

# Advancement in the Mesothelioma Diagnostics in Primorsko-Goranska County of Croatia

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## ABSTRACT

*The purpose is to find out whether the diagnostics and registration of patients with mesothelioma in the Littoral – Mountainous County of Croatia corresponds to the world trends. Further, the intention was to show the incidence of the disease and suggest the measures of prevention in the county of 400.000 inhabitants and its center Rijeka with 140.000 people. To that purpose 43 patients with mesothelioma were monitored in two groups: 25 shipyard workers, mean age 66, and 18 workers in other occupations, mean age 62. Statistically the group did not differ significantly in the incidence of plaques, left or right side effusion. The pleural puncture showed the significance ( $p < 0.05$ ) for incidence of rouse cells. In 20 patients out of 43 mesothelioma was confirmed by taking the material for pathohistology by means of VATS (video assisted thoracoscopy) and in 14 patients by TTB (transthoracic biopsy) with CT control. Spirometric values showed moderate restrictive difficulties. Although a considerable improvement in diagnosing mesothelioma has been achieved in the last five years an improved prevention activity by occupational medicine is required not only by periodic checkups of the exposed persons and examinations for retired workers with respiratory difficulties, but also by stimulating work case histories.*

**Key words:** mesothelioma, occupational medicine, prevention, video assisted thoracoscopy, transthoracic biopsy

## Introduction

Malignant mesothelioma distinct from metastasising carcinoma is a relatively rare pleural tumour<sup>1</sup>. It is most frequent in the form of multiple nodules or diffuse tumour<sup>2</sup>. Histologically, epitheloid (40–60%), sarcomatoid (20–30%) and biphasic mesothelioma are to be distinguished<sup>3</sup>. Although carcinogenic action of inhaled asbestos fibre is considered the cause of mesothelioma, the new research finds only the ultra – thin fractions of such fibre in diameter 0.2 micrometers and length of only a few micrometers to cause mesothelioma<sup>4</sup>. The mesothelioma patients usually have a work-related exposition, though in some cases also viral infection by SV 40 virus is mentioned<sup>5</sup>. The resulting changes such as pleural thickening, unilateral pleural effusion and tumour invasion on adjoining structures are monitored by modern CT apparatus<sup>6–8</sup>. Besides CT, MR (magnetic resonance) and fluorodeoxyglucosae positron emission tomography (PET)

are becoming useful diagnostic methods in distinguishing safely diffuse pleural thickening (DTP) from mesothelioma, as well as in locating distant metastases<sup>9</sup>. For all the use of the mentioned modern apparatus a diagnosis is the safest if pathohistologically confirmed. There are nowadays established immunohistochemical markers such as calretinin, WT-1, cytokeratin and thrombomodulin, and on the other hand the so-called negative markers CEA and CD 15 that differentiate mesothelioma from adenocarcinoma<sup>10,11</sup>. Immunomarkers are of great help to the pathologist as benign tumours of reactive proliferation and malignant mesothelioma may imitate one another<sup>12</sup>. Pathologists are also agreed on another mesothelioma characteristic: an early infiltrative growth, that is invasion on adjoining structures<sup>13,14</sup>. In asbestosis the asbestos burden is defined as the number of asbestos bodies or the number of asbestos fibre found in the tissue<sup>15</sup>.

Contrary to asbestosis, in mesothelioma the cases of finding malignant cells in sputum are rare since mesothelioma seldom invades bronchial lamina<sup>16</sup>. Mesothelioma may also occur as primary tumour of peritoneum, and it may metastasise into various organs as breast or seldom into distant organs such as liver<sup>17,18</sup>. It does not metastasise into distant organs for the illness is soon terminal. Nowadays the median survival period is 12 months<sup>19</sup>. Surgical resection, radiotherapy and chemotherapy are the established guidelines in treating mesothelioma<sup>20</sup>.

This research intends to survey the situation regarding diagnosing malignant mesothelioma in the Littoral – Mountainous County of Croatia, its registration, comprehensiveness of health control, monitoring and treatment in relation to the contemporary world trends.

## Material and Methods

### Examinees

The data shown refer to 43 patients with diagnosed mesothelioma who in the five-year period (2003–2008)

passed through Department of Pulmology, Clinical Hospital Center Rijeka, Littoral – Mountainous County, Croatia.

On the basis of the work – related exposition they were monitored in two groups: the mesothelioma patients who used to work in the shipyards in Rijeka or in other yards along the Adriatic coast, and the second group that was not directly connected to jobs in shipyards. Most of them are retired.

### Shipyards workers

The group of ex shipyard workers numbers 25 people. Their mean age was 66 (range 52–82). The mean height was 173 cm (range 165–187), the mean weight was 75 kg (54–95 range), that is the mean BMI 24 (range 18–33).

### Workers employed on other jobs

This group consisted of 18 workers. Their mean age was 62 (range 51–76). The mean height was 173 cm (range 164–189), the mean weight was 79 kg (range 64–110), that is the mean BMI 25 (range 23–32).

TABLE 1  
OCCURENCE OF MESOTHELIOMA IN SHIPYARD, LITTORAL-MOUNTAINOUS COUNTY

No	Sex	Age	Pleural placs	PH-VATS	PH-TTB	PP-ml. cell	PP-rouse cell	PP- Ery,Ly	L. eff.	R. eff.
1	M	60	1	0	0	0	0	0	0	1
2	M	67	1	0	1	1	0	0	0	1
3	M	82	1	0	1	0	0	0	0	1
4	M	53	1	1	0	0	0	0	0	1
5	M	66	0	0	1	1	0	0	1	0
6	M	79	1	0	0	0	0	0	0	1
7	M	75	1	0	0	0	0	0	0	1
8	M	70	1	0	1	0	0	0	1	0
9	M	77	1	0	0	0	0	0	0	1
10	M	64	1	1	0	0	1	0	1	0
11	M	71	1	1	0	0	0	0	0	1
12	M	53	1	1	0	0	0	1	1	0
13	M	76	0	1	0	0	1	0	1	0
14	M	74	1	1	0	1	0	0	0	1
15	M	58	0	1	0	0	0	0	0	1
16	M	60	1	0	1	1	0	0	0	1
17	M	63	1	1	0	0	0	1	1	0
18	M	74	0	1	0	1	0	0	0	1
19	M	81	1	0	1	0	0	0	1	0
20	M	65	0	0	1	0	0	0	0	1
21	M	57	1	1	0	0	0	0	0	1
22	M	60	1	1	0	1	0	0	1	0
23	M	70	1	0	1	0	0	0	1	0
24	M	53	1	1	0	1	0	0	0	1
25	M	52	1	1	0	0	0	1	0	1

PH-VATS – example taken for pathohistology by video assisted thoracoscopy; PH – TTB – example taken for pathohistology by trans-thoracic biopsy; PP – ml cell – malignant cells received by pleural puncture; PP – rouse cell – rouse cells received; PP – Ery, Ly-erythrocytes and lymphocytes received by pleural puncture; L. eff. – left; R. eff. – right pulmonal effusion

## Methods

The research was approved by Ethical Committee of School of Medicine, University of Rijeka, Class NO 641-01/09-01/04, Office NO 2170-24-01-3-09-01, February 9<sup>th</sup> 2009.

In 34 patients out of 43 the diagnosis was confirmed histopathologically. In 20 patients the histopathology findings was confirmed by VATS (video-assisted thoracoscopy), and in 14 patients by TTB (transthoracic biopsy).

VATS is an operation performed in thoracal surgery. A resection is performed in order to enable an unobstructed approach to the tumour formation so as to take the tissue for pathohistologic analysis by means of biopsy. An endoscope is introduced to reach the targeted spot.

TTB is by far an easier test for the patient under local anaesthesia. The patient usually lies on his belly or by side, so needle biopsy is performed dorsally or by side for cyto analysis or tissue analysis<sup>21-23</sup>. The radiologist sets the needle and directs it under CT control to the wanted spot. For these tests MSCT 16 Siemens apparatus is used at the Department of Radiology of University Hospital Center Rijeka.

## Results

### Shipyard workers

By VATS operative technique assisted by the endoscope, the material was obtained in 13 patients for pathohistologic analysis, which was positively confirmed.

By TTB method, method of CT guided needle biopsy, the material was obtained in 8 patients, positively confirmed by the pathohistology laboratory (Table 1).

The patients, former shipyard workers, were submitted to spirometric examination. The FVC (forced vital capacity) obtained spirometrically by the spirometer MIR 1, showed the mean value 57% (29–83 range). FEV1 (forced expiratory volume in first second) averaged 60% (33–97 range), and the Tiffenau index (FEV1/FVC) had the median value of 107% (85–133 range). FEF 50% (forced expiratory flow at 50% FVC) averaged 56% (29–95 range).

### Workers in other occupations

By VATS operative technique assisted by the endoscope the material was obtained in 7 patients for pathohistologic analysis, which was positively confirmed.

By TTB method, method of CT guided needle biopsy, the material was obtained in 6 patients, positively confirmed by the pathohistology laboratory (Table 2).

Also this group was submitted to spirometric testing.

FVC (forced vital capacity), which was obtained by spirometric examination by the spirometer MIR 1, averaged 58% (27–82 range). FEV1 (forced expiratory volume in first second) averaged 61% (30–89 range), and the Tiffenau index (FEV1/FVC) had the median value 107% (92–121 range). FEF 50% (forced expiratory flow at 50% FVC) averaged 54% (28–93 range).

TABLE 2  
OCCURRENCE OF MESOTHELIOMA IN OTHER OCCUPATIONS, LITTORAL-MOUNTAINOUS COUNTY

No	Sex	Age	Pleural placs	PH-VATS	PH-TTB	PP-ml. cell	PP-rouse cell	PP- Ery,Ly	L.eff.	R.eff.
1	M	64	1	1	0	0	1	0	0	1
2	M	69	1	0	0	0	1	0	0	1
3	M	64	0	0	1	0	1	0	1	0
4	M	56	1	0	0	0	0	0	1	0
5	M	59	1	0	1	0	1	0	0	1
6	M	63	0	0	0	0	1	0	0	1
7	F	68	1	0	0	0	1	0	0	1
8	M	62	1	0	1	0	0	1	0	1
9	M	61	1	1	0	0	0	1	1	0
10	M	59	1	1	0	0	0	1	0	1
11	M	56	1	0	0	0	1	0	0	1
12	M	57	0	1	0	0	0	0	0	1
13	F	69	1	0	1	1	0	0	1	0
14	M	56	1	1	0	1	0	0	1	0
15	M	74	1	1	0	0	0	0	0	1
16	M	51	0	0	1	0	0	0	1	0
17	M	56	1	1	0	0	0	0	0	1
18	M	76	1	0	1	0	0	0	0	1

PH-VATS – example taken for pathohistological analysis by video assisted thoracoscopy; PH –TTB – example taken for pathohistological analysis by transthoracic biopsy; PP – ml cell – malignant cells received by pleural puncture; PP – rouse cell – rouse cells received; PP – Ery, Ly – erythrocytes and lymphocytes received by pleural puncture; L. eff. – left pulmonic effusion; R. eff. – right pulmonic effusion

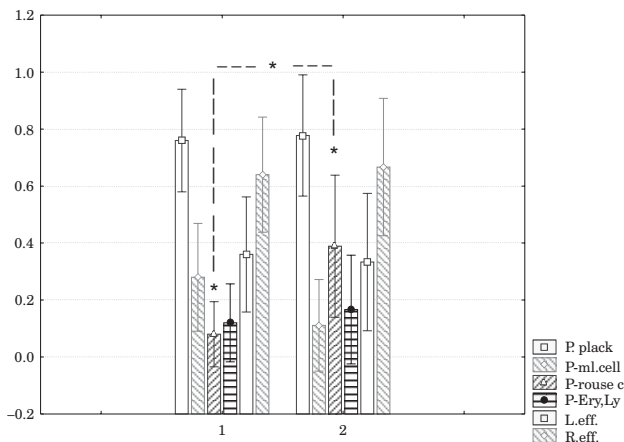


Fig. 1. Comparison of two groups of examinees. There are significant statistical differences between frequencies of rouse cells received by pleural puncture from the shipyard workers and the workers in other occupations,  $p < 0.05$ . P. plack, pleural placks, P.-ml.cell, malignant cells received by pleural puncture, P.-rouse c, rouse cells received by pleural puncture, P.-Ery,Ly, erythrocytes and lymphocytes received by pleural puncture, L.eff., left effusion, R.eff., right effusion.

The list specifying occupation of patients employed in other jobs is shown in Table 3.

FVC (forced vital capacity), considerably diminished compared to the normal values, shows negative correlation in relation to the age, correlation  $r = -0.635$ .

Both groups of patients had a similar effusion in the left and the right side of the lungs. They did not differ

statistically significantly in the incidence of pleural placks either. The patients differed significantly in the results of routine pleural puncture (performed for effusion elimination or reduction) for rouse cell (Figure 1).

Axial CT scan in the course of diffuse form of pleural malignant mesothelioma needle biopsy, is shown on Figure 2.

Solitary form of pleural malignant mesothelioma is shown during percutaneous CT-guided needle biopsy (Figure 3).

### Discussion

It is hard to say whether the number of 43 diagnosed mesothelioma in the last 5 years in the Littoral – Mountainous County of Croatia is a high or a small number. Namely, the county center – the town of Rijeka has a population of about 140.000 and the whole county about 400.000. The main industry is shipbuilding and many occupations are connected with it and with the sea. Fishermen spend a greater part of their working life on boat, engineers test engines after they are built into a ship, locksmiths install various metal parts etc. Some of occupations may not be connected with shipbuilding but environmental impact can be noticed. Our county is very much like the Province of Trieste, which is larger, and the number of registered illnesses is higher<sup>24</sup>. It is known that latency, the time from the first exposure to the sickness incidence, for mesothelioma is mainly 30–40 years<sup>25</sup>. As the mean age was 66, i.e. 62 for the patients in question, that is the time that just corresponds to the latest period. There is no exact record of the work exposition, that is of the patients' overall years of service, but it can be worked out approximately on the basis of the patient's age at the time of the illness incidence. The why the relevant data are lacking is that the monitoring began 5 years ago, as well as diagnosing the illness by up-to-date



Fig. 2. Percutaneous CT-guided needle biopsy (TTB). Axial CT scan in the course of diffuse form of pleural malignant mesothelioma.



Fig. 3. Percutaneous CT-guided needle biopsy (TTB). Axial CT scan in the course of solitary form of pleural malignant mesothelioma.

**TABLE 3**  
THE PATIENTS' DATA ACCORDING TO THE OCCUPATION

N0	Sex	Age	Occupation
1	M	64	Worker in crude oil manufacturing (retired)
2	M	69	Carpenter (retired)
3	M	64	Carpenter (retired)
4	M	56	Engine technician
5	M	59	Upholsterer (retired)
6	M	63	Upholsterer (retired)
7	F	68	Housewife
8	M	62	Fire-fighter (retired)
9	M	61	Engine technician (retired)
10	M	59	Housekeeper (retired)
11	M	56	Housekeeper
12	M	57	Fisherman
13	F	69	Housewife
14	M	56	Plumber
15	M	74	Painter (retired)
16	M	51	Locksmith
17	M	56	Fisherman
18	M	76	Housekeeper (retired)

Different working places with different occupations of the patients directly or indirectly exposed to asbestos

means, i.e. with pathohistologic verification of the material obtained by VATS or with TTB. The patients admitted to the Department of Pulmology arrived in a very bad condition, complaining of severe chest pain and dyspnoea. Five years ago the Clinical Institute for Radiology introduced CT – guided TTB taking of material for pathohistology analysis and parallelly the VATS diagnosing was begun. The patients did not even come to the occupational medicine as they were mainly retired workers that went directly to hospital because of severe respiratory difficulties. But from the beginning of 2008 the things changed considerably so that workers as well as the retired ones in respective industries with any respiratory difficulties are publicly invited to report to the occupational medicine. High financial indemnities (retrogradely) have been allotted by the government in cooperation with the Institute for patients with asbestosis and indemnities for the families of those that died of mesothelioma as well as the free treatment. Standard questionnaires for verification of the mentioned diagnoses should be introduced like those used by European Occupational Medicine services<sup>26</sup>. Occupational medicine besides Pulmology, radiology, surgery and oncology is an unavoidable branch of medicine in integrating diagnostics and all the data, primarily taking a correct case history, which was inadequate up to now. In such diagnoses

case histories should go back 3–4 decades, which is a problem, but there are always exceptions to the rule, since there are some very young people with mesothelioma<sup>27</sup>.

Occupational medicine in Croatia has taken the leading role in preventing damages in people professionally exposed to ionising radiation<sup>28</sup>. Considering prevention of mesothelioma the situation is different because for years in future there will be people with new diagnoses that were exposed to unallowable concentration of asbestos in the course of their working life. In shipyards that are not repairing yards, i.e. where new ships are built, in our county asbestos raw material has not been used for 20-odd years.

It is not only shipbuilding that originates mesothelioma. Construction, contacts with minerals like crocidolite, crizotyl, cause lung and pleural diseases.

A surgical pathologist's experience is important in distinguishing benign hiperplasya from mesothelioma<sup>29</sup>. Namely, every thickening is not mesothelioma<sup>30,31</sup>. But many pleural thickenings such weakening of lung functions that life is impossible.

Nevertheless, in the so-called »dangerous industries« various professional lung diseases have been described but with no case of mesothelioma<sup>32</sup>. It means that the majority of people never get mesothelioma regardless of a long professional exposition.

Among the diseased in our county there are two women. In one of them the work-related cause cannot be determined so a house pattern is supposed (the wall material in the apartment, the stove) and the other one used to live in the vicinity of a shipyard (environmental exposure). The professional literature states that it is mainly men that get sick in the environs with asbestos more than women, that work in the industry of their environment<sup>33,34</sup>. The number of people with pleural placks, as well as the size of these placks in the diseased is increasing with the years.

It is important to include the patients in a rehabilitation program that relieved anxiety and depression<sup>35</sup>.

In the conclusion, a substantial advancement in the Littoral – Mountainous County has been achieved in the last five years in diagnosing malignant mesothelioma based on pathohistologic findings. Occupational medicine cannot take preventive measures retrogradely because the number of new cases here as well as in the world is on the increase, but it can by work history mark the »dangerous« working places, classify them by industries and raw materials, intensify periodical examinations, and coordinate the work of pulmologist, radiologist, surgeon and oncologist, filing all the documents to the patient's case history, hoping that the new immuno and genetic therapy will lead to the change in the prognosis of this still an extremely serious illness.

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## NAPREDAK U DIJAGNOSTICI MEZOTELIOMA U PRIMORSKO-GORANSKOJ ŽUPANIJI U HRVATSKOJ

### SAŽETAK

Cilj istraživanja je utvrditi da li dijagnostika i registracija pacijenata sa mezoteliomom u Primorsko-goranskoj županiji odgovara svjetskim trendovima. Nadalje, cilj je prikazati incidenciju bolesti i predložiti mjere prevencije u županiji od 400,000 stanovnika i njenim središtem gradom Rijekom sa 140,000 ljudi. U tu svrhu 43 pacijenta sa mezoteliomom prikazana su u dvije grupe: 25 brodograđevnih radnika, prosječne starosti 66 godina i 18 radnika na drugim poslovima, prosječne starosti 62 godine. Statistički, grupe se nisu značajno razlikovale po incidenciji pleuralnih plakova, lijevostranog ili desnostranog izljeva. Pleuralna punkcija pokazala je značajnost ( $p < 0,05$ ) za incidenciju nadraženih stanica. U 20 pacijenata, od ukupno 43 pacijenata sa mezoteliomom, bolest je dokazana uzimanjem materijala za patohistološku analizu pomoću VATS-a (video asistirane torakoskopije) i u 14 pacijenata pomoću TTB-a (transtorakalne biopsije) uz kontrolu CT-a. Spirometrijske vrijednosti pokazale su umjerene restriktivne smetne ventilacije. Iako je postignuto značajno poboljšanje u dijagnostici mezotelioma u zadnjih 5 godina, potrebna je pojačana preventivna aktivnost od strane medicine rada kroz provođenje periodičkih pregleda izloženih osoba i ispitivanja umirovljenih radnika sa respiratornim smetnjama, ali također i stimuliranja uzimanja radnih anamneza.