapy has recently received a favorable opinion in Europe for the first-line treatment in patients with locally advanced or generalized NSCLC with high PD-L1 expression and without *EGFR* mutations or *ALK* and *ROS1* rearrangements in tumor cells. The drug is not reimbursed in Poland so far.

Phase III studies with pembrolizumab used in combination with CHT (platinum-based regimens) KEYNOTE-189 (non-squamous carcinoma) [88] and KEYNOTE-407 (squamous-cell carcinoma) [89] showed a significant increase in overall survival in the case of squamous-cell carcinoma; however, the benefits were numerically clearly smaller (median 22 *vs.* 11 months [88] and 16 *vs.* 11 months [89]). The benefits of adding CHT to pembrolizumab were independent of PD-L1 expression level, but the greatest reduction in the risk of death was found in patients with high expression (50% or more cells). The use of pembrolizumab and CHT in first-line treatment is currently reimbursed in Poland for both histological types, in patients with PD-L1 expression below 50%.

Atezolizumab (PD-L1 inhibitor) was evaluated in an IMpower-150 study [90] in the first-line treatment of patients with non-squamous-cell carcinoma. In this study, the value of chemotherapy (carboplatin and pemetrexed) in combination with bevacizumab with or without atezolizumab was also analysed (in both arms, the maintenance treatment with bevacizumab or bevacizumab and atezolizumab was used). In the group of patients receiving atezolizumab, significantly higher 12-and 24-month overall survival rates (67% *vs.* 43%, and 61% *vs.* 34%) and increased overall survival (median 19 *vs.* 15 months) were found compared to CHT with bevacizumab. Serious adverse events were more frequent in patients treated with atezolizumab (59% *vs.* 50%). The reduction in the risk of death was related to PD-L1 expression. The phase III study IMpower-130 showed that atezolizumab in combination with CHT (carboplatin and nab-paclitaxel) in patients with non-squamous-cell carcinoma significantly increases the overall survival compared to CHT alone (median 20 and 15 months) [91]. However, a significant increase in overall survival was not achieved with the use of atezolizumab with CHT in patients with squamous-cell carcinoma (significant benefits only in patients with high PD-L1 expression) [92].

The phase III CheckMate 9LA study compared CHT (only 2 cycles with platinum derivative, nab-paclitaxel, or pemetrexed depending on histology) alone or in combination with nivolumab and ipilimumab. The median overall survival was significantly longer for immunotherapy with CHT (16 *vs.* 11 months), with acceptable treatment toxicity profile [93]. Immunochemotherapy was more effective regardless of the histological type, PD-L1 expression and other clinical features. Reducing the number of CHT cycles may be associated with better treatment tolerance [75].

The value of pembrolizumab monotherapy versus CHT alone was assessed in the phase III study KEYNOTE-042 in patients with squamous-and non-squamous-cell carcinoma with PD-L1 expression levels of at least 1% in the total population and in the subgroups according to PD-L1 expression (1% or more, 20% or more, and 50% or more), showing significant differences in favour of immunotherapy (median overall survival 17 *vs.* 12 months, 18 *vs.* 13 months, and 20 *vs.* 12 months) [94]. Based on these results, pembrolizumab in monotherapy was registered by the US Food and Drug Administration.

A preplanned phase III study IMpower-110 also showed a significantly increased median overall survival in patients with NSCLC with a PD-1 expression level of at least 1% receiving atezolizumab monotherapy compared to CHT (20 and 13 months, respectively) [95].

The incidence of serious adverse events of immunotherapy alone is lower, in an indirect assessment, than that observed with the combination of checkpoint inhibitors and CHT. A rational solution would be the use of immunotherapy alone or in combination with CHT, depending on the patients' characteristics, taking into account the extent and location of neoplastic lesions, comorbidities, and organ capacity. Due to the European registration and reimbursement rules in Poland, the use of immunotherapy alone is possible only in patients with PD-L1 expression in more than 50% of tumour cells (in other situations, pembrolizumab with CHT).

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 (e.g. rash, diarrhoea, liver dysfunction and hypopituitarism [or hypothyroidism] inflammatory bowel disease, alveolitis, disorders of the cardiovascular system). Side effects of immunotherapy usually appear after 2–6 weeks of treatment. Early diagnosis and appropriate management allow most patients to continue treatment [96, 97].

Second-line systemic treatment

Chemotherapy

In selected patients without *EGFR, ALK,* and *ROS1* gene disorders and with progression after prior palliative CHT producing an objective response of at least 3 months duration, the use of docetaxel or pemetrexed in the second-line treatment may be considered [98]. In RCTs with second-line treatment, neither the superiority of multidrug CHT over monotherapy [99] nor the efficacy of other cytotoxic drugs apart from docetaxel and pemetrexed has been demonstrated. Second-line treatment can only be used in patients with good PS and without persistent complications of previous CHT. Pemetrexed is slightly more effective than docetaxel in the second-line treatment of patients with non-squamous-cell carcinoma [98].

Molecularly targeted treatment

The use of targeted therapy in second-line treatment after previous CHT is justified only in patients who, despite the presence of molecular disorders, did not receive this treatment in the first line. In patients with *EGFR* gene mutation, in whom one of the EGFR TKIs (afatinib, erlotinib, or gefitinib) was used as a first-line treatment, and the disease progressed after remission, the T790 mutation in exon 20 of the *EGFR* gene should be tested (liquid biopsy or re-sampling of tissue material) [100]. Phase III clinical trial in patients with this mutation showed superiority of osimertinib compared to chemotherapy — median duration of progression-free survival was 10 and 4 months (reduction of relative risk by 70%) [101].

Based on the results of prospective studies, in patients with *ALK* gene rearrangement, it is justified to use crizotinib (only after previous CHT), alectinib, ceritinib, lorlatinib or brigatinib (after previous CHT or another ALK inhibitor) as second-line treatment. However, in patients with *ROS1* gene rearrangement after previous CHT, it is possible to use crizotinib (registered indication). Molecular disorders should be determined based on reliable tests (preferably within one medical referral). The duration of treatment should depend on its tolerance and outcomes.

The use of crizotinib in patients with progression after a previous CHT prolongs progression-free survival by 5 months and reduces the relative risk of progression or death by 51% compared to treatment with docetaxel or pemetrexed [102]. In a phase III trial, crizotinib was compared with brigatinib (a second-generation ALK TKI) in patients not previously receiving ALK-targeted treatment (27% of patients who had previously received CHT). In the group of patients previously receiving CHT, the relative risk of disease progression or death decreased by 65% in the brigatinib group [103]. In the case of failure of first-line treatment with crizotinib and CHT, ceritinib [104] and alectinib [105] showed high efficacy (prolongation of progression-free survival by 4 and 8 months).

The efficacy of dabrafenib (BRAF kinase inhibitor) and trametinib (MEK kinase inhibitor) was assessed in a phase II study of NSCLC patients with *BRAF* V600E mutation after failure of prior systemic treatment. The median progression-free survival and objective response rates were 9.7 months and 63.2%. Treatment with dabrafenib and trametinib in patients with the *BRAF* V600E mutation is currently not reimbursed in Poland [106].

The use of docetaxel in combination with nintedanib (an anti-angiogenic drug) in patients with advanced adenocarcinoma with progression after previous platinum-based multidrug CHT reduced the risk of death by 25% in comparison with docetaxel monotherapy [107]. 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 3 months from the end or 9 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 [108]. In patients with non-squamous-cell carcinoma, the decrease of relative risk of death compared with docetaxel was 27% with nivolumab [109] and atezolizumab [110] 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%) [111].

Radiotherapy

Patients with advanced NSCLC symptoms in the chest may be alleviated with palliative RT, which can be used in various regimens (e.g. 20 Gy in 5 fractions in 5 days, 30 Gy in 10 fractions in 12 days, or 16 Gy in 2 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, good palliative results may be achieved with en-

dobronchial 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 [112] or denosumab [113] 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 showed an increase in survival in a subset of NSCLC patients in addition to the anti-osteolytic effect [113].

Pleurodesis

In patients with recurrent pleural effusion, a good palliative effect may be achieved with 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 [114].

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 the transdiaphragmal approach during thoracotomy could be performed). In patients who are not eligible for adrenalectomy, stereotactic radiotherapy for adrenal metastasis may be considered. Treatment of primary chest changes should be carried out according to previously presented principles [115].

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 a 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 [115].

The presence of a single cancer lesion in the opposite 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 TKIs 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 TKIs in the first-line treatment (I, A).
— Patients with non-small-cell lung cancer with *ROS1* gene rearrangement should receive the ROS1 tyrosine kinase inhibitor in the first-line treatment (II, A).
— Patients with disseminated non-small-cell lung cancer with PD-L1 expression in at least 50% of cells, and without *EGFR* gene mutation and *ALK*/*ROS1* gene rearrangements should receive pembrolizumab in the first-line treatment (I, A).
— Patients with metastatic non-small-cell lung cancer with PD-L1 expression less than 50%, without *EGFR* mutation and *ALK*/*ROS1* gene rearrangements, should receive pembrolizumab in combination with chemotherapy or chemotherapy alone in the first-line treatment (doublet regimens 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 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 in the case of *ALK* gene rearrangement, immunotherapy (nivolumab or atezolizumab), 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 treatment with EGFR or ALK/ROS1 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 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 an 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) [116]. The limitation of the use of the PE regimen is the presence of renal dysfunction — in this situation cisplatin can be replaced with carboplatin (in a dose calculated according to Calvert's formula for AUC 6) [116]. 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) [117]. Anthracyclin-containing chemotherapy is contraindicated in patients with significant cardiovascular disorders and cannot be used simultaneously with chest X-rays [118, 119]. The value of CHT with cisplatin or carboplatin in combination with irinotecan in the first-line treatment of stage IV SCLC [120] has not been confirmed in the European population.

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, or treatment intensification [119].

Chemoimmunotherapy

The phase III IMpower133 trial compared chemotherapy with carboplatin and etoposide with or without atezolizumab in patients with stage IV SCLC. Atezolizumab was used in combination with CHT as a maintenance therapy. The overall survival time was 2 months longer in the atezolizumab group (median — 12.3 and 10.3 months; statistical significance), and the incidence of serious adverse events was similar in both arms of the study. There was no correlation with the degree of PD-L1 expression [121]. A similar benefit in terms of overall survival in patients with stage IV SCLC was demonstrated in the phase III CASPIAN study — the addition of durvalumab to CHT (regimens with cisplatin or carboplatin and etoposide) resulted in a significant increase in overall survival (median 12.9 and 10.5 months). Treatment tolerance was similar in both groups of patients [122]. Phase III study with pembrolizumab in combination with CHT did not show significant benefit in terms of overall survival [123].

Atezolizumab in combination with CHT in patients with stage IV SCLC is reimbursed in Poland.

Radiochemotherapy

In patients with an LD (stages I–III according to TNM classification), determined on the basis of a properly 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 [124]. If CHT and RT cannot be initiated simultaneously, it should be attempted to start RT no later than simultaneously with the second cycle of CHT [125]. The use of simultaneous RCHT should not reduce the due intensity of CHT [126].

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

The irradiated area includes the primary lesion and metastatic local lymph nodes, as well as the area of adjacent unchanged lymph nodes. Currently, RT is conventionally fractionated at a dose of 60–66 Gy — 30–33 fractions or hyperfractionated (45 Gy in 2 fractions of 1.5 Gy per day for 3 weeks, minimum interval between fractions — 6 hours) is recommended. It is also recommended that modern RT techniques (similar to NSCLC). The use of hyperfractionated RT as part of RCHT allows for slightly longer survival but at the cost of a greater risk of neutropenia [126].

The results of the phase III study show that the use of chest irradiation (30 Gy — 10 fractions) after an objective response to CHT is achieved in patients with stage IV SCLC increases the time to disease progression and the 2-year survival rate (13% *vs.* 3%) [127]. Benefits are observed primarily in patients with cancer dissemination limited to the chest organs. These observations justify the consideration of chest irradiation in patients with stage IV SCLC after achieving a response to CHT.

In patients with stage I–III and stage IV cancer who have responded to RCHT or CHT, elective cranial irradiation allows a reduction in the risk of brain metastases and an extension of the survival time [128, 129]. A Japanese phase III study showed a similar overall survival rate in patients with stage IV SCLC who, after responding to CHT, underwent elective brain RT or follow-up with MR imaging of the CNS [130].

Surgical treatment

Surgical treatment in small-cell lung cancer is used very rarely — 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 should be preceded by a full assessment of tumour burden (including PET-CT or mediastinoscopy). If the diagnosis of SCLC is established intraoperatively and there is a possibility of radical resection, a lobectomy with radical lymphadenectomy should be performed (pneumonectomy is not recommended because extensive surgery makes 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 was used [131, 132].

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) [131].

Small-cell lung cancer — treatment of relapsing patients

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

In patients with relapse of SCLC at least 3 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 3 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 PS, topotecan monotherapy can be used (1.5 mg/m^2 intravenously — day 1–5, every 21 days) [133]. The number of second-line CHT cycles depends on treatment tolerance and objective benefits.

In patients with relapse limited to the chest, who were not previously irradiated, a palliative RT (5 × 20 Gy or 1 × 8 Gy) should be considered.

In the 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.

Recommendations

— In the majority of patients with small-cell lung cancer in stages 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 stages T1–2 N0 (III, A).
— In patients with small-cell lung cancer in stages 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 or chemoimmunotherapy with atezolizumab should be used (I, A), and if response is achieved, elective irradiation of the central nervous system (I, A) and — in selected patients — chest irradiation should be considered (I, B).
— Before 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).

Overcoming smoking habits

Smoking during and after treatment of lung cancer significantly worsens outcomes, increases the overall risk of death and the risk of cancer-related death, as well as the risk of second cancers, intensifies toxicity, and significantly increases treatment costs [134]. Most patients continue their addiction after cancer diagnosis, despite the numerous beneficial effects of smoking cessation. Cancer is a 'learning moment' for everyone, and it is also the best opportunity to discuss the addiction with HCP and make a decision to quit smoking. Paying more attention to smoking cessation at diagnosis and active intervention can motivate patients to stop smoking.

Recommendations

— All lung cancer patients should undergo the assessment for smoking and be informed about the benefits of stopping smoking.
— Treatment of tobacco dependence should be an integral and routine part of multidisciplinary lung cancer care and family care.

Follow-up after treatment

The aim of observation in patients with lung cancer treated with radical intention is the early detection of relapse, complications of treatment, and independent primary cancer. The results of a prospective, randomised 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 the 3-, 6-, and 12-month intervals [135]. There is no indication for an active search for asymptomatic metastases in other organs (abdominal cavity, brain, bones) [136]. The schedule of control tests in palliative patients should take into account individual clinical situation. An inter-

esting solution, potentially increasing the effectiveness of control tests compared to their traditional form, is to match the dates of appointments with the symptoms reported by patients electronically [137].

Recommendations
— In patients with lung cancer treated with radical intention in the first 24 months after radical treatment, it is recommended that chest computed tomography examination scans should be performed every 6 months and every 12 months during the following 3 years (I, B).
— In the remaining patients, the control test schedule should be individualised (III, C).

Carcinoid tumours

Epidemiological and pathological characteristics

Carcinoid tumours account for 1–2% of primary respiratory tract neoplasms and 5% of thymic neoplasms. Approximately 25% of all carcinoids occur in the lungs. Lung and thymic carcinoids can occur in the course of multiple endocrine neoplasia type 1 syndrome (MEN-1), diffuse pulmonary neuroendocrine cell hyperplasia, or in people with a family history of such malignancies [138].

Compared to lung cancers, carcinoid tumours are usually diagnosed in younger people and have no proven association with smoking. Carcinoids, apart from SCLC and large-cell carcinoma, belong to neoplasms with neuroendocrine differentiation. Carcinoid tumours indicate higher histological maturity than SCLC and large-cell carcinoma — a typical carcinoid is characterised by a high degree of differentiation, while an atypical carcinoid is moderately differentiated [10].

The natural course and prognosis of carcinoids depends on differentiation grade. Typical carcinoids (about 70% of cases) are characterised by slow endobronchial growth and sporadic metastases, and atypical carcinoids infiltrate locally and are prone to spread to the lymph nodes and other organs. In a small proportion of patients diagnosed with carcinoids, secretion of peptide hormones and neuroamines (e.g. serotonin, somatostatin, and adrenocorticotropic hormone) is observed together with secondary symptoms [138].

Diagnostics

The diagnostics of carcinoid tumours are identical to those used in lung cancer, but in patients with symptoms secondary to increased secretion of peptide hormones and neuroamines, the hormonal profile should be additionally determined, and a somatostatin receptor scintigraphy should be considered [138]. The stage of carcinoid tumours is determined using the TNM classification [30].

Treatment

Surgery is the primary method of lung carcinoids treatment. The extent of resection depends on the tumour size and location. In typical carcinoids, lobectomy is most often performed, and in selected cases (limited endobronchial lesions), sparing surgery or laser removal may be considered. The principles of surgical management in atypical carcinoids are identical to those used in NSCLC (sparing surgery is contraindicated). The value of systemic treatment and RT in initial or postoperative treatment has not been confirmed [138].

The value of CHT in lung carcinoids (especially typical) is limited. In the case of advanced, typical carcinoids with slow progression, symptomatic treatment is indicated, and in the case of symptoms of hypersecretion and the presence of somatostatin receptors, the use of somatostatin analogues. Chemotherapy (platinum- or temozolomide-based regimens) may be used in patients with atypical advanced carcinoid tumours, but they are less chemosensitive than SCLC. In selected situations, it is justified to use radioisotope therapy targeting somatostatin or everolimus receptors (these methods are not reimbursed in Poland) [138].

Follow-up after treatment

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

Recommendations
— The diagnosis of respiratory carcinoids should be based on tissue histological examination (IV, A).
— Complete resection is a treatment of choice in carcinoid patients (IV, A).
— The use of chemotherapy and other systemic treatments, as well as somatostatin analogues and isotope therapy, should be individualised (IV, A).

Malignant pleural mesothelioma

Epidemiological and pathological 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 credibility [139]. 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 was 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 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 [140].

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, which is characterised by a particularly aggressive course [139]. The 2021 WHO classification introduced the concept of mesothelioma *in situ* [10].

Diagnostics

Diagnostics include identification of pleural lesions and confirmation of their malignant character, differentiation with metastases of another cancer, and extent assessment. For this purpose, close cooperation among the pathologist, radiologist, and clinician is necessary. An appropriate volume of material samples should also be obtained for IHC studies (Fig. 7). In the majority of patients, mesothelioma is diagnosed at the local and regional stages (metastases in distant organs are relatively rare).

Medical history

Medical history includes information about exposure to asbestos and symptoms associated with the localisation of primary lesions and local spread along the pleural surface (chest wall pain, dyspnoea, signs of threatening cardiac tamponade).

Physical examination

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

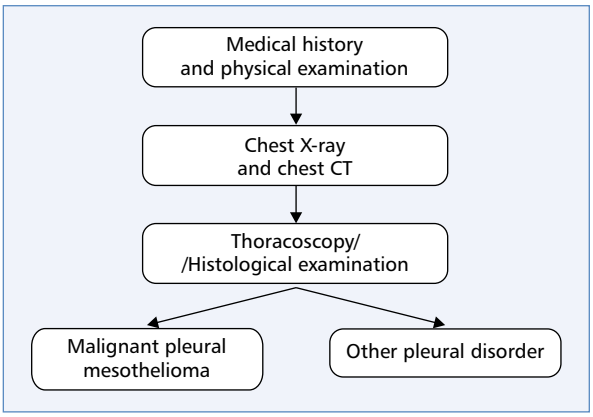


Figure 7. Principles of diagnostic procedures in malignant pleural mesothelioma; CT — computed tomography

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 when treatment with radical intention is considered [141]. Performing earlier pleurodesis significantly hindered 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.

Pathological evaluation

In pathological 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 type with desmoplastic subtype). Diagnosis is based on histological evaluation and IHC assays (assessment of specific proteins in mesothelioma cells — calretinin, vimentin, cytokeratin, mesothelin, thrombomodulin, osteopontin, and the BAP-1 protein of prognostic importance in epithelial mesothelioma), including clinical data [139, 140]. The material for histopathological examination is most often obtained with thoracoscopy; during the procedure, numerous excisions of suspicious pleural lesions should be undertaken. Pleural mesothelioma should not be diagnosed solely on the basis of cytological examination of pleural effusion or material

obtained with fine-needle aspiration [139]. The so-called cytoblocks made of the collected fluid enable performing IHC tests and may be helpful, but they do not allow for the assessment of stromal infiltration [an important feature for the diagnosis of mesothelioma (especially — *in situ* character)] [10].

Staging

In the assessment of malignant pleural mesothelioma, the Union for International Cancer Control (UICC) classification from 2017 applies (Tab. 6, 7) [30].

Treatment

Patients with malignant pleural mesothelioma should be treated only in specialised centres with extensive experience in this field and the possibility of using all methods of diagnosis and treatment (surgery, RT, and CHT) [142].

Radical surgical treatment is possible only in the epithelioid histological type in stages I, II, and III (without the N2 feature) after careful qualification, including the assessment of PS, tumour extent, and the coexistence of other diseases (especially cardiovascular diseases). Before qualification for radical treatment, mediastinoscopy is necessary [141–144]. 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 the mediastinal lymph nodes is most often performed. The choice of surgical treatment method is a subject of controversy — extrapleural pneumonectomy seems to be more justified in patients with a lower risk of relapse and with very good or good PS and in the absence of other diseases of clinical significance, but it is much more burdensome [143, 144]. In some patients undergoing radical resection, adjuvant 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 a randomised study showed better local control of pleural effusion with the use of videothoracoscopic pleurectomy, but this procedure had no effect on overall survival [145].

In some patients (particularly those with epithelioid type) who are not eligible for resection, moderate prolongation of survival and periodic symptom alleviation can be achieved after the use of palliative CHT. Eligible for treatment are patients with good PS with objective response assessment feasibility.

Systemic treatment of mesothelioma includes the use of antimetabolites (pemetrexed, gemcitabine, and raltitrexed) and cisplatin, doxorubicin and vinorelbine. The most effective 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 that are repeated every 3 weeks [146]. Assessment of CHT effectiveness requires the use of modified RECIST criteria, which results from the plane character of mesothelioma lesions and the frequent coexistence of pleural effusion. Selected patients (good PS, lack of persistent effects of earlier treatment) may have a short-term benefit from the second-line CHT (e.g. vinorelbine, doxorubicin, gemcitabine) [142, 147].

The results of randomised trials indicate that the addition of antiangiogenic drugs — bevacizumab [148] or nintedanib [149] — increases the effectiveness of CHT with cisplatin and pemetrexed. Neither drug is reimbursed in Poland for the treatment of patients with pleural mesothelioma.

The benefits of adding immunotherapy with durvalumab to chemotherapy (cisplatin and pemetrexed) demonstrated in a phase II trial require confirmation [150]. The combination of nivolumab and ipilimumab is valuable; in the phase III CheckMate 743 studies, an increase in overall survival by 4 months (18 *vs.* 14 months) was found compared to chemotherapy (pemetrexed with platinum derivative) [151].

Radiotherapy for mesothelioma is used:

— as postoperative 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 tumours.

The development of RT techniques, in particular the introduction of intensity modulated radiation therapy, 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 part of a combined treatment (postoperative RT and CHT) [152].

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

Follow-up after treatment

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

Recommendations

— A standard imaging study for suspected malignant pleural mesothelioma is chest computed tomography (IV, A).
— The diagnosis of malignant pleural mesothelioma should be based on the result of histological examination of the material (numerous sections)

Table 6. Staging of malignant pleural mesothelioma (UICC, 2016) [30]

Features	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 metastases
M1	Distant metastases present

Table 7. Stages of malignant pleural mesothelioma (UICC, 2016) [30]

Stages	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

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 the N2 feature, the possibility of complete resection should be considered. If this is not feasible, the surgical procedure should be aimed at controlling the accumulation of pleural effusion (pleurodesis, decortication or insertion of a tunneled pleural catheter) (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 part of a combined

treatment involving surgery and chemotherapy. Radiotherapy can also be considered a 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 the most common, and in children, neoplasms of neural origin dominate. In adults, mediastinal tumours are most often located in the anterior part, and in children, they are found in the 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 patients have general symptoms (usually paraneoplastic syndromes) [153]. 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, which is probably related to an earlier diagnosis [153].

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

Diagnostics

The complexity of mediastinal tumours makes it necessary to cooperate with many specialists (specialists in radiodiagnostics, pathologists, pneumonologists, thoracic surgeons, oncologists, and — in the case of myasthenia gravis — a neurologist).

Also to medical history and physical examination (including assessment for paraneoplastic symptoms), a CT scan should be performed (radiographs of anterior mediastinum usually show a circular or oval opacity with clear borders). Chest MR examination is useful in the imaging diagnostics of thymic neoplasms and in the differentiation between solid tumours and cysts [154]. In addition, serum markers (AFP — alpha-fetoprotein and beta-HCG — the beta subunit of human chorionic gonadotropin) should be assessed to differentiate from embryonal tumours. Due to the low incidence of metastases in distant organs, PET-CT imaging is of limited usefulness.

Pathological 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) [155].

The current WHO classification includes thymic epithelial cell morphology and the number of T lymphocytes, and distinguishes 6 types of thymomas with different prognoses [156]:

— A — thymoma with no nuclear atypia, and accompanied by a few 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 lymphocytes;
— B3 — thymoma predominantly composed of epithelial cells that have a round or polygonal shape and 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

Thymic tumour staging is assessed according to the TNM classification [30, 157], which replaced the Masaoka staging system [158] (Tab. 8–10).

Treatment

Treatment of patients with thymic tumours should be carried out in specialised 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 followed with RT and/or CHT [159]. In patients with myasthenia before surgery, 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). After complete resection of the thymomas in stage I, patients do not require additional RT or CHT. Postoperative RT should be considered in thymomas in stage IIB

Table 8. The Masaoka-Koga Stage Classification for Thymic Malignancies [158]

Stages	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 tumourstumours (UICC, 2016) [30]

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

Table 9. TNM classification of thymic tumourstumours (UICC, 2016) [30]

Features	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)

and histological types B2 or B3 (other patients in stage II do not require RT). Postoperative RT is routine management in thymomas in advanced stages 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 the probable presence of persistent cancer. The irradiated area should include a thymic lodge with an appropriate margin. In thymic carcinoma, adjuvant RT (50–54 Gy with a boost up to 60–66 Gy in the area at risk of recurrence) is used in stages II–IVA [159, 160]. It is recommended that modern RT techniques be used (like those in lung cancer).

In patients with locally advanced stages (stages III and IVA), combined treatment is recommended, including initial CHT, resection (possible in 50–70% of patients), and postoperative RT [159]. In patients who do not qualify for a complete resection, RCHT is used [161].

Thymomas are relatively chemosensitive (70–100% of objective responses) — CHT is used in combination with local treatment or alone [162]. The following regimens are most often used:

— CAP — cisplatin 50 mg/m2 intravenously —– day 1, doxorubicin 50 mg/m2 intravenously — day 1, cyclophosphamide 500 mg/m2 intravenously — day 1, cycles every 21 days;
— ADOC — cisplatin 50 mg/m2 intravenously — day 1, doxorubicin 40 mg/m2 intravenously — day 1, vincristine 0.6 mg/m2 intravenously — day 3, cyclophosphamide 700 mg/m2 intravenously — day 4, cycles every 21 days;

— PE — cisplatin 60 mg/m2 intravenously — day 1, etoposide 120 mg/m2 per day intravenously — day 1, 2, and 3, cycles every 21 days;
— KP — carboplatin AUC 6 — day 1, paclitaxel 200 mg/m2 intravenously — day 1, 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 tumours, the first CT scan should be performed after 3 months, followed by every 12 months for the first 5 years and then every 2 years. For patients treated for stage III or IVA thymomas and for thymic cancer, CT scans should be repeated every 6 months for 2 years and then every 12 months. Observation is recommended for at least 10 years [159].

Mediastinal germ-cell tumours

Mediastinal germ-cell tumours occur mainly in men (90% cases), and they are divided into seminomas and non-seminomas (in women, dysgerminoma and other than dysgerminoma). Most often they are located in the 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 [163, 164].

Mediastinal neurogenic tumours

Neoplasms of nervous system origin occur primarily in the posterior mediastinum and most often come from the 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 for mediastinal mesenchymal tumours is surgical resection [164].

Recommendations

— The standard imaging test for suspected mediastinal neoplasm is a chest computed tomography examination 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 indications for postoperative radiotherapy in thymic tumours are clinical stage IIB and histopathological types B2 and B3, as well as stages 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, preoperative chemotherapy or chemotherapy in combination with radiotherapy should be considered (IV, A).
— Chemotherapy is used for disseminated 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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