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Clinical recommendations for diagnosis, treatment and follow-up of non-small-cell lung cancer, small-cell lung cancer and malignant pleural mesothelioma

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Goals: to increase awareness of thoracic oncology; to update management practice guidelines for non-small-cell lung cancer (NSCLC), small-cell lung cancer (SCLC) and malignant pleural mesothelioma (MPM).

Objectives: to better meet the needs of thoracic patients; to share the knowledge on the treatment of thoracic cancers; to establish commonly accepted algorithms on the management of NSCLC, SCLC and MPM in the Euroregion Neman; to increase scientific and surgical co-operation among Vilnius University, Medical University of Bialystok and Grodno State Medical University and other European medical universities.

Key words: lung cancer, malignant pleural mesothelioma, diagnosis and treatment recommendations

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in both men and women. The age-standardised incidence rate of lung cancer in the European Union in males is 73.95/100 000 and in females 17.31/100 000, whereas the age-standardised mortality rate in males is 59.7/100 000 and in females 15.47/100 000 per year (EUCAN, 1998). The age-standardised rates are well-accepted parameters providing a better comparability of various populations as they are free of differences related to age-structure variations in particular populations (once the proposed modification is accepted, new data are to set up). The incidence rates of lung cancer in Lithuania are 81.0/100 000 per year in men and 14.2/100 000 per year in women (1). For Poland, the respective rates are 63.0/100 000 and 13.8/100 000.

Non-small-cell lung cancer (NSCLC) accounts for approximately 80-85% of all cases. The incidence of small-cell lung cancer (SCLC) is decreasing and currently represents 15–20% of lung cancers. About 90% of lung cancer mortality among men and about 80% among women are attributable to smoking (2).

Malignant pleural mesothelioma (MPM) is a rare malignancy. The incidence of MPM varies in the European Union

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from 0.9/100 000 to 1.3/100 000 per year. Within the next 20 years the incidence is estimated to double. The incidence rates of MPM in Lithuania are 3.0/100 000 per year in men and 1.6/100 000 per year in women (3). For Poland, the respective rates are 1.1/100 000 and 0.6/100 000. Asbestos is a well-established etiological factor for MPM, with occupational exposure in 70–80% of those affected.

The underneath options for diagnosis, treatment and follow-up of NSCLC, SCLC and MPM are based on the evidence derived from prospective clinical studies and the outcomes.

MATERIALS AND METHODS

I. Non-small cell lung cancer

Diagnosis

Pathological diagnosis should be established according to the WHO classification based on one of the following:

- histology – bronchoscopy, tru-cut or surgical (mediastinoscopy, mediastinotomy, thoracotomy) biopsy;
- cytology – fine needle aspiration (transbronchial or transthoracic of the primary tumour, peripheral lymph nodes), bronchial lavage, pleural fluid or sputum collection.

Staging and risk assessment

Investigations to determine the disease extent should include:

- history and complete physical examination;
- chest X-ray and CT scan of the chest and upper abdomen (MRI for specific situations – mediastinum and chest wall invasion assessment);
- neurological history and examination with the brain CT scan and / or MRI if malignant involvement is suspected;
- PET/CT scan in resectable patients;
- mediastinal lymph nodes biopsy in resectable patients if chest CT scan shows nodes >1 cm in the shortest transverse axis;
- bone isotopic scan in the presence of bone pain, elevated serum calcium level or elevated alkaline phosphatase level;
- biopsy (MRI or PET scan optional) to rule out metastatic disease in otherwise potentially resectable patients with an isolated adrenal mass or liver lesion (4, 5).

Staging should be performed according to the TNM-2002 system and stage grouping categories as shown in Table 1 are recommended.

Treatment

Stage I-II disease

Surgery is the standard treatment in early stage disease (6). Mediastinal lymph node resection is mandatory (7, 8). The determination of tumour resectability should be made by a surgical thoracic oncologist. Spirometry and other cariopulmonary function tests should be performed prior to surgery. Post-operative (adjuvant) chemotherapy with 3–4 cycles of a doublet containing platinum compound combined with one of new-generation agents is recommended for patients with pT2N0M0, pT2N1M0, pT1N1M0, pT3N0M0 (for patients classified as pT1N0M0 – observation only). Postoperative radiotherapy in completely resected (R0) patients is not recommended (9–12).

Radiotherapy is the treatment option of choice (combined with chemotherapy in patients with a good performance status) in patients with medical contraindications for surgery or in patients refusing surgery.

Stage III disease

Patients with resectable stage IIIA (cT3N1M0) – radical resection with lymph node removal followed by adjuvant chemotherapy for 3–4 cycles (13).

Patients with marginally resectable stage IIIA (N2-positive – mediastinoscopy and / or modern imaging technique mandatory) – upfront platinum-based doublet chemotherapy with a new generation agent (gemcitabine, vinorelbine, taxoid) for 2–3 cycles followed by radical resection with lymph node removal is a widely used therapeutic option; however, the role of surgery in this setting is still disputable and chemoradiotherapy could be an alternative option (14).

Patients with unresectable stage IIIA and stage IIIB – combined (preferably concurrent) radiochemotherapy is the standard of care in patients with a good performance status; radiotherapy alone is still an option for patients not being suitable for the combined approach (platinum-containing two-drug chemotherapy recommended every 3 weeks when combined with radiotherapy; consolidation chemotherapy still investigational). Multimodality treatment should only be performed at experienced institutions (15).

Stage IV disease

Platinum-based doublet combination chemotherapy with a new generation agent (gemcitabine, vinorelbine, taxoid) for good performance status (PS 0-1) patients is recommended aiming at survival prolongation, quality of life improvement and symptom control (16); 3–4 cycles of front-line chemotherapy should be applied; there is no evidence yet to perform maintenance therapy; platinum-free combinations (i.e. docetaxel and gemcitabine or vinorelbine and gemcitabine) may also be beneficial for patients unable to tolerate platinum compounds; the majority of elderly patients (age ≥70 years) and patients with inadequate performance status (PS ≥ 2) are not candidates for combination therapy and either single-agent therapy (i. e. gemcitabine, taxoid, or vinorelbine) or best supportive care could be an option; the use of molecularly-oriented agents (e. g., antiangiogenic monoclonal antibodies) is still experimental despite promising data (17).

Second-line chemotherapy

Second-line chemotherapy has recently been established as a standard therapy for NSCLC, because it improves disease-re-

Table 1. **Stage grouping categories of lung cancer**

Occult carcinoma	Tx	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T1, T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	Any T	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

lated symptoms and survival in patients with a good performance status. Docetaxel has been the first agent registered in this indication based upon the outcome of two randomized phase III studies. Pemetrexed has also been registered for second-line therapy due to a more favourable toxicity profile based on a randomized phase III study. The small molecules (i. e. erlotinib) are another second-line treatment option.

Response evaluation

Response evaluation is mandatory after 2–3 cycles of chemotherapy with the use of objective measurements as well as symptom assessment.

Follow-up

The optimal follow-up approach is a matter of controversy. However, it is recommended to perform physical examination and chest radiography (preferably with CT) every 3 months in the first 2 years, then every 6 months for 3 years, and eventually annually.

Smoking cessation counselling should be provided to all patients after primary treatment.

II. Small-cell lung cancer

Diagnosis

Pathological diagnosis should be made according to the WHO classification. The initial examinations are similar to NSCLC.

In addition to complete history and physical examination, staging procedures should at least include the following: chest X-ray, CT scan of the chest and upper abdomen, complete blood count, liver and renal function tests, LDH, and sodium. Additional tests to define limited disease in patients with symptoms or abnormal physical examination suggesting metastases are bone scintigraphy, CT or MRI of the brain, and a bone marrow biopsy.

Staging and risk assessment

Patients are usually grouped according to a simple two-stage system developed by the Veteran's Administration Lung Cancer Study Group into limited disease (LD) and extensive disease (ED).

Limited disease

The definition is based on the possibility of encompassing all detectable disease within a "tolerable" radiotherapy port. Patients with limited disease have tumour deposits restricted to one hemothorax with regional lymph node metastases including the ipsilateral lobar, ipsilateral supraclavicular, mediastinal and contralateral hilar nodes.

Extensive disease

It represents any tumour beyond the bounds defined above, including ipsilateral lung metastases and malignant pleural effusion.

Treatment

Limited disease

Standard regimens, also for patients diagnosed at surgery, are either based on ethoposide-platinum or cyclophosphamide-doxorubicin and should be given in 4–6 cycles. Maintenance chemotherapy does not result in any substantial improvement of survival (18).

Etoposide-cisplatin is widely regarded as state-of-the-art chemotherapy for limited disease patients, particularly because this regimen can be combined with concurrent irradiation without unacceptable toxicity.

Chest radiotherapy (45 Gy) increases local control and survival; it should be given to all patients with limited disease. Several studies suggest starting thoracic radiotherapy early in the course of chemotherapy.

Prophylactic cranial irradiation is indicated in patients with a complete remission from limited disease because it reduces the lifetime risk of cerebral metastases and improves the survival.

Extensive disease

Chemotherapy with the same regimens (cisplatin / carboplatin + ethoposide) as for limited disease, given in 4–6 cycles also improves the survival of patients with extensive disease and is usually the most effective way to reduce clinical symptoms.

Second-line chemotherapy

Patients with relapse or progression from a response to first-line chemotherapy should be considered for second-line chemotherapy with an alternative regimen. In case of response duration of 3 months or more after the first-line treatment, reinduction with the initial chemotherapy should be considered.

Response evaluation

Response evaluation should be performed early (prior to the second cycle) because the lack of response requires pathological diagnosis verification and frequently an early change of treatment (alternative chemotherapy regimen or radiotherapy).

Follow-up

For patients with limited disease treated with curative intent history and physical examination including relevant radiological tests should be performed every three months during the first two years, every 6 months thereafter, and any time if clinically indicated. For patients with extensive disease, no evidence exists of active follow-up of asymptomatic patients (specific examinations when clinically indicated).

Smoking cessation counselling should be provided to all patients after primary treatment.

III. Pleural mesothelioma

Diagnosis

Patients typically present with chest pain and increasing shortness of breath. The diagnosis is usually suggested by imaging studies (unilateral pleural mass, pleural effusion). Occupational history must be obtained.

Thoracentesis or thoracoscopy (preferably video-assisted) with pleural biopsy is recommended to provide sufficient material for diagnosis (cytological examination of the pleural effusion is not advised, since it often shows equivocal results).

There are three main histological types – epithelioid, sarcomatoid and mixed – with about 60% being epithelioid. Light microscopy is often insufficient for differentiating between

Table 2. **The new international staging system for MPM**

Stage	TNM	Comments
Ia	T1aN0M0	Primary tumour limited to ipsilateral parietal pleura
Ib	T1dN0M0	Stage Ia plus focal involvement of visceral pleura
II	T2N0M0	Stage Ia or Ib plus confluent involvement of diaphragm or visceral pleura or involvement of the lung
III	Any T3M0	Locally advanced, potentially resectable tumour; ipsilateral bronchopulmonary or hilar lymph node involvement; subcarinal or ipsilateral mediastinal lymph node involvement
	Any N1M0	
	Any N2M0	
IV	Any T3	Locally advanced, technically unresectable tumour; contralateral mediastinal, internal mammary and ipsilateral or contralateral supraclavicular lymph node involvement; distant metastases
	Any N3	
	Any M1	

MPM and benign mesothelial disorders or metastatic tumours (predominantly adenocarcinoma). For this reason, immunohistochemistry or electron microscopy is frequently necessary to establish the diagnosis.

Chest X-ray and CT scan show pleural effusions, pleural thickening, pleural masses or tumour obliterating pleural cavity (19).

Staging and risk assessment

Staging includes history, complete physical examination and chest radiography examinations. If local therapy is being considered, a MRI of the chest and upper abdomen should be performed. Accurate initial staging is important as this will both provide prognostic information and suggest the most appropriate therapeutic options.

The new international staging system for MPM emphasizes the extent of disease in a traditional TNM system and stratifies patients into similar prognostic categories (see Table 2).

The Cancer and Leukemia Group B (CALGB) and the EORTC prognostic scores may be used. They include performance status, age, gender, histological type, weight loss, pleural fluid status, duration of symptoms prior to diagnosis, white blood count, and level.

MPM rarely metastasize to distant sites, and most patients present with a locally advanced disease.

Treatment

Surgery

Extra pleural pneumonectomy with excision of the diaphragm and the pericardium *en block* has the potential of a complete removal of tumor. An alternative surgical approach is pleurectomy with decortication. Both approaches produce similar results as single treatments.

Surgical resection cannot ensure microscopically negative surgical margins in the majority of patients. Therefore, many institutions recommend to combine surgical approach with chemotherapy and / or radiotherapy. Treatment of MPM should only be attempted by expert surgeons and chest oncology teams.

Palliative surgical procedures include parietal pleurectomy or pleurodesis.

Radiotherapy

The use of conventional radiotherapy is limited, because it is impossible to avoid high-dose irradiation of the underlying lung. A conventional dose can be delivered in a palliative attempt. Modern radiotherapy techniques can deliver high dose radiotherapy with curative intent after extrapleural pneumonectomy. Prophylactic radiotherapy has been shown to reduce the incidence of port metastases.

Chemotherapy

A combination of pemetrexed and cisplatin improves survival and quality of life in comparison with cisplatin alone as documented in a randomized phase III trial and therefore. Pemetrexed may be consideredas the first chemotherapeutic standard. Symptom improvement may also be obtained with gemcitabine in combination with cisplatin. Available data indicate a similar management for extrapleural malignant mesothelioma. Platinum analogues, doxorubicin and several antimetabolites (methotrexate, raltitrexate, pemetrexed) have shown a modest single agent activity.

Follow-up

The suggested follow-up includes routine clinical examination and chest radiograph tests**.**

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SMULKIŲJŲ IR NESMULKIŲJŲ LĄSTELIŲ PLAUČIŲ VĖŽIO IR PIKTYBINĖS PLEUROS MEZOTELIOMOS DIAGNOZAVIMO, GYDYMO IR STEBĖJIMO KLINIKINĖS REKOMENDACIJOS

S a n t r a u k a

Darbo esmė: pagerinti torakalinės onkologijos žinias bei įtvirtinti praktinius įgūdžius diagnozuojant, gydant ir stebinti ligonius, sergančius smulkiųjų, nesmulkiųjų ląstelių plaučių vėžiu ir piktybine pleuros mezotelioma.

Tikslai: padėti ligoniams, sergantiems piktybinėmis plaučių ligomis; pasidalyti konservatyvaus ir chirurginio krūtinės navikų gydymo patirtimi; parengti Europos Nemuno regiono šalims (Vokietija, Lenkija, Lietuva, Baltarusija) tinkančius gydymo algoritmus, smulkiųjų ir nesmulkiųjų ląstelių plaučių vėžio, piktybinės pleuros mezoteliomos klinikines rekomendacijas bei pagerinti tarptautinį mokslinį bendradarbiavimą tarp Vilniaus, Bialystoko, Gardino ir Manheimo universitetų.

Raktažodžiai: plaučių vėžys, piktybinė pleuros mezotelioma, diagnostikos ir gydymo rekomendacijos