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Surgical treatment of malignant pleural mesothelioma. Experience in the interdisciplinary approach in Slovenia

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Background. *The aim of the study was to identify perioperative morbidity and mortality, the category and mode of adjuvant treatment, local recurrence and survival in patients treated by extrapleural pneumonectomy (EPP) for malignant pleural mesothelioma (MPM).*
Methods. *From 2000 to 2003, 18 patients with MPM were referred to the Department of Thoracic Surgery in Ljubljana, and 17 of them were operated on. Two patients underwent explorative thoracotomy, and 15 patients were evaluated. Five female and nine male patients (aged 52-68 years) were treated by EPP and one male patient by pleurectomy. Eight patients received both adjuvant chemotherapy (ChT) and radiotherapy (RT), with cisplatin 100 mg/m^2 + mitomycin C 6-10 mg/m^2 or gemcitabine 1000 mg/m^2 and external beam radiation with 24 Gy - 58 Gy respectively, three patients received no adjuvant therapy, three patients were treated by adjuvant ChT, two of them were given cisplatin 100 mg/m^2 + mitomycin C 6-10 mg/m^2, and one patient cisplatin 100 mg/m^2 on the first day and gemcitabine 250 mg/m^2 in prolonged 6 hours infusion on the first and on the eighth day. One patient was treated only by adjuvant RT.*
Results. *There were no perioperative deaths and the postoperative morbidity was 42%. Of the 15 evaluable patients, and in the median follow up of 40 months (28-64), we noticed nine (60.0%) recurrences, seven local and two abdominal. Eight (53.3%) patients died, all because of the local progress of disease. Of the 3/15 patients without adjuvant treatment, one patient (T1bN0M0) is well 46 months after the operation, one patient (T2N0M0) got recurrence in abdomen, was treated with ChT and reoperation, and is still alive 31 month after the first surgical treatment. One patient (T2N0M0) died two months after the surgery due to local recurrence. In ChT+RT group, 6/8 patients died: the patient at stage T1aN0M0 died after nine months, the patient at stage T1bN0M0 died after nine months, two patients at the stage T2N0M0 died after four and 23 months respectively, the patient at stage T3N0M0 after 11 months, and the patients at stage T3N2M0 died seven months after the operation. Two out of eight patients are alive: the patient at stage T1bN0M0 is alive 43 months, and the patient at stage T2N0M0 is alive 28 months after the operation. In the ChT group, 1/3 patient (T2N0M0) died 6 months after the operation, 2/3 patients (T2N0M0 and T3N0M0) are well after 43 and 20 months respectively. The patient treated with adjuvant RT only is well 50 months after the surgical treatment. The median survival time was 20 months for the whole group of patients operated on, the 1-year survival rate was 53.3% and 2-year survival rate was 46.7%.*

Conclusions. *In selected patients with MPM, complete surgical resection is indicated, followed by chemotherapy and radiotherapy. The operation could be performed safely with acceptable mortality and morbidity. Our group of patients is too small, the adjuvant therapies were too different to favour any of the treatment mode applied. Further randomised studies and standardised protocols are needed to evaluate the best mode of treatment for each patient.*

Key words: pleural neoplasms; mesothelioma – surgery – drug therapy - radiotherapy

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Introduction

Malignant pleural mesothelioma (MPM) is a rare disease and it is rarely curable. Most frequently the patients with mesothelioma had been exposed to asbestos. Recently, the presence of a DNA tumour virus (simian virus 40) in tumour cells has suggested a connection between the simian virus 40 and human mesothelioma.[1,2] Mineral oils, liquid paraffin, recurrent pulmonary infections, tuberculous pleuritis, exposure in leather and petrochemical industry, environmental exposure to copper, nickel and glass fibres are cited as non-asbestos risk factors.[3]

MPM grows from the visceral or parietal pleura. For a long period of time it can be localised at the pleura, but later it infiltrates the lung parenchyma, the diaphragmatic muscle, the endothoracic fascia, the mediastinal fat, the soft tissues of the chest wall, and even the ribs and the pericardium. It usually involves the lower part of thoracic cavity and the lower pulmonary lobe.[4]

MPM is more frequent in males, who usually fall ill between the ages 50 and 70 years. In 80% of patients, the illness starts with dyspnea, chest pain and pleural effusion.[5] Patients often suffer from irritating cough and fever.

MPM grows up from multipotential mesothelial or subserous cells. The tumour histology affects the survival prognosis, which makes it important to diagnose the epithelial, mixed or sarcomatous type of tumour.[3] Occasionally the mesothelioma is hard to distinguish from metastatic adenocarcinoma and the early stage of the benign mesothelial hyperplasia.[3] Immunohistochemical studies are required, and in same cases even electron microscopy, to establish a conclusive diagnosis.

Due to slowly evolving symptoms and non-specific clinical picture, the diagnosis is frequently delayed. The average time interval between the first symptoms of the disease and the diagnosis is from three to six months.

A sufficient amount of tissue is needed for diagnosis, and it is obtained by thoracoscopy, videothorascopic procedure or needle puncture. An invasive diagnostic procedures may causes a malignant seeding.[6]

The prognosis of the disease is poor. Median survival of untreated patients is four to twelve months.[7,8] Nevertheless, it can stretch up to five years for 10-15% of patients, in whom the progression of the disease is, for unknown reasons, slow.[3]

Surgical treatment promises the most, but only for selected patients. It is appropriate for patients with the epithelial tumour, stage I or II. The prognosis is more favourable for patients who are in good condition, younger than 50 years and not in pain.[4] The nature of the tumour, which spreads over anatomically large and heterogeneous area, makes the microscopically complete resection rarely possible.[9] The operation alone is usually not sufficient. Additional methods are applied prior to, in the course of, or after the surgical removal of the tumour. Postoperative irradiation,[5,10,11] systemic[12,13] and intrapleural chemotherapy[14-16] are very common. Modern methods of treatment, such as photodynamic therapy,[17,18] immunotherapy, genetic treatment and intracavitary chemotherapy with heat, seem promising, but are yet to produce permanent improvement.[19]

For the majority of patients, the surgical treatment of MPM is not viable and it is hardly ever successful. Only 10-15% of patients with MPM are operated on. A typical candidate for the operation is a patient in stage I or II of the disease, with the epithelial type of MPM. Two methods of surgical treatment are used: pleurectomy and extrapleural pneumonectomy (EPP).

Pleurectomy is the more frequent of the two methods, with less complications, and lower postoperative mortality rate. This operation is less radical, and localised recurrences are more common.[3,20] Nevertheless, the operation is equally successful, if the tumour can be completely resected.[21]

EPP is a more radical operation than pleurectomy, more difficult for the patient, with higher postoperative mortality and morbidity rates. Its long-term survival prognosis improves when combined with radiotherapy and chemotherapy.[22] The surgical procedure involves a complete resection of the lungs, parietal pleura, pericardium, and diaphragm. Regional lymph nodes are removed as well. The early postoperative mortality should not exceed 10%.

Methods

The four-year period of surgical treatment of MPM has been retrospectively analysed at the Clinical Department of Thoracic Surgery of the Clinical Centre in Ljubljana. The data were obtained from the medical records provided by the University Clinic of Respiratory and Allergic Diseases Golnik, by the Department of Thoracic Surgery of the Clinical Centre, and by the Institute of Oncology in Ljubljana. The data pertaining to survival were obtained from the Cancer Register at the Institute of Oncology, and through telephone contacts with patients and their family physicians.

During the period between the years 2000 and 2003, the Clinical Department of Thoracic Surgery, Clinical Centre Ljubljana, admitted 18 patients diagnosed with MPM. They were aged between 32 and 68 years, the average age was 58.5 years. Seven of them were females, eleven were males.

Ten patients had been exposed to asbestos, or had been diagnosed with asbestosis of lungs. All of them came from the region of Gorica, four of them from Kanal, a place with merely 1500 inhabitants.[23]

All but three patients had been diagnosed with MPM prior to the admission to our department. In nine cases the diagnosis was based on needle biopsy, in five cases additional thoracoscopy[24] was performed to confirm the inconclusive needle biopsy-based diagnosis. The diagnosis based on thoracoscopy was always conclusive. One patient was diagnosed by thoracoscopy, without previous needle biopsy. Two patients were diagnosed by minithoracotomy at our department, one with the help of video-thoracoscopy.

All patients had a history of chest pain on the affected side and/or dyspnea. Other symptoms were: irritating cough (3), general discomfort and fatigue (3), loss of weight (2) and fever. All except one had thoracic effusion.

Surgical treatment was chosen in the case of epithelial type of tumour, stage I, II or III according to IMIG (International Mesothelioma Interest Group) classification,[3] if the patient's status made the procedure possible.

In addition to usual blood tests and ECG, bronchoscopy, pulmonary function tests, the ultra-sound of liver, and computerised tomography (CT) of the thorax and of the upper abdomen were performed in all patients.

Table 2. Stage in radical operated patients with malignant pleural mesothelioma

Stage – IMIG classification	Number
T1aN0M0	1
T1bN0Mo	6
T2N0M0	4
T3N0M0	3
T3N2M0	1

Results

Of the 18 patients chosen for the operation, one female patient did not undergo it due to her rapidly deteriorating general condition. In two patients, only explorative thoracotomy was performed, the other 15 patients were evaluated. EPP was performed on 14 patients, one patient underwent pleurectomy.

None of the patients died in the first 30 days after the operation. Six of the radically operated patients (42%) developed minor postoperative complications, which were not life-threatening, nor did they affect further treatment or length of hospitalisation (Table 1).

Most of the radically operated patients had major posterolateral thoracotomy performed, with the removal of the 6^{th} rib, and in three patients double thoracotomy was indicated. Goratex fabric was used for the reconstruction of the diaphragm and of the pericardium, except in one patient, whose diaphragm was replaced with a Vycril net.

The patients remained in hospital from 6 to 14 days, 10 days on the average.

Thirteen radically operated patients had the epithelial, and two the mixed type of mesothelioma. Most of them were at stage I and II of the disease (Table 2).

Table 1. Type and number of operative complications in patients with malignant pleural mesothelioma, treated by the extrapleural pneumonectomy and pleurectomy

Type of complications	Number
Tahiarrythhmia	3
Unexplained fever	1
Chylothorax	1
Bronchial fistula	1

None of the patients received neoadjuvant treatment. The patients who underwent explorative thoracotomy and not the operation were treated differently. One of them received chemotherapy and radiotherapy, the second one just chemotherapy. The patient who was not operated was treated for symptoms only. Three operated patients in stage I had no adjuvant treatment. Eight patients underwent chemotherapy and radiotherapy, three patients just chemotherapy, one patient only radiotherapy (Table 3).

Of the patients who took cytostatic drugs after the operation during the first three years, four were given mitomycin C 6-10 mg/m^2 and cisplatin 100 mg/m^2 each three weeks. The treatment was often adjusted to the patien's condition, side effect of drugs, and the response to treatment. On the average, it lasted three months, in one case only a month, and in another case five months. One of the patients was given cisplatin, metotraxat, adriamycine and gemcitabine because of an early extensive progression.

In the course of further treatment, three patients were given gemcitabine 1000 mg/m^2 instead of mitomycin C during the last year,

Table 3. Mode of the treatment and survival

Mode of the treatment	Number of patients	Median survival in month	Alive
OP + CT + RT	8	10	4
OP + CT	3	20	2
OP	3	31	2
OP + RT	1	50	1
Total	15	20	7

OP = operation; CT = chemotherapy; RT = radiotherapy

Table 4. Type and mode of adjuvant treatment of the operated patients

Patient	Start of CT	Completed CT	CT	Start of RT	Completed RT	Tumour dose in Gy
F.K.	17.04.00	07.09.00	Mito C+Cispl	23.10.00	22.11.00	40
E.S.	26.06.00	24.09.00	Cispl+MTX+Adria+Gemz	07.07.00	04.10.00	58
S.B.				08.05.01	08.06.01	54
B.P.	13.11.01	13.03.02	Mito C+Cispl	18.03.02	27.03.02	27
F.Z.	26.01.02	20.03.02	Mito C+Cispl			
J.B.	07.01.02	09.04.02	Mito C+Cispl	02.07.02	31.07.02	50
V.K.	25.02.02	14.05.02	Mito C+Cispl	29.07.02	08.08.02	41
A.M.M.	15.10.02	02.12.02	Mito C+Cispl	06.02.03	12.03.03	50
I.L.	25.09.02	23.12.02	Mito C+Cispl			
D.S.	23.04.03	01.07.03	Cispl+Gem	21.07.03	19.09.03	54
I.P.	12.06.03	27.08.03	Cispl+Gem	15.10.03	06.11.03	24
B.R.	08.12.03	03.02.04	Cispl+Gem in prolong inf.			

KT = chemotherapy; RT = radiotherapy; Mito C = mitomycin C; Cispl = cisplatin; MTX = Methotrexat; Adria = adriomycine; Gem = gemcitabine

while the dosage of cisplatin remained the same.

The above eight patients had postoperative radiotherapy of hemithorax, at the dosage from 24 to 58 Gy.

Three patients took cytostatic drugs without radiotherapy. Two patients were administered cisplatin 100 mg/m^2 and gemcitabine 1000 mg/m^2, one patient cisplatin 100 mg/m^2 and gemcitabine 250 mg/m^2 in prolonged 6-hour infusion on the first and on the eighth day. One female patient underwent radiotherapy and no chemotherapy (Table 4).

The median survival of all operated patients, regardless the adjuvant treatment, was 20 months. One-year survival rate was 53.3%, and two-year survival rate was 46.7%.

The median survival of the patients who received postoperative chemotherapy and radiotherapy, as well as of those treated with chemotherapy without radiotherapy, was 11 months, while the patients without adjuvant treatment had median survival of 31 months. The female patient who underwent radiotherapy after the operation (Table 3) survived longest (50 months). The patients with explorative thoracotomy and adjuvant ChT and RT, as well as the patient treated for symptoms only, survived for a little over 8 months.

Discussion

The exposure to asbestos and lung asbestosis were definitely established in 10/18 (55%) patients, and very probable in two other cases (65%). It is especially distressing that most of them came from a geographically small region of Gorica, and that Kanal, a small place with about 1500 inhabitants, drastically stands out.[23] Asbestos, a primary etiological agent of MPM, was present in 66% of patients, which is a little lower than the percentage reported by other authors.[1-3] Other etiological factors, such as the infection with the simian virus 40, were not explored. Two of the patients, however, had been employed in petrochemical industry.

The symptoms had been present for several months, up to half a year, on the average. Only in one female patient had the x-ray examination revealed changes a year before, and adenocarcinoma of lungs had been initially diagnosed.

The disease affects males more than females. Other studies report ratios even more detrimental for males[3,5] than is the case in our study (1 : 2.4).

The disease usually starts with dyspnea and pleural effusion, as well as chest pain in the affected side.[3,5,7] All patients had the history of one or more of these symptoms.

The diagnosis is not easy, since symptoms such as chest pain, dyspnea, fatigue and cough are non-specific, and, on the other hand, histopathologist can find it difficult to distinguish MPM from adenocarcinoma.[3,5] In our group, needle biopsy was in five cases insufficient for a definite diagnosis.

In order to determine the stage of the disease, the CT of the thorax and of the upper abdomen was performed on all candidates for the operation. The CT was underestimated only in two patients (13.3%). In both cases the tumour had spread to mediastinal organs and was consequently inoperable. No MRI was performed, although it is recommended, since it is more precise than CT in determining the penetration of the tumour in the mediastinum and in the diaphragm.[5]

In the course of the four years, EPP was performed on 14 patients, which is more than in the previous period of time. In the analysis of the MPM patients in Slovenia between 1980 and 1977, Debevec *et al* report that only 24 of 156 patients with MPM were operated on. Explorative thoracotomy was done for half of them, and EPP only for five patients.[25]

In most cases, extensive posterolateral thoracotomy was performed, with the resection of a rib. Double thoracotomy was performed in three patients, which was mostly the surgeon's choice. The approach must provide grounds for a safe and radical surgery on extensive area involving vital and sensitive structures such as functional pulmonary veins, the heart and the inferior vena cava.

When performing EPP, we try to resect parietal pleura, lungs, pericardium and diaphragm in one piece, without opening the pleural cavity. This is achieved only rarely because of its adhesion to the thoracic wall, mediastinum, pericardium and diaphragm, as well as due to previous diagnostic procedures in the pleural cavity. The defect of the pericardium and of the diaphragm was in all but one patients restored with a Goretex patch. This fabric is very suitable, it causes no complications, but it is very expensive. A Vycril net used in one operated patient proved satisfactory as well, and is frequently being used. In each operation, the canal made by previous diagnostic biopsies was radically resected, either as a separate procedure or during the thoracotomy.

None of the operated patients died during the early postoperative period, which is a very good result. At present, the early postoperative mortality is 5-10%.[3,5,10,22,26] Early postoperative deaths are mostly due to sudden drop of blood pressure because of the dislocation of mediastimun and blood in-put disorders, haemorrhage, infection of the remaining pulmary lobes, bronchial fistula and the subsequent empyema in the pleural cavity, and mediastinitis. Herniation of the heart can result from the defect of the pericardium, unless it has been meticulously reconstructed.[5]

Various postoperative complications are reported for EPP. They occur in 50% and even more patients. In our group, 42% of patients experienced complications, but none of them was extensive. Only one female patient had to be readmitted because of a bronchial fistula.

Pleurectomy is a less demanding procedure, with fewer complications and low early postoperative mortality, but it is also less radical than EPP. The median survival after this operation is from 9 to 20 months, as reported by different authors.[7] Radical resection from the visceral pleura, where the disease usually recurs, is problematic.[9] Local recurrence is 10% for EPP, and 52% for pleurectomy.[27] Decortication always indicates adjuvant treatment. It was performed in only one female patient at the stage T1aN0M0. After the operation, she underwent adjuvant treatment involving chemotherapy and radiotherapy. The patient died nine months after the operation due to local progress of mesothelioma.

Most authors agree that EPP alone is not sufficient, and that adjuvant treatment is necessary.[3,5,11,20] Median survival after EPP is from 9 to 19 months,[7] not unlike the survival after decortication. This is due to the fact that decortication is more frequently indicated at lower stages of the tumour.

Not all of the authors report such optimistic results. Mattson reports that 100 operated patients, who underwent adjuvant treatment involving five different modes of irradiation and systemic chemotherapy, had the median survival of 8 months and only 20% had two-year survival.[11]

Adjuvant treatment most frequently involves chemotherapy and irradiation of complete hemithorax at high tumour dose,[5,11] or only irradiation of hemithorax at high tumour dose.[10]

Median survival of the whole group of our operated patients was 20 months, which is significantly better than the survival of patients in the same period and who were not operated on[28] and whose median survival was 11 months. The groups were not randomised. Patients who were not operated on were probably at a higher stage of the disease, had different histological type of tumour, and were in worse performance status than the patients operated on, so that the two groups cannot be validly compared.

Most of our patients (12/15) received adjuvant treatment after the operation, but not in the same mode. They were prescribed different cytostatic drugs, different dosages, different number of cycles, as well as different radiation doses. Five recent patients were treated with a cytostatic drug of the 3rd generation, which shows better results.[29-31] The IMRT method of irradition, which could be very effective,[32,33] was not available in our case. A small number of patients (3) had no adjuvant treatment. The small size of the sample of treated patients makes any evaluation of the efficiency of individual methods of treatment unreliable. There are indications that the results tend to be the same as those reported by DaValle[34] that in a group of 17 patients the survival length showed no correlation with the adjuvant treatment. His study, however, was not controlled and randomised. At least one more year of follow-up observation would be needed for a valid evaluation of our methods of treatment.

Different and multiple methods of treatment indicate that the MPM disease is still unmanageable, fatal for most patients, irrespective of how it is treated. In spite of aggressive local treatment, loco-regional recurrences of the tumour are almost inevitable, if the rest of the pleural cavity, pericardium and abdomen are considered loco-regional. Better results are obtained in carefully selected patients at initial stage, who are treated with a radical local resection of the tumour and adjuvant radiotherapy.

In future, neoadjuvant cytostatic treatment, applied and recommended by Stamatis,[35] who reports 31% of three-year survival, will have to be considered. The same author points out that the use of cytostatic drugs after EPP can be detrimental to the other side of the lungs. For that reason he recommends that the treatment starts with three cycles of cisplatin and gemcitabine medication, radical resection after three to four weeks, and radiotherapy of hemithorax after four to six weeks.

Conclusions

The incidence of MPM has been growing. In patients with epithelial tumour at stage I and II, surgery is indicated besides the oncological treatment. If sufficient, or if the disease is strictly localised, pleurectomy is performed. EPP is a more radical procedure, relatively safe and with acceptably low postoperative mortality and morbidity. It is crucial that the best method of neoaduvant and/or adjuvant treatment after a radical operation is agreed upon.

References

1. McDonald JC, McDonald AD. The epidemiology of mesothelioma in historical context. *Eur Respir J* 1996; **9:** 1932-42.

2. Pass HI, Donington JS, Wu P, Rizzo P, Nishimura M, Kennedy R, et al. Human mesotheliomas contain the simian virus-40 regulatory region and large tumor antigen DNA sequences. *J Thorac Cardiovasc Surg* 1998; **116:** 854-9.

3. Rusch VW. Mesothelioma and less common pleural tumors. In: Pearson FG, Ginsberg RJ, Cooper JD, Hiebert CA, Deslauriers J, Patterson GA, et al, editors. *Thoracic surgery*. 2nd edition. New York: Churchill Livingstone; 2002. p. 1241-63.

4. Roberts JR. Surgical treatment of mesothelioma: pleurectomy. *Chest* 1999; **116:** 446S-9S.

5. Sugarbaker DJ, Garcia JP. Multimodality therapy for malignant pleural mesothelioma. *Chest* 1997; **112:** 272S-5S.

6. Boutin C, Rey F, Viallat RJ. Prevention of malignant seeding after invasive diagnostic procedures in patients with pleural mesothelioma: a randomized trial of local radiotherapy. *Chest* 1995; **108:** 754-8.

7. Ruth S, Baas P, Zoetmulder FA. Surgical treatment of malignant pleural mesothelioma. A review. *Chest* 2003; **123:** 551-61.

8. Zellos L, Sugarbaker DJ. Current surgical management of malignant pleural mesothelioma. *Curr Oncol Rep* 2002; **4:** 354-60.

9. Lee YC. Light RW, Musk AW. Management of malignant pleural mesothelioma: a critical review. *Curr Opin Pulm Med* 2000; **6:** 267-74.

10. Rusch VW, Rosenzweig K, Venkatraman E, Leon L, Raben A, Harrison L, et al.A phase II trial of surgical resection and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. *Thorac Cardiovasc Surg* 2001; **122:** 788-95.

11. Mattson K, Holsti LR, Tammilehto L, Maasilta P, Pyrhonen S, Mantyla M, et al. Multimodality treatment programs for malignant pleural mesothelioma using high-dose hemithorax irradiation. *Int J Radiat Oncol Biol Phys* 1992; **24:** 643-50.

12. Huncharek M, Kelsey K, Mark EJ, Muscat J, Choi N, Carey R, et al. Treatment and survival in diffuse malignant pleural mesothelioma: a study of 83 cases from the Massachusetts General Hospital. *Anticancer Res* 1996; **16:** 1265-8.

13. Hasturk S, Tastepe I, Unlu M, Cetin G, Baris YI. Combined chemotherapy in pleurectomized malignant pleural mesothelioma patients. *J Chemother* 1996, **8:** 159-64.

14. Rusch V, Saltz L, Venkatraman E, Ginsberg R, McCormack P, Burt M, et al. A phase II trial of pleurectomy/decortication followed by intrapleural and systemic chemotherapy for malignant pleural mesothelioma. *J Clin Oncol* 1994, **12:** 1156-63.

15. Lee JD, Perez S, Wang HJ, Figlin RA, Holmes EC. Intrapleural chemotherapy for patients with incompletely resected malignant mesothelioma: the UCLA experience. *J Surg Oncol* 1995; **60:** 262-7.

16. Colleoni M, Sartori F, Calabro F, Nelli P, Vicario G, Sgarbossa G, et al. Surgery followed by intracavitary plus systemic chemotherapy in malignant pleural mesothelioma. *Tumori* 1996; **82:** 53-6.

17. Pass HI, Temeck BK, Kranda K, Thomas G, Russo A, Smith P, et al. Phase III randomized trial of surgery with or without intraoperative photodynamic therapy and postoperative immunochemotherapy for malignant pleural mesothelioma. *Ann Surg Oncol* 1997; **4:** 628-33.

18. Moskal TL, Dougherty TJ, Urschel JD, Antkowiak JG, Regal AM, Driscoll DL, et al. Operation and photodynamic therapy for pleural mesothelioma: 6-year follow-up. *Ann Thorac Surg* 1998; **66.** 1128-33.

19. Kaiser LR. New therapies in treatment of malignant pleural mesothelioma. *Semin Thorac Cardiovasc Surg* 1997; **9:** 383-90.

20. Soysal O, Karaoglanoglu N, Demiracan S, Topcu S, Tastepe I, Kaya S, et al. Pleurectomy/decortication for palliation in malignant pleural mesothelioma: results of surgery. *Eur J Cardiothorac Surg* 1997; **11:** 210-3.

21. Rusch VW, Venkatraman ES. Important prognostic factors in patients with malignant pleural mesothelioma, managed surgically. *Ann Thorac Surg* 1999; **68:** 1799-804.

22. Grondin SC, Sugarbaker DJ. Pleuropneumonectomy in the treatment of malignant pleural mesothelioma. *Chest* 1999; **116:** 450-4.

23. *Krajevni leksikon Slovenije*. Ljubljana: DZS; 1995. p. 182.

24. Debeljak A, Kecelj P, Kern I, Eržen J, Kovač V, Rott T. Medical thoracoscopy in pleural malignant mesothelioma. In: Zaltloukal P, Petruželka L, editors. *Lung Cancer. Current Topics.* Prague: Monduzzi Editore; 2001. p. 81-6.

25. Debevec M, Kovač V, Debeljak A, Eržen J, Remškar Z, Kern I. Maligni plevralni mezoteliom. Analiza bolnikov v Sloveniji 1980-1997. *Zdrav Vestn* 2000; **69:** 599-606.

26. Aziz T, Jilaihawi A, Prakash D. The management of malignant pleural mesothelioma; single centre experience in 10 years. *Eur J Cardiotorac Sur*g 2002; **22:** 298-305.

27. Baldini EH, Recht A, Strauss GM, DeCamp MM Jr, Swanson SJ, Liptay MJ, et al. Patterns of failure After trimodality therapy for malignant pleural mesothelioma. *Annal Thorac Surg* 1997; **63:** 334-8.

28. Debeljak A, Kecelj P, Kern I, Triller N, Remškar Z, Eržen J, et al. Diagnoza malignega plevralnega mezotelioma. In: Debeljak A, Turel M, editors. Simpozij bolezni plevre in simpozij presaditev pljuč. Nova Gorica, 2.-3. april 2004. Celje: Združenje pneumologov Slovenije, 2004. p. 27-34.

29. Lee Kindler H. Systemic therapy for mesothelioma: old and new. *Lung Cancer* 2003; **41(Suppl 3):** S54.

30. Nowak AK, Byrne MJ, Williamson R, Ryan G, Segal A, Fielding D, et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. *Br J Cancer* 2002; **87:** 491-6.

31. Kovac V, Zwitter M, Smrdel U, Debeljak A, Cesar R. Low-dose gemcitabine in prolonged infusion and cisplatin for malignant pleural mesothelioma: a phase I – II trial. In: Jassem J, editor. Gdansk: Medimond S.r.l., Monduzzi Editore; 2004. p. 131-4.

32. Ahamad A, Stevens CW, Smythe WR, Liao Z, Vaporciyan AA, Rice D, et al. Promising early local control of malignant pleural mesothelioma following postoperative intensity modulated radiotherapy (IMRT) to the chest. *Cancer J* 2003; **9:** 476-84.

33. Baldini EH. External beam radiation therapy for the treatment of pleural mesothelioma. *Thorac Surg Clin* 2004; **14:** 543-8.

34. DaValle MJ, Faber LP, Kittle CF, Jensik RJ. Extrapleural pneumonectomy for diffuse malignant mesothelioma. *Ann Thorac Surg* 1986; **42:** 612-8.

35. Stamatis G. Malignant pleural mesothelioma.The role of surgical resection. Highlights in thoracic surgery. Monday 13th October. 2nd EACTS/ESTS Joint Meeting, Vienna, Austria 12-15 October 2003.