Original Article

Treatment Failure after Extrapleural Pneumonectomy for Malignant Pleural Mesothelioma

Tristan D Yan, BSc (Med), MBBS, PhD, MoMo Tin, MBBS, Michael Boyer, MBBS, PhD, FRACP, Jocelyn McLean, RN, MN, Paul G. Bannon, MBBS, PhD, FRACS, Brian C McCaughan, MBBS, FRACS

From the University of Sydney (Drs Yan, McLean, Bannon and McCaughan), Department of Cardiothoracic Surgery, Royal Prince Alfred Hospital; the Baird Institute for Applied Heart and Lung Surgical (Drs Yan, McLean, Bannon and McCaughan), Australia; Department of Medical Oncology (Drs Tin and Boyer), Royal Prince Alfred Hospital; Sydney Cancer Center (Drs Tin and Boyer), Australia; Department of Radiation Oncology, Royal Prince Alfred Hospital, Sydney, Australia

ABSTRACT

Background Extrapleural pneumonectomy (EPP) has been used as a treatment option for selected patients with malignant pleural mesothelioma (MPM). The primary end-point of this study was disease-free survival (DFS). Prognostic indicators for local and overall DFS were statistically analyzed.

Methods Between October 1994 to April 2008, 59 patients who had complete macroscopic cytoreduction after EPP formed the basis of this report. In recent years, selected patients received adjuvant radiotherapy and pemetrexed combined with cisplatin or carboplatin. The clinicopathologic data of all patients were prospectively collected in a computerized database. Statistical analysis was performed by using Kaplan-Meier method and compared using the log-rank test. Cox-regression model was used for multivariate analysis.

Results The mean age at the time of EPP was 59 (S.D. = 8) years. Nineteen patients (32%) experienced perioperative complications. The median survival was 21 months (range 2 to 104). The local disease recurrence rate was 51%. The median local DFS was 22 months (0 to 73). The overall disease recurrence rate was 64%. The median overall DFS was 18 months (range 0 to 73). In multivariate analysis, epithelial subtype ($p = 0.026$) and adjuvant radiotherapy ($p = 0.023$) were independently associated with an improved local DFS. Adjuvant radiotherapy ($p = 0.011$) was also independently associated with an improved overall DFS.

Conclusions This study demonstrated that that local disease failure was still a considerable clinical problem following complete EPP. The data also showed that patients with epithelial histology and receiving adjuvant radiotherapy were associated with an improved disease control.

KeyWords: pleural mesothelioma; extrapleural pneumonectomy; radiotherapy

J Thorac Dis 2009; 1:23–8.

Malignant pleural mesothelioma (MPM) is an aggressive cancer for which treatment options are limited. The clinical course is marked by relentless local growth of the tumor, with patients' deaths most commonly due to cardiac or pulmonary involvement. In its early stages, MPM remains localized to a single hemithorax and therapeutic efforts have therefore focused on local treatment modalities, be it surgical resection, radiotherapy and intrapleural chemotherapy (1-4). Extrapleural pneumonectomy (EPP) is a radical surgical approach, which can potentially eradicate macroscopic disease in selected patients (5). The perioperative outcome of EPP has improved significantly in recent years, because of better surgical techniques and perioperative care (6, 7). However, the long-term survival is still unsatisfactory due to high incidence of recurrence, especially locoregional treatment failure, at the site of the surgeons' best effort. Recent evidence suggests that improvements in locoregional disease control have occurred through the addition of high dose hemithorax radiation and more potent chemotherapeutic regimens to EPP (3, 8-10). The multimodality approach to surgically eradicate gross disease followed by additional radiotherapy and/or chemotherapy to control residual microscopic disease has a strong locoregional treatment rationale.

In the current literature, the clinical evidence for disease recurrence after EPP is still limited and the predictors of local disease failure and their impact on subsequent outcome have not been clearly defined. To address these issues, the outcomes for MPM patients who underwent EPP were evaluated. The primary end-point of this study was disease-free survival (DFS), determined from the time of EPP intervention. Prognostic indicators for local and overall DFS were statistically analyzed.

The authors have no commercial, proprietary, or financial interest in the products or companies described in this article.

Corresponding author: Tristan D. Yan, BSc (Med), MBBS, PhD. University of Sydney, Department of Cardiothoracic Surgery, Royal Prince Alfred Hospital, Sydney, Australia. Tel: +61-2-95501933, Fax: +61-2-95506669. E-mail: tristan.yan@unsw.edu.au

Submitted November 10, 2009. Accepted for publication November 29, 2009.

Available at www.jthoracdis.com

ISSN: 2072-1439/$ - see front matterr

Materials and methods

Between October 1994 to April 2008, 424 patients with a tissue diagnosis of MPM were treated by a thoracic surgical team, lead by the same surgeon (B.C.M.). Seventy patients (17%) were selected for EPP. The criteria for EPP were the extent of disease limited to the ipsilateral hemithorax with no transdiaphragmatic, transpericardial or extensive chest wall involvement, a good performance status, normal renal and liver function tests, adequate cardiac and pulmonary function assessment. Informed consent was obtained from all patients prior to surgery. Four patients who died within the same hospital admission were excluded from this study. Another seven patients who had positive macroscopic resection margin were also excluded. The remaining 59 patients who had complete macroscopic cytoreduction after EPP formed the basis of this report. The clinicopathologic data of all patients were prospectively collected in a computerized database.

Preoperative assessment

Preoperative assessment included a review of all prior clinical information, physical examination, serum chemistry and hematology, chest X-ray, computed tomography (CT) of the chest and upper abdomen and pulmonary function testing. Since the year 2000, positron emission tomography (PET) became available at our institution. A few patients received preoperative pemetrexed combined with cisplatin or carboplatin prior to EPP.

Operative techniques

EPP was performed with en bloc resection of the lung, pleurae, ipsilateral hemi-diaphragm and pericardium. EPP was approached from an extended posterolateral thoracotomy incision at entire costal surface of the lung and extending over the apex of the pleura, mobilizing mediastinal pleura down to the hilum. The main pulmonary vessels were ligated and divided separately and the bronchus was stapled. Upon control of these structures it is possible to continue the dissection anteriorly by entering the pericardium and proceed to the resection of the pericardium and the hemi-diaphragm, en bloc with the lung and the parietal pleura. Systematic mediastinal lymph node dissection was routinely performed and the specimens were submitted for histological examination. The pericardial and diaphragmatic defects were repaired with 2 mm Gore-Tex dual mesh?. All tissue specimens were submitted for histopathological examination.

Postoperative management

Adjuvant radiotherapy following EPP was introduced in 2002, in an attempt to improve locoregional disease control (3, 10). Patients were referred to a radiation oncologist for assessment within 6 weeks of surgery. Selection criteria for radiotherapy include good performance status, adequate residual cardio-pulmonary function and satisfactory recovery from surgery. Radiotherapy would commence within 12 weeks of surgery. In most of the patients, a four-beam mixed photon and electron technique was employed, delivering a total dose of 45 Gy in 25 daily fractions to the entire hemithorax, ipsilateral mediastinum bed and ipsilateral chest wall. Chemotherapy was not routinely used as an adjuvant therapy. However, in recent years some evidence suggested that pemetrexed plus cisplatin or carboplatin resulted in superior survival time (11-13). In the present study cohort, a proportion of patients received pemetrexed combined with cisplatin or carboplatin.

Follow–up and statistical analysis

All patients were followed prospectively at three-monthly intervals for the first year and six-monthly thereafter until the last time of contact or death. The follow-up review included clinical examination and assessment of chest CT scans. If indicated abdominal CT scans were used to detect any concurrent extrathoracic recurrence. The follow-up status was regularly updated in the database for each patient by a data manager.

The statistical analyses of 11 potential prognostic factors used local DFS and overall DFS as the primary end-points, determined from the time of EPP. Disease recurrence was defined as clinical or radiologic evidence of tumor with or without symptoms. Local disease recurrence was referred to disease recurrence in the ipsilateral chest wall, where EPP was performed. Overall disease recurrence was referred to disease recurrence in lymph nodes, contralateral chest, abdomen and any other systemic site (14). These prognostic factors included age, gender, self-reported prior occupational asbestos exposure, left side versus right of disease, histopathologic subtype, presence versus absence of lymph nodes, whether preoperative PET was performed, whether preoperative chemotherapy was given, presence versus absence of perioperative morbidity and whether postoperative radiotherapy and/or pemetrexed-based chemotherapy regimens were given. Univariate analysis was performed by using Kaplan-Meier method and compared using the log-rank test. For multivariate analysis, a Cox-regression (Cox proportional hazards model) with forward stepwise selection of covariates and with entering and removing limits of $p < 0.10$ and $p > 0.05$ was used. The statistical analyses were performed using SPSS for Windows (Version 14.5; SPSS GmbH, Munich, Germany). A significant difference was assumed for $p < 0.05$.

Results

Patients characteristics

All 59 patients had complete macroscopic cytoreduction following EPP. The follow-up was complete, with a median follow-up of 14 months (range 2 to 104). The mean age at the time of EPP was 59 (S.D. = 8) years. There were 47 (80%) male patients. Thir-

Table 1 Patterns of disease recurrence after extrapleural pneumonectomy for malignant pleural mesothelioma

Site of disease recurrence	No. of patients with recurrence	% of all patients (n =59)	% of recurrences (n = 38)
Ipsilateral hemithorax	30	51	79
Abdomen	7	12	18
Contralateral hemithorax	4	7	11
Other distant sites	3	5	8

ty-nine patients (66%) had prior occupational asbestos exposure. Twenty-nine patients (49%) had left-side and 30 patients (51%) had right-side EPP. Forty-nine patients (83%) had epithelial and 10 patients (17%) had biphasic or sarcomatoid tumors. Twenty-two patients (37%) had lymph node metastasis. Thirty-seven patients (67%) had preoperative PET. Five patients (9%) had preoperative pemetrexed chemotherapy. Twenty-four patients (41%) received adjuvant ipsilateral radiotherapy and 12 patients (20%) received pemetrexed combined with either cisplatin or carboplatin postoperatively. Nineteen patients (32%) experienced perioperative complications. In the descending order of frequency, these adverse events included atrial fibrillation (n = 5), empyema (n = 4), pleural effusion (n = 3), right-side heart failure (n = 2), hemothorax (n = 1), bronchopulmonary fistula (n = 1), constrictive pericarditis (n = 1), hydropneumothorax (n = 1) and small bowel herniation through chest wall (n = 1).

Overall survival and disease-free survival

The median survival was 21 months (range 2 to 104), with actuarial 1-, 2-, 3- and 5-year survival of 67%, 45%, 32% and 15%, respectively. Twenty-two patients (37%) remained alive at the last time of follow-up. The local disease recurrence rate was 51% (n = 30), with 1- and 2-year local DFS of 67% and 40%, respectively. The local disease recurrence rate was 29% of patients who were fit enough to tolerate adjuvant radiotherapy. Ten patients (17%) recurred within 6 months; 18 patients (31%) recurred within 12 months and 28 patients (47%) recurred within 24 months. The median local DFS was 22 months (0 to 73). The overall disease recurrence rate was 64% (n = 38), with 1- and 2-year overall DFS of 63% and 30%, respectively. The median overall DFS was 18 months (range 0 to 73). Table 1 demonstrates the patterns of disease recurrence after EPP in these 59 patients. It shows that the most common site of treatment failure was in the ipsilateral hemithorax (51%), followed by abdomen (12%) and contralateral hemithorax (7%).

Factors affecting local disease-free survival

Eleven clinicopathologic factors were analyzed for their prognostic significance in local DFS. Three clinicopathologic factors were found to be associated with an improved local DFS in univariate analysis: prior occupational asbestos exposure (p = 0.027), epithelial histologic subtype (p = 0.004) (Figure 1) and adjuvant radiotherapy (p = 0.005) (Figure 2) (Table 2). Age at the time of surgery (p = 0.880), gender (p = 0.183), side of disease (p = 0.628), lymph node involvement (p = 0.288), PET scan (p = 0.081), perioperative morbidity (p = 0.722), preoperative pemetrexed chemotherapy (p = 0.658) and postoperative pemetrexed combination chemotherapy (p = 0.117) were not significant prognostic indica-

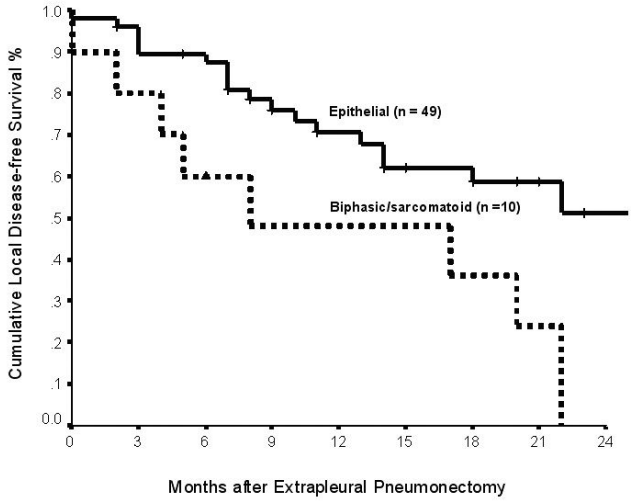

Fig.1 Local disease-free survival after complete extrapleural pneumonectomy for malignant pleural mesothelioma, stratified by histologic subtype (p = 0.004).

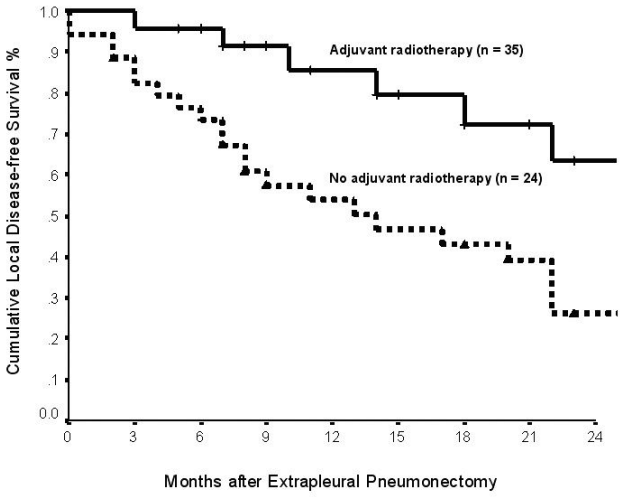

Fig.2 Local disease-free survival after complete extrapleural pneumonectomy for malignant pleural mesothelioma, stratified by adjuvant radiotherapy (p = 0.005).

Table 2 Risk factors for local disease-free survival and overall disease-free survival after complete extrapleural pneumonectomy for malignant pleural mesothelioma

Risk Factor	Univariate Analysis	Multivariate Analysis		
	P	HR	95% CI	P
Local disease–free survival				
Asbestos exposure				
Yes vs. no	0.027	–	–	ns
Histologic subtype				
Epithelial vs. non-epithelial	0.004	4.929	1.055 – 2.361	0.026
Adjuvant radiotherapy				
Yes vs. no	0.005	5.204	0.140 – 0.861	0.023
Overall disease–free survival				
Histologic subtype				
Epithelial vs. non-epithelial	0.020	–	–	ns
Adjuvant radiotherapy				
Yes vs. no	0.007	6.513	0.177 – 0.797	0.011

tors for local DFS in the univariate analysis. In multivariate analysis, epithelial subtype (hazard ratio: 4.929; 95% confidence interval: 1.055 - 2.361; p = 0.026) and adjuvant radiotherapy (hazard ratio: 5.204; 95% confidence interval: 0.140 - 0.861; p = 0.023) were independently associated with an improved local DFS.

Factors affecting overall disease–free survival

Two clinicopathologic factors were found to be associated with an improved overall DFS in univariate analysis: epithelial histologic subtype (p = 0.020) and adjuvant radiotherapy (p = 0.007) (Figure 3) (Table 2). Age at the time of surgery (p = 0.918), gender (p = 0.086), asbestos exposure (p = 0.088), side of disease (p = 0.608), lymph node involvement (p = 0.117), PET scan (p = 0.102), perioperative morbidity (p = 0.434), preoperative pemetrexed chemotherapy (p = 0.912) and postoperative pemetrexed combination chemotherapy (p = 0.201) were not significant prognostic indicators for overall DFS in the present series. In multivariate analysis, only adjuvant radiotherapy (hazard ratio: 6.513; 95% confidence interval: 0.177 - 0.797; p = 0.011) was independently associated with an improved overall DFS.

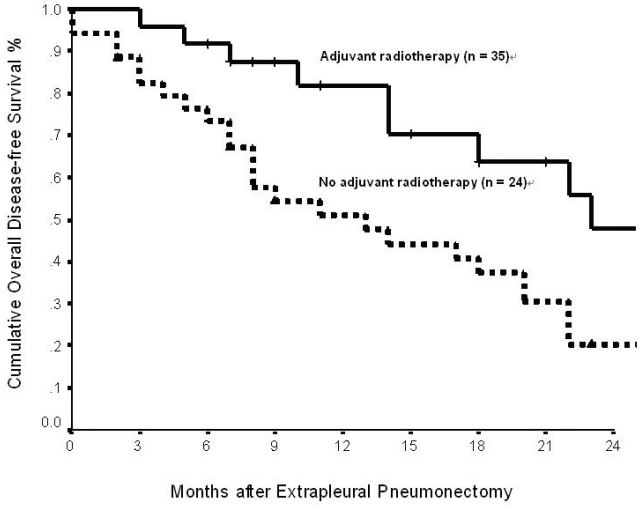

Fig.3 Overall disease–free survival after complete extrapleural pneumonectomy for malignant pleural mesothelioma, stratified by adjuvant radiotherapy (p = 0.007).

Discussion

In the United States, data from Surveillance, Epidemiology and End Results (SEER) showed a steep rise in the MPM incidence through the 1990s, with a recent leveling off of the rate of increase, but no evidence that the peak incidence has been passed in this country (15). Much higher incidence rates are seen in the United Kingdom and Australia due to the widespread use of asbestos, a potent inducer of mesothelioma (16). The incidence is expected to continue to increase in areas of the world, where asbestos use has not been curtailed (17). There is substantial public interest in recent years, because millions of people have been exposed to asbestos in the environment, especially the workplace. The association with MPM has created considerable medical-legal implications involving billions of dollars in compensation costs for industry and government.

MPM is a locally aggressive disease. Complete macroscopic cytoreduction can only be achieved with EPP. It begins with exposure of the parietal pleura, followed by its dissection from the chest wall, diaphragm and mediastinum. Mediastinal node dissection is performed, followed by en bloc resection of the diaphragm, pericardium, lung and pleura. However, despite the best surgical efforts, the cancer recurs and patients eventually die from disease progression. Many centers have combined EPP with adjuvant radiotherapy and/or systemic chemotherapy (3, 8-10). One of the advantages with EPP is that the lung has been removed. Consequent-

ly, radiation toxicity is not as limiting as it is for pleurectomy/decortication, and higher does can be delivered. Patients who can undergo complete cytoreductive surgery and tolerate adjuvant chemoradiation have experienced improved median survival as compared with historical controls.

The present study demonstrated locoregional recurrence is the most common cause of treatment failure after complete EPP. The local disease recurrence rate was 51% and the median local DFS was 22 months. This could be related to the presence of microscopic residual disease and/or biological aggressiveness of the tumor. Baldini and co-workers studied the patterns of failure after EPP with or without adjuvant chemoradiotherapy and found a recurrence rate of 54% and a median time to first failure of 19 months (18). Stewart and colleagues reported a local disease recurrence rate of 68% and a median time to local disease progression of 21 months after EPP (19). However, it has to be acknowledged that a direct comparison of recurrence rates between series is difficult as patient characteristics and treatment protocols may differ.

One of the objectives of this study was to identify clinical and treatment-related data that influence the risk of treatment failure. The univariate analysis indicated that a short local DFS was associated with absence of prior occupational exposure of asbestos, non-epithelial histologic subtype and not receiving adjuvant radiotherapy. The association between the absence of prior occupational exposure of asbestos and reduced local DFS is unclear and this prognostic factor fell out in the multivariate analysis. A possible explanation of this correlation is related to both the absence of an appreciable threshold for asbestos-induced mesothelioma and the fact that MPM can occur with very low-level exposure (20, 21). It has been hypothesized that some patients may have higher inherent susceptibility and these susceptible individuals may suffer from more aggressive disease (22). Outside this high susceptibility group, there may be a dose-response relationship between asbestos fiber burden and the prognosis (22).

This paper confirmed that patients with sarcomatoid or biphasic histologic subtypes fared as a group less well than patients with epithelial histology. Stewart et al. also showed that in patients who underwent EPP, epithelial histology was associated with delayed disease progression when compared with biphasic subtype (19). Sugarbaker and colleagues identified that the individuals with epithelial histology who had no positive lymph nodes and complete EPP achieved a 46% estimated 5-year survival (2). A limitation of EPP surgery from a surgical oncologic standpoint has been that the margin of resection is usually a single tissue plane, which means that with an aggressive histology, EPP may be insufficient to result in a reliable cure.

Adjuvant radiotherapy after EPP was described by the Brigham group in 1997 (18). Thirty-five of 49 patients were given four to six cycles of postoperative chemotherapy followed by radiation (median dose 31 Gy). Sixteen irradiated patients developed local recurrence (18). They noted that many patients developed disease recurrence in the chest and abdomen despite aggressive therapy. The relapse in the abdomen was hypothesized to result from the continuity of the chest and peritoneal cavity after resection of the diaphragm. This establishment of the continuity of the chest and abdominal cavities presumably allows tumor cells disseminate in the abdomen. In the present study, although the most common site of relapse after EPP was the ipsilateral thorax, 12% of patients presented with abdominal recurrence. Encouraging results were reported from Memorial Sloan Kettering Cancer Center. From 1995 to 1998, 54 patients underwent EPP followed by adjuvant radiotherapy (median dose 54 Gy) (3). The median survival was 18 months. Only 7 patients (13%) developed locoregional treatment failure and in contrast, 35 patients (65%) had distant recurrence, with the peritoneum and contralateral pleural being the most common sites (3). The present study demonstrated that adjuvant radiotherapy was associated with an improved local disease control compared with patients who did not receive radiotherapy. However, outside the setting of a randomized controlled trial, subgroup analysis comparing the patients with or without adjuvant treatments is fraught with potential biases, in that the beneficial treatment effects may be attenuated by confounding factors, such as patient selection and performance status that were not revealed by this comparative analysis.

In conclusion, this study demonstrated that that local disease failure was still a considerable clinical problem following complete EPP, occurring in 51% of all patients and in 29% of patients who were fit enough to tolerate adjuvant radiotherapy. The data also offered insights into the predictors of treatment failure following complete EPP and showed that patients with epithelial histology and receiving adjuvant radiotherapy were associated with an improved disease control.

Acknowledgement

The authors thank Catherine Kennedy RM RA, for maintaining the thoracic database.

References

1. Brancatisano R, Joseph M, McCaughan B. Pleurectomy for mesothelioma. Med J Aust 1991; 154: 455-60.
2. Sugarbaker DJ, Flores RM, Jaklitsch MT, Richards WG, Strauss GM, Corson JM, et al. Resection margins, extrapleural nodal status and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. J Thorac Cardiovasc Surg 1999; 117: 54-65.
3. 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. J Thorac Cardiovasc Surg 2001; 122: 788-95.
4. 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.
5. Grondin S, Sugarbaker D. Pleuropneumonectomy in the treatment of malignant pleural mesothelioma. Chest 1999; 116: 450-4.
6. Sugarbaker DJ, Jaklitsch MT, Bueno R, Richards W, Lukanich J, Mentzer SJ, et al. Prevention, early detection, and management of complications after 328 consecu-

tive extrapleural pneumonectomies. J Thorac Cardiovasc Surg 2005; 129: 1202-3.
7. de Perrot M, McRae K, Anraku M, Karkouti K, Waddell TK, Pierre AF, et al. Risk factors for major complications after extrapleural pneumonectomy for malignant pleural mesothelioma. Ann Thorac Surg 2008; 85: 1206-10.
8. Sugarbaker DJ, Heher EC, Lee TH, Couper G, Mentzer S, Corson JM, et al. Extrapleural pneumonectomy, chemotherapy, and radiotherapy in the treatment of diffuse malignant pleural mesothelioma. J Thorac Cardiovasc Surg 1991; 102: 10-5.
9. Sugarbaker D, Norberto J. Multimodality management of malignant pleural mesothelioma. Chest 1998; 113: 61-5.
10. Yajnik S, Rosenzweig KE, Mychalczak B, Krug L, Flores R, Hong L, et al. Hemithoracic radiation after extrapleural pneumonectomy for malignant pleural mesothelioma. Int J Rad Oncol Biol Physic 2003; 56: 1319-26.
11. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003; 21: 2636-44.
12. Ceresoli GL, Zucali PA, Favaretto AG, Grossi F, Bidoli P, Del Conte G, et al. Phase II study of pemetrexed plus carboplatin in malignant pleural mesothelioma. J Clin Oncol 2006; 24:1443-8.
13. Castagneto B, Botta M, Aitini E, Spigno F, Degiovanni D, Alabiso O, et al. Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma (MPM). Ann Oncol 2008; 19: 370-3.
14. Rusch V, Piantadosi S, Holmes E. The role of extrapleural pneumonectomy in malignant pleural mesothelioma. J Thorac Cardiovasc Surg 1991; 102: 1-9.
15. Price B, Ware A. Mesothelioma trends in the United States: an update based on Surveillance, Epidemiology, and End Results Program data for 1973 through 2003. Am J Epidemiol 2004; 159:107-12.
16. Robinson BW, Lake RA. Advances in malignant mesothelioma. N Engl J Med 2005; 353: 1591-603.
17. Kazan-Allen L. Asbestos and mesothelioma: worldwide trends. Lung Cancer 2005; 49: 3-8.
18. 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. Ann Thorac Surg 1997; 63: 334-8.
19. Stewart DJ, Martin-Ucar A, Pilling JE, Edwards JG, O'Byrne KJ, Waller DA. The effect of extent of local resection on patterns of disease progression in malignant pleural mesothelioma. Ann Thorac Surg 2004; 78: 245-52.
20. Hansen J, de Klerk NH, Musk AW, Hobbs MS. Environmental exposure to crocidolite and mesothelioma: exposure-response relationships. Am J Respir Crit Care Med 1998; 157: 69-75.
21. Hodgson J, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann Occup Hyg 2000; 44: 565-601.
22. Christensen BC, Godleski JJ, Roelofs CR, Longacker JL, Bueno R, Sugarbaker DJ, et al. Asbestos burden predicts survival in pleural mesothelioma. Environ Health Perspect 2008; 116: 723-6.