Malignant Pleural Mesothelioma: Ethiology, Pathology and Diagnosis

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The **objective** of our work was to evaluate the incidence, ethiology, biology, classification and diagnostic methods of malignant pleural mesothelioma, a disease rare in Lithuania. The incidence rate of pleural mesothelioma in Lithuania among males in 1992–2001 was 3.5 cases (95% CI 2.5–4.4) and among females 1.7 cases per 1000000 (95% CI 0.9–2.4). **Materials and methods**. During the period 1992–2001, 125 cases of pleural mesothelioma were diagnosed in Lithuania. Various surgical diagnostic methods were used: videothoracoscopy in 35 (28.0%) cases, pleural biopsies in 72 (57.6%) cases, diagnostic "mini" thoracotomies in 18 (14.4%) cases. Conventional X-rays and ultrasound were used in 125 cases (100%), chest CT scans in 57 (45.6%), and chest X-ray and CT scans in 38 (30.4%) cases. In 5 cases (4.0%) we performed chest CT scans and MRI. Malignant pleural mesothelioma in all cases was proven morphologically. **Results**. We found in 38 cases (30.4%) epithelioid, in 47 (37.6%) sarcomatoid and in 40 (32.0%) cases biphasic mesotheliomas. The patients' distribution according to the to stage of the disease was as follows: stage I in 12 cases (9.6%), stage II in 29 (23.2%) cases, stage III – 52 (41.6%) cases and stage IV in 32 (25.6%) cases. **Conclusions.** 1. The incidence of pleural mesothelioma among males was 3.5 cases and among females 1.7 cases per 1000000, and there is no clear relation between asbestos consumption and the incidence rate in Lithuania. 2. There is no main histologic type of MPM in Lithuania: 38 (30.4%) epithelioid, 47 (37.6%) sarcomatoid and in 40 (32.0%) cases of biphasic mesotheliomas were found. 3) Most patients arrive with the advanced stages of the disease (III – 52 (41.6%), IV – 32 (25.6%)), and effective treatment is not possible for them. 4. The main diagnostic methods are ultrasound, X-ray, CT, MRI, videothoracoscopy, pleural biopsies and "mini" thoracotomies.

Key words: malignant pleural mesothelioma, diagnosis, incidence, ethiology, pathology

INTRODUCTION

The history of malignant mesothelioma is relatively short. The existence of primary tumours of the serous membranes has been proven in the 20s and 30s of the 20th century. It was not before the 60s that a considerable number of mesotheliomas has been documented, especially in cohorts of workers with histories of heavy asbestos exposure. The reliability of the diagnoses at that time was not as high as today, because of the lack of immunohistochemical analyses, which have been introduced in the mid-80s and considerably improved since the mid-90s.

Pleural mesotheliomas are much more common than peritoneal ones (pleura : peritoneum about 10 : : 1). Primary pericardial localisation accounts for about 1% of all mesotheliomas, and the tunica vaginalis testis is a very rare primary localization. Secondary pleural tumours are about 100 times more frequent than primary (1). Men are affected much more frequently than women, and the most common age of onset is the 6th decade.

The most important etiologic agent is still asbestos. The latency periods between the exposure and the onset of mesothelioma symptoms is about 30 years on average, but can range between about 10 and more than 50 years in single cases. All commercially used asbestos types can induce mesotheliomas (2).

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Major types of asbestos:

1. Crocidolite. It is also known as blue asbestos. It is used mainly as a reinforcing agent for binding with cement, rubber and plastics, friction materials (brake linings), packing and joining products.

2. Chrysotile. Chrysotile is also called white asbestos, although the fibers are pale green. It is more suitable for spinning and weaving and is more heat-resistant than other asbestos fibers, so it is used mainly as a fire-resistant and insulator material.

3. Amosite. It is a pale, silvery fibrous mineral. It is also called brown asbestos.

Asbestos and mesothelioma

In 1960 – Wagner reported the link between asbestos and mesothelioma as described above (3).

The incidence in South Africa is amongst the highest anywhere. It is 6 × higher than in England and at least as high as in Western Australia. The male : female ratio is 2.5 : 1.

The mining industry – if we remove the unknown and no exposures, mining-related exposures represent 40% of those mesotheliomas for which exposure is known.

Secondary industry. Three major occupations at risk stand out:

1) the maitenance of steam locomotive and other railway-related procedures,

2) the asbestos cement industry,

3) boilermakers and other artisans who use asbestos for insulation applications.

Some regions are characterized by natural outcrops of asbestos or asbestos-like minerals that may exert an effect on the health of local dwellers.

A high proportion (26%) of mesothelioma in patients in South Africa is attributed to environmental origin, particularly in the Northern Cape area.

Similar observations have been made in Corsica (North-Eastern part), Cyprus, Greece (North-Western part), Turkey (notably in Cappadocian region of Central Anatolia).

Incidence of pleural mesothelioma in Lithuania

During the period 1992–2001, 125 cases of pleural mesothelioma were diagnosed in Lithuania. The incidence rate among males was 3.5 cases per 1000000 (95% CI 2.5–4.4) and among females 1.7 cases per 1000000 (95% CI 0.9–2.4). No differences were found for the incidence rates in 1992–1997 and in 1997–2001. The incidence rates showed a geographical variation (RR from 4.5, 95% CI 3.7–5.5 in Kupiskis to 0.4, 95% CI 0.2–0.7 in Skuodas) (Fig. 3). For males, in urban population the incidence was somewhat higher than in rural (RR = 1.2 95% CI 0.8–1.6 and RR = 0.8, 95% CI 0.5–1.1) (Table 1); in female mesothelioma incidence rates no differences were found (RR = 0.9, 95% CI 0.5–1.5 and RR = 1.1, 95% CI 0.6–1.7) (Fig. 2).

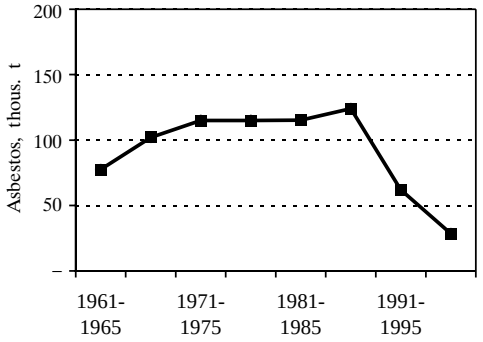

Fig. 1. Dynamics of asbestos stock usage in Lithuania

Table 1. **Incidence rate of pleural mesothelioma and CI according to place of residence**

Place ofresidence	Incidence rate (RR)	
	Males	Females
Town	1.2 (0.8–1.6)	0.9 (0.5–1.5)
Village	0.8 (0.5–1.1)	1.1 (0.6–1.7)

Using the Statistic Department data, assessing import and export, there were used more than 700 thousant tons of asbestos stock in Lithuania. (Fig. 1). It was only white asbestos (chryzotile) from Russia and Kazakhstan.

Pleural mesothelioma incidence rates for 1992–2001 are shown in Fig. 2. The differences in incidence rates between males and females were small; only in the first year of the study period we saw a higher incidence in males than in females. No differences were found in the incidence rates of the later years.

The incidence rates of pleural mesothelioma of Lithuanian towns is shown in the map for both genders together (Fig. 3).

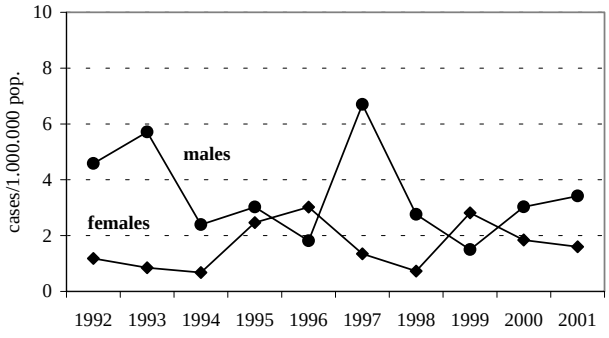

Fig. 2. Incidence rates of pleural mesothelioma in Lithuania in 1992–2001

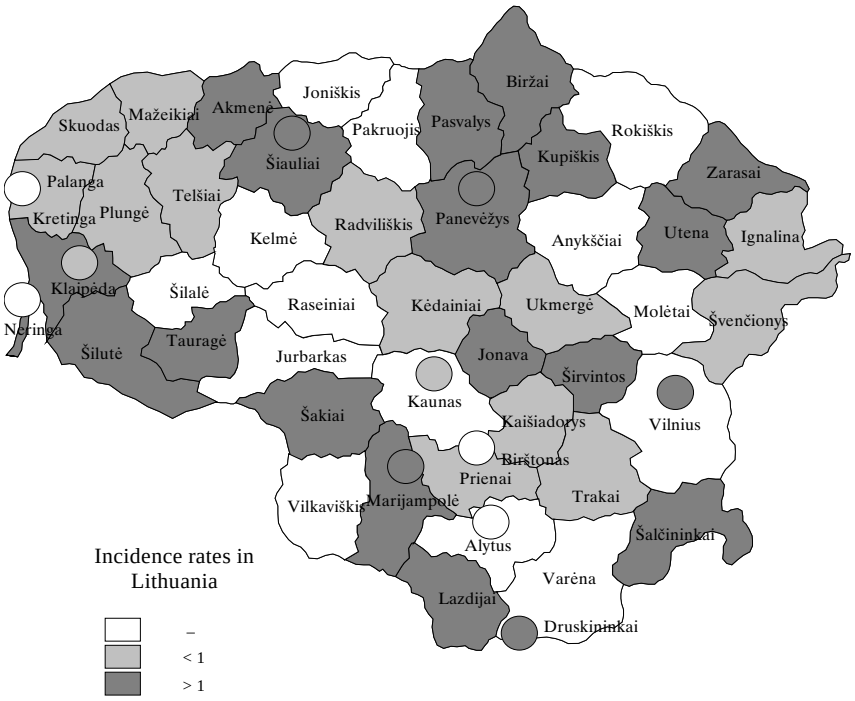

Fig. 3. Incidence rate of pleural mesothelioma in Lithuania, 1992–2001 (there were no malignant pleural mesothelioma cases in districts marked with white color)

The incidence of mesothelioma was higher in Šiauliai and Akmenė districts (where 80% of raw asbestos imported in Lithuania are used) than in the whole country (RR = 2.7, 95% CI 2.1–3.4, and RR = 1.7, 95% CI 1.2–2.3). For the period 1992–2001 there were 7 cases of mesothelioma in total for both sexes in these districts, and only one patient had been employed at one of the asbestos-cement factories.

We overview the main diagnostic techniques of malignant pleural mesothelioma, the possibilities of their usage in Lithuania.

PATHOLOGY, TUMOR BIOLOGY OF MESOTHELIOMA

Pathogenesis

The exact mechanisms of mesothelioma pathogenesis are unknown. Like in other malignant tumours, many genetic alterations seem to be involved in mesothelioma initiation and progression. An involvement of the oncogenes *myc* (myelocytomatosis virus family), *ras* (rat sarcoma virus), *raf* (RAS activated fragment) and *met* (N-methyl-N'-nitroso-guanidin treated human osteosarcoma cell line) have been discussed. The detected losses on chromosome arms and gains on chromosomes can also be found in many other solid tumours, so there was no specific alteration attributable only to mesotheliomas. On the other hand, the combination of chromosomal alterations is somewhat characteristic of mesotheliomas, with statistically significant differences between epithelioid and sarcomatoid mesotheliomas (4). A negative correlation has been found between gains on chromosome 7p and survival. Oncogenes as ERB-B1 (Erythroblastomatosis virus) and multidrug-resistance gene (p-glycoprotein gene) have been suspected to be involved (5).

Histology

The spectrum of conventional histological findings is exstremely broad, ranging from well-differentiated papillary epithelioid to undifferentiated mesothelioma with multiple giant cells. In the WHO Blue Book on lung and pleural tumours (6), no recommendation for the tumour grading for mesotheliomas are given, and only three ICDO-numbers for malignant mesothelioma subtypes do exist (ICDO 9051/3-9053/3): predominantly epithelioid, sarcomatoid, and biphasic mesotheliomas. Beside these three main histological patterns, some variants exist: the low cellular desmoplastic mesothelioma with high amounts of fibers, well differentiated peritoneal mesothelioma, the small cell mesothelioma variant, the deciduoid variant of peritoneal mesothelioma, a rare pleural mesothelioma subtype, showing unusual mesodermal components (mesodermoma).

The diagnosis of mesothelioma has to be validated. Because of the diagnostic uncertainty in some cases, the former European Mesothelioma Panel presented a classification for the diagnostic certainty of mesotheliomas in 1993 (7), which is still valid. The categories are: A – certain, B – probable, C – possible mesothelioma, D – probably no and E – definitely no mesothelioma. For medicolegal purposes, in Germany the categories A and B are diagnostically sufficient for mesothelioma diganosis.

MATERIALS AND METHODS

Staging of mesothelioma

In 1997, the International Mesothelioma Interest Group (IMIG) was formed and met at the Tri-Annual Meeting of the International Association for the Stu-

dy of Lung Cancer, IASLC (Colorado Springs, 1997). A staging system had been devised by several of the members and was approved by the group at that time. The staging system is quite complex, reflecting the complex presentation and modes of spread of this unique neoplasm. The two most important purposes of the classification were to:

1. Separate out that relatively small group of patients with early MPM who may be potentially curable by aggressive surgical means.

2. To distinguish between later stage presentations of MPM, which are still at a resectable stage, and late MPM, which is unresectable and therefore must be treated with radiation and/or chemotherapy.

International Mesothelioma Interest Group Staging for Diffuse Malignant Pleural Mesothelioma

T = Tumor

T1a Tumor limited to the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura. No involvement of the visceral pleura.

T1b Tumor involving the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura. Scattered foci of tumor also involving the visceral pleura.

T2 Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura), with at least one of the following features:
– involvement of the diaphragmatic surface
– confluent visceral pleural tumor (including the fissures), or exstension of tumor from visceral pleura into the underlying pulmonary parenchyma

T3 Describes locally advanced but potentially resectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura), with at least one of the following features:
– involvement of the endothoracic fascia
– extension into the mediastinal fat
– solitary, completely resectable focus of tumor, extending into the soft tissues of the chest wall
– nontransmural involvement of the pericardium

T4 Describes locally advanced technically unresectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral), with at least one of the following features:
– diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction
– direct transdiaphragmatic extension of tumor to the peritoneum
– direct extension of tumor to the contralateral pleura
– direct extension of tumor to one or more mediastinal organs
– direct extension of tumor into the spine
– tomor extending through to the internal surface of the pericardium with or without a pericardial effusion; or tumor involving the myocardium

N = Lymph nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastases
N1 Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes
N2 Metastases in the subcarinal or ipsilateral mediastinal lymph nodes, including the ipsilateral internal mammary nodes
N3 Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes

M= Metastases

MX Presence of distant metastases cannot be assessed
M0 No distant metastasis
M1 Distant metastasis present

A relation between the above-mentioned IMIG staging and TNM classification is shown in Table 2.

During the period 1992–2001, in Lithuania 125 cases of pleural mesothelioma were diagnosed.

We used the following non-invasive diagnostic methods: conventional X-ray and ultrasound were used in 125 cases (100%), chest CT scans in 57 (45.6%), and chest X-ray and CT scans in 38 (30.4%) cases. In 5 cases (4.0%) we performed chest CT scans and MRI (Table 3).

Table 2. **Relation between IMIG staging and TNM classification for malignant pleural mesothelioma**

I	T1, N0, M0 T2, N0, M0
II	T1, N1, M0 T2, N1, M0
III	T3, N0, M0 T3, N1, M0 T1, N2, M0 T2, N2, M0 T3, N2, M0
IV	Any T, N3, M0 T4, any N, M0 Any T, any N, M1

Table 3. **Non-invasive diagnostic methods**	
Diagnostic method(s)	Cases (%)
X-ray + ultrasound	125 (100%)
CT	57 (45.6%)
X-ray + CT	38 (30.4%)
CT + MRI	5 (4.0%)

Table 4. **Surgical diagnostic methods**	
Diagnostic method(s)	Cases (%)
Videothoracoscopy	35 (28.0%)
Pleural biopsies	72 (57.6%)
"Mini"thoracotomies	18 (14.4%)

Pleural malignant mesothelioma in all cases was proved morphologically. Various surgical diagnostic methods were used: videothoracoscopy in 35 (28.0%) cases, pleural biopsies in 72 (57.6%) cases, and diagnostic "mini" thoracotomies in 18 (14.4%) cases. (Table 4).

RESULTS

We found in 38 cases (30.4%) epithelioid, in 47 (37.6%) sarcomatoid and in 40 (32.0%) cases biphasic mesotheliomas. (Table 5).

The patients' distribution due according to stage of the disease is shown in Table 6.

We overview below the main **diagnostic techniques** of malignant pleural mesothelioma, the possibilities of their usage in Lithuania.

Table 5. **Morphology of malignant mesothelioma**	
Morphology	Cases (%)
Epithelioid	38 (30.4%)
Sarcomatoid	47 (37.6%)
Biphasic	40 (32.0%)

Table 6. **Patients' distribution according to the stage of the disease**	
Stage of disease	Cases (%)
I	12 (9.6%)
II	29 (23.2%)
III	52 (41.6%)
IV	32 (25.6%)

Transthoracic ultrasound (US)

The sonographic diagnostics of the chest is limited by its bony delimitation (ribs, spinal column, sternum, clavicula) and the gas content of the lung. The normal lung cannot be judged. In pleural pathological processes ultrasound is however surprisingly expressive. Morbid modifications can be detected, if they have proceeded to the chest wall, the diaphragm or the upper chest apperture.

The Use of Magnetic Resonance Imaging in Malignant Mesothelioma

Magnetic resonance imaging (MRI) with its multiplanar capabilities has a limited role but is used in assessing patients for radical surgery. It has a role in differentiating benign *versus* malignant pleural disease and may also be used in the evaluation of patients with mesothelioma following surgical treatment and chemotherapy.

Mediastinal pleural involvement, circumferential pleural thickening, nodularity, irregularity of pleural contour, and infiltration of the chest wall/or diaphragm are suggestive of malignant pleural disease. Metastatic pleural disease may appear identical to MPM and there is no reliable way to differentiate the histology. Using morphological features in conjunction with signal intensity features Hierholzer er al. (8) found that MRI had a sensitivity of 100% and a specificity of 93% in the detection of malignant pleural disease.

There are several main imaging methods: CT, contrast enhanced (CE) CT, MRI and CE MRI. CE MRI is more accurate than unenhanced MRI alone.

Positron emission tomography in the diagnosis of mesothelioma

FDG-PET imaging in oncology is based on changes in metabolic pathways of glucose. For the glucose metabolism, three key enzymes for glycolysis (glucokinase, phosphofructokinase, pyruvate kinase) and four key enzymes for gluconeogenesis (glucose-6-phosphatase, fructose-1,6,-diphosphatase, phosphoenolpyruvate carboxykinase, pyruvate carboxylase) were identified. The velocity and direction of these opposite metabolic pathways are determined by the amount and the activity of these enzymes. In tumors glycolytic enzymes are upregulated, whereas the gluconeogenetic enzymes are downregulated. These changes are coupled to the progression of tumor development.

Possible applications of PET for the imaging of mesothelioma are to detect and stage the extent, to differentiate malignant and benign lesions in patients with asbestos exposure who present with an atypical diffuse pleural thickening or pleural effusion with a

normal CT scan, assessment of disease progression, and evaluation of disease response to treatment.

DISCUSSION

The main diagnostic methods of malignant pleural mesothelioma are X-ray, CT, transthoracic ultrasound, MRI, PET, thoracoscopy. Some of them are more or less common in Lithuania (X-ray, CT, somewhere MRI), and are in use for diagnosing malignant pleural mesothelioma. Ultrasound is one of the most common diagnostic methods, but not so popular for diagnosing pleural mesothelioma, maybe due to a low incidence of this disease. Positron emission tomography is inaccessible in Lithuania – there is no such devices here.

In our experience the most common methods allowed us to suggest malignant pleural mesothelioma were x-ray and CT. And the main information was accepted from morphological diagnosis verification by taking biopsy or removing part or whole pleura by thoracoscopy or open thoracotomy.

We believe that our description of the diagnostic methods will allow more doctors in Lithuania to suspect or diagnose malignant pleural mesotheliomas.

CONCLUSIONS

1. Incidence of pleural mesothelioma among males was 3.5 cases (95% CI 2.5–4.4) and among females 1.7 cases per 1000000 (95% CI 0.9–2.4)), and there is no clear relation between asbestos consumption and incidence rate in Lithuania.

2. There is no main histological type of MPM in Lithuania: 38 (30.4%) epithelioid, 47 (37.6%) sarcomatoid and in 40 (32.0%) cases of biphasic mesotheliomas were found.

3. Most patients arrive with a late stage of disease (I – 12 (9.6%), II – 29 (23.2%), III – 52 (41.6%), IV – 32 (25.6%)), and no effective treatment is possible for them.

4. The main diagnostic methods are: ultrasound, x-ray, CT, MRI, videothoracoscopy, pleural biopsies and “mini” thoracotomies.

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PIKTYBINĖ PLEUROS MEZOTELIOMA: ETIOLOGIJA, PATOLOGIJA IR DIAGNOSTIKA

S a n t r a u k a

Šio darbo **tikslas** – įvertinti Lietuvoje retos ligos – piktybinės pleuros mezoteliomos – sergamumą, etiologiją, biologiją, klasifikaciją ir diagnostikos metodus. Standartizuoti sergamumo pleuros mezotelioma rodikliai Lietuvoje 1992–2001 metais vyrams buvo 3,5 atv./1000000 (PI 95% 2,5–4,4) ir moterų – 1,7 atv./1000000 gyventojų (PI 95% 0,9–2,4). Darbo medžiaga ir metodai. 1992–2001 m. Lietuvoje diagnozuoti 125 pleuros mezoteliomos atvejai. Buvo naudoti įvairūs chirurginiai diagnostikos metodai: 35 atvejais (28,0%) videotorakoskopija, 72 atvejais (57,6%) pleuros biopsijos, 18 atvejais (14,4%) diagnostinės “mini” torakotomijos. Įprastiniai rentgenologiniai ir ultragarsiniai tyrimai naudoti visais 125 atvejais (100%), krūtinės ląstos kompiuterinės tomografijos (KT) skenavimas – 57 atvejais (45,6%) bei krūtinės ląstos rentgenologinis ir KT skenavimas – 38 atvejais (30,4%). Penkiais atvejais (4,0%) atlikome krūtinės ląstos KT skenavimą ir branduolinio magnetinio rezonanaso (BMR) tyrimus. Piktybinė pleuros mezotelioma visais atvejais buvo įrodyta morfologiškai. **Rezultatai**. 38 atvejais (30,4%) diagnozavome epitelioidinę, 47 (37,6%) sarkomatoidinę ir 40 (32,0%) atvejų – dvifazę mezoteliomą. Pagal ligos stadijas ligoniai pasiskirstė: I stadija – 12 atvejų (9,6%), II stadija – 29 atvejai (23,2%), III stadija – 52 atvejais (41,6%) ir IV stadija – 32 atvejai (25,6 %). **Išvados.** 1. Vyrų sergamumas pleuros mezotelioma buvo 3,5 atv. 1000000 gyventojų ir moterų – 1,7 atv. 1000000 gyventojų. Nenustatėme aiškios priklausomybės tarp asbesto naudojimo ir sergamumo rodiklių Lietuvoje. 2. Lietuvoje nėra vyraujančio piktybinės pleuros mezoteliomos histologinio tipo, rasta 38 (30,4%) epitelioidinės, 47 (37,6%) sarkomatoidinės ir 40 (32,0%) dvifazės mezoteliomos atvejų. 3. Daugumai ligonių nustatėme pažengusią ligos stadiją (III st. – 52 ligoniai (41,6%), IV st. – 32 ligoniai (25,6%)). 4. Pagrindiniai diagnostiniai metodai: ultragarsinis bei rentgenologinis tyrimas, KT, BMR, videotorakoskopija, pleuros biopsijos ir “mini” torakotomijos.