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A Retrospective Analysis of Epidemiology Prognostic Factor and Response of Treatment of Malignant Pleural Mesothelioma

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ABSTRACT

Background: malignant pleural mesothelioma (MPM) represents a common malignant disease. It is an aggressive tumor arising from the mesothelial cells lining the pleura. There is an extremely poor prognosis and a vast majority of MPM patients are diagnosed in an advanced stage. Rapid progression of the disease, no effective therapeutic approach and resistance to chemotherapy and radiotherapy resulted in a median survival time of less than 12 months. **Aim of the Work:** this study aimed to analyze the clinic pathological profile, the various prognostic factors and treatment response of malignant mesothelioma patients in our center in terms of overall survival and progression free survival. **Patients and Methods:** this retrospective was conducted on Malignant Mesothelioma patients who presented to the Department of Clinical Oncology, Ain Shams University from 1 January, 2011 to 31 December, 2014. **Results:** the mean age of the included patients were 61.04 years with male predominance 50.6% and female 49.1%. Occupational risk was documented in only 11.1% of included patients; most patients live in the industrial environment (67.9%) and the rest in non industrial environment (32.1%). All patients had negative family history of cancer. All patients had negative surgical history, 66.7% of patients had positive history of asbestos exposure. The commonest co morbidity among the studied patients were HTN as it was accounted for 24.7% of the included patients followed by diabetes mellitus in 16% of patients on the other hand, only 3.7% of patients had no co morbidity. Dyspnea was the commonest symptoms (77.8%) among the included patients, followed by cough (33.3%) and chest pain in 12.3%, the other symptoms with lower presentation included hemoptysis and anemia. P.S 1(28.4%) was recorded among the included patients and 53.1% patients had P.S 2 while, rest of patients 18.5% had P.S 3. Patients were diagnosed by CT chest and pleural biopsy either US guided or CT guided, chest X ray, thoracoscopic biopsy, FNAC and open pleural biopsy. The results also showed that the median PFS among the included patients was 2 months. Median OAS was 6.1 months. **Conclusion:** best survival data in patients with MPM were currently reported from groups using multimodality treatment including MCR achieved either by EPP or extrapleural decortication for patients qualifying as far as tumor stage and functional reserve were concerned. In general, several treatment combinations have been applied ranging from systemic (neo- or adjuvant) to localized chemotherapy, neo- or adjuvant radiotherapy and others. **Recommendations:** The choice of the surgical procedure should be tailored according to tumor stage, performance status, and institutional experience. Morbidity and mortality of these treatment approaches have been reduced at experienced centers indicating that this complex treatment should be performed at dedicated high volume mesothelioma centers.

Keywords: epidemiology, malignant pleural mesothelioma.

INTRODUCTION

Malignant pleural mesothelioma (MPM) is considered to be a relatively rare tumor. In Great Britain, the incidence in males was 3.4/100 000, in France it was 2.3/100 000 and in the Netherlands it was 3.2/100 000 [(1)]. In Egypt, epidemiological data on MPM incidence was not available since there was no comprehensive national population-based cancer registry. However, official statistics, as well as Egyptian National Cancer Institute (NCI) and Hospital based registries, showed that MPM incidence in Egypt was rising markedly. The NCI hospital-based registry showed an increase in the relative frequency of MPM from 0.47% in 2001 to 1.3% in 2003 [(2)].In Egypt, according to NCI; Cairo University cancer registries pleural malignancy constituted 1.4% ranking 16th [(3)].

A study performed in Clinical Oncology Department, Ain Shams University showed that 304 patients were referred to the clinic between January 2003 and December 2008, for further management after being diagnosed with MPM. One hundred and ninety patients (62.5%) came from endemic areas (Shoubra El Kheima, Helwan, and El Hawamdia) and/or had a history of occupational asbestos exposure; the majority (101 patients) came from Shoubra El Kheima. One hundred and fifty-six patients (51.3%) had a history of smoking and the majority (128 patients) were men [(4)].According to Ain Shams Clinical Oncology Department in 2015 malignant mesothelioma constituted about 4.4%.

Occupational exposure to asbestos accounts for

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more than 80% of the cases makes MPM a preventable disease. Although the Western world is moving towards a levelling-off of ARD (Asbestos related disease) incidence, the continued use of asbestos in the developing world may lead to a global epidemic of MPM [(5)].The latency period of MM, i.e., the time elapsed from exposure to the offending agent (in particular, the aforementioned mineral fibers) to diagnosis is long; however, the time elapsed from the onset of malignancy to diagnosis is indeed short, MM producing symptoms shortly after its initial growth [(6)].A germ line mutation in the BAP1 gene has been linked to predisposition in some cases of MPM, Somatic mutations may also play a role in the development of MPM [(5)]. Patients with suspected malignant mesotheliomoa often have dyspnea and chest pain, they can also have pelural effusion,fatigue, insomnia, cough, chest wall mass, loss of appetite and loss of weight [(6)].

The recommended initial evaluation for suspected MPM includes: 1) CT of the chest with contrast, 2) Thoracentesis for cytologic assessment and 3) Pleural biopsy (eg, thoracoscopic biopsy [preferred].

However, cytologic samples are often negative even when patients have MPM [(7)].

Calretinin, WT-1, D2-40 and cytokeratin (CK) 5/6 are useful markers for the diagnosis of MPM, as markers that are typically positive in mesothlioma [(8)]. The histologic subtypes of mesothelioma include epithelioid (most common), biphasic or mixed and sarcomatoid. Patients with epithelioid histology have better outcomes than those with either mixed (biphasic) or sarcomatoid histologies [(8)].

The clinical factors relevant to management of MPM included basic epidemiologic variables, clinical condition, common blood assays, imaging assessment and gross tumor features, as well as the anatomic extent of the disease, many of these variables have been combined into prognostic categories to reinforce their predictive power [(9)]. As regard to the treatment of MPM, trimodality therapy using chemotherapy, surgery and hemithoracic RT has been used in patients with MPM. Median survival up to 29 months has been reported for patients who complete trimodality therapy. Nodal status and response to chemotherapy can affect survival in a small retrospective series; trimodality therapy using extrapelural pneumonectomy (EPP) did not improve survival when compared to patients who did not receive EPP [(10)]. Surgery is used for staging procedures or with palliative or curative intent. Using VATS or thoracoscopy, large biopsy samples can be obtained for proper pathological, molecular and IHC analyses. During this procedure, the local extent of the tumor can be examined. Pleural effusions can be drained and, if required, a decortication or pleurodesis can be carried out [(11)].

Radiotherapy (RT) can be used for different indications in mesothelioma as palliation [(12)], as preventive treatment and as part of a multimodality treatment [(13)].

A combined first-line regimen using cisplatin and pemetrexed (category 1) is considered the gold standard for MPM and is currently the only regimen approved by the U.S. Food and Drug Administration for MPM [(14)]. A phase III randomized trial assessed cisplatin/pemetrexed versus cisplatin alone in patients who were not candidates for surgery; the combined regimen increased survival when compared with cisplatin alone (12.1 vs. 9.3 months, P=.02) [(15)]. Other acceptable first-line combination chemotherapy options recommended by NCCN include: 1) Pemetrexed and carboplatin, which was assessed in 3 large phase II studies (median survival = 12.7, 14 and 14 months, respectively) [(16)]. A comparison of 1,704 patients with medically inoperable MPM treated with cisplatin/ pemetrexed or carboplatin/pemetrexed as part of an expanded access trial found that outcomes with the regimens were similar. The carboplatin/pemetrexed regimen is a better choice for patients with poor PS and/or comorbidities. Acceptable first-line single-agent options include pemetrexed or vinorelbine [(17)]. 2) Gemcitabine and cisplatin, which were also assessed in phase II studies (median survival = 9.6 to 11.2 months).

Gemcitabine and cisplatin may be useful for patients who cannot take pemetrexed [(18)].

Second-line chemotherapy options include, pemetrexed (if not administered first line) (category 1), vinorelbine, or gemcitabine [(19)]. Data suggested that rechallenging with pemetrexed was effective if patients had a good response to first-line pemetrexed [(20)]. Limited data are available to guide second-line therapy, although several agents are in clinical trials [(21)].

With all currently available therapies, response rates remain low and the goal of treatment must be optimal palliation. Two major symptoms, dyspnea and chest wall pain, remain the focus of palliative efforts in patients with advanced malignant mesothelioma. Because of the poor aeration of the lung, fatigue becomes debilitating with little help from supplemental oxygen [(22)]. Evidence of the palliative benefit of chemotherapy

was available for vinorelbine, pemetrexed/cisplatin and the combination of mitomycin, vinblastine and cisplatin [15].

The role of chemotherapy in the palliative treatment of MPM was the subject of an ongoing clinical trial sponsored by The British Thoracic Society and Cancer Research UK (Study ID No. MS-01). This trial was comparing chemotherapy with 'active symptom control', which can include palliative surgery and radiotherapy. Although chemotherapy, when applied judiciously, may help control some symptoms, adequate pain control and attention to respiratory function form the basis of effective palliation in MPM [23].

AIM OF THE WORK

This study aimed to retrospectively analyze the clinic pathological profile, the various prognostic factors and treatment response of malignant mesothelioma patients in our center in terms of overall survival and progression free survival.

PATIENTS AND METHODS

This retrospective was conducted on malignant mesothelioma patients who presented to the Department of Clinical Oncology, Ain Shams University from 1 January,2011 to 31 December, 2014.

PATIENTS

Inclusion criteria

- All patients with pathologically confirmed MPM were included in the analysis
- Age> 18 years.
- Non-pregnant women
- No prior chemotherapy and or radiotherapy.
- Adequate hematologic, renal, and liver functions as defined by:

Absolute neutrophil count (ANC) >2x10 9/L.
Platelet count ≥ 100 x 10 9/L.
Hemoglobin ≥10 gm /dl.
Total bilirubin ≤ Upper normal limit. SGOT (AST) and or SGPT (ALT) ≤2.5 x upper normal limit. Serum creatinine ≤1.5 x upper normal limit

METHODS

In this retrospective study patients were subjected to:

A) History and clinical examination:

History:

Personal history included:

- Age
- Sex
- Residence
- Occupation

Past history

-Medical comorbidities and previous treatments

Present history:

-symptoms and its duration
-Personal and family history of cancer.
-Performance status
-Asbestos exposure

Pathological history

- Histopathological subtype
- Site of tumor
- TNM staging

Clinical examination

- Including assessment of performance status,
- General examination,
- Locoregional evaluation, chest, heart, abdominal and neurological examination.

B) Work up

1-laboratory investigations

- Complete blood picture with total and differential count.
- Liver function tests "bilirubin, liver enzymes and serum albumin, and Renal function tests "blood urea and serum creatinine.

2-Radiological

- Plain X ray chest and or CT when needed, pelviabdominal ultrasound, CT abdomen

3-Histopathological studies for all patients:

Immunohistochemical examination done on tumor specimens imbedded in paraffin blocks

C) Staging: was done by CT chest

Treatment history

- Type
- Adequacy
- Compliance.

Evaluation and Follow up:

The tolerability of chemotherapy was evaluated before each cycle of chemotherapy Hematologic assessment performed before each cycle. &Toxicity. Clinical examination was performed every 3 months in the first 2 years and every 6 months there after. Radiological assessment included CT chest and pelviabdominal every 3 cycles of chemotherapy. After completion of chemotherapy all patients have been subjected to follow up with CT chest & pelviabdomen and the chest and pelviabdominal CT with contrast every 6 months in the first 2 years and every 1 year thereafter.

The time and the site(s) of relapse (local, regional or distant) of each patient were recorded. The patients who developed treatment failure either local or distant have been evaluated clinical, radiological (CT) and histopathological "when

indicated" to determine site and extent of treatment failure.

-Response

A complete response (CR) was defined as the complete disappearance of all disease with no new lesions. A partial response (PR) was defined as 50% or more reduction from baseline of the sum of the products of the perpendicular diameters of target lesions when only bidimensionally measurable disease was present, or as 30% or more decrease in the sum of the greatest diameters of target lesions when only un-idimensionally measurable lesions were present.

When both types of diseases were present, PR was defined as a reduction of either type of disease as defined above, with the other type at least stable, with non-measurable lesions being at least stable, and no new lesions.

Tumor progressive disease (PD) was defined as the appearance of new or relapsed lesions, a 50% or higher increase in the sum of products of all bidimensionally measurable lesions over the smallest sum observed when only bidimensional disease was present, or a 25% or higher increase in the sum of the longest dimension of unidimensionally measurable lesions over smallest sum observed when only unidimensional disease was present [(15)].

Toxicity to treatment: was assessed after each cycle of chemotherapy to evaluate the treatment tolerability.

Disease free Survival and Progression free survival:

Disease free survival (DFS) was calculated from the date of diagnosis to the date of disease recurrence and or distant metastasis and **Overall survival** (OS) from the date of diagnosis to the date of death or the date of last follow up. The median duration of DFS and OS were calculated using the Kaplan-Meier method.

The study was approved by the Ethics Board of Ain Shams University.

Data collection and Analysis

The collected data were revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 15.0 for windows; SPSS Inc, Chicago, IL, 2001.

Data were presented and suitable analysis was done according to the type of data obtained for each parameter.

Descriptive statistics

Mean, standard deviation (± SD), minimum and maximum values (range) for numerical data, frequency and percentage of non-numerical data.

Analytical statistics

The Independent-Samples T Test was used to assess the statistical significance of the difference between the study groups means. Chi-Square test was used to examine the relationship between two qualitative variables.

RESULTS

This retrospective study was conducted on 81 patients with pathologicaly proven malignant mesothelioma, who presented to the Clinical Oncology Department of Ain shams University Hospital from 1Jan. 2011 to 31Dec. 2014.

Clinicopathologic and demographic criteria of the studied population

Table 1: distribution of the studied cases according to demographic and clinical data (n=81)

	No.	%
Age		
<50	5	6.2
50 – 59	34	42.0
60 – 69	23	28.4
70 – 79	17	21.0
≥80	2	2.5
Min. – Max.	39.0 – 84.0	
Mean ± SD.	61.04 ± 9.46	
Sex		
Male	41	50.6
Female	40	49.4
Occupation		
Non risky	72	88.9
Risky	9	11.1
Address		
Non industrial	26	32.1
Industrial	55	67.9
Family history		
Irrelevant	81	100.0
Relevant	0	0.0
Surgical history		
Irrelevant	81	100.0
Relevant	0	0.0
Risk factor		
Non	27	33.3
Exposure to asbestos	54	66.7
Comorbidity		
Non	47	3.7
Asthmatic	3	3.7
Cardiac	4	4.9
HCV	1	1.2
HTN	20	24.7
DVT	2	2.5
CHD	1	1.2
DM	13	16.0
Hepatic	3	3.7

IHD	1	1.2
Arrhythmia	1	1.2
Anal cancer	1	1.2
Hypothyroidism	1	1.2
Symptoms of presentation		
Asymptomatic	1	1.2
Chest pain	10	12.3
Cough	27	33.3
Dyspnea	63	77.8
Anemia	1	1.2
Hemoptysis	2	2.5
ECOG performance		
PS1	23	28.4
PS2	43	53.1
PS3	15	18.5
Diagnostic investigation		

Diagnostic investigation	No.	%
Open pleural biopsy	5	6.2
CXR	75	90
Excisional biopsy from SC axillary nodule	1	1.2
FNAC from effusion	15	18
Ct guidedPleural biopsy	58	69.6
Thoracoscopic pleural biopsy	11	13.2
Us guided pleural biopsy	2	2.4
Ct chest	81	100

This table showed that the mean age of the included patients were 61.04 years with male predominance 50.6% and female 49.1%. Occupational risk was documented in only 11.1% of included patients, most patients live in the industrial environment (67.9%) and the rest in non industrial environment (32.1%). All patients had negative family history of cancer.

All patients had negative surgical history, 66.7% of patients had positive history of asbestos exposure. The commonest comorbidity among studied patients were HTN as it accounted for 24.7% of the included patients followed by diabetes mellitus in 16% of patients on the other hand only 3.7% of patients had no co morbidity.

Dyspnea was the commonest symptom (77.8%) among the included patients, followed by cough 33.3% and chest pain in 12.3%, the other symptoms with lower presentation includes hemoptysis and anemia. P.S 1(28.4%) was recorded among the included patients and 53.1% patients had P.S 2, while rest of patients 18.5% had P.S 3. Patients were diagnosed by CT chest and pleural biopsy either US guided or CT guided, chest X-ray, thoracoscopic biopsy, FNAC and open pleural biopsy.

Table 2: distribution of the studied cases according to histopathological type(n=81)

Histopathologicaltype	No.	%
Epithelial	67	82.7
Biphasic	4	5.0
Sarcomatoid	10	12.3

This table showed that 82.7% of patients had epithelial type mesothelioma,12.3% had sarcomatoid type and 5% had biphasic.

Table 3: distribution of the studied cases according to stage(n=81)

Stage	No.	%
I	1	1.2
Ib	9	11.1
II	36	44.4
III	20	24.7
IV	15	18.5

This table showed that stage II was the commonest stage in the included patients 44.44% followed by stage III in 24.7% ,IV in 18.5%,Ib in 11.1% and I in 1.2%.

Table 4a: distribution of the studied cases according to surgery(n=81)

Surgery	No.	%
No	47	58.0
Curative	1	1.2
Palliative	33	40.7

Table 4 b: distribution of the studied cases according to surgery (n=81)

Surgery	No.	%
Chest tube	17	21.0
Debulking	1	1.2
Decortication	5	7.4
Palliative Debulking surgery	1	1.2
Pleurodesis	8	9.9

This table showed that 58.0% of patients had no surgical interference and 40.7% had palliative surgical interference but only 1.2% patients had curative interference

Table 5: distribution of the studied cases according to radiotherapy (n=81)

Radiotherapy	No.	%
No	60	74.1
Adjuvant radiotherapy	2	2.5
Palliative radiotherapy	19	23.5

This table showed that 74.1% of patients had no radiotherapy on the other hand 2.5% had adjuvant radiotherapy and 23.5% had palliative radiotherapy

Table 6: distribution of the studied cases according to chemotherapy1st line(n=81)

	No.	%
Gem/Carb	3	3.7
Gem/CIS	54	66.7
Alemta	1	1.2
Alemta/carb	2	2.5
Alemta/Cis	2	2.5
Carboplatin	2	2.5
Navilbine	1	1.2
VIP/CIS	1	1.2
BSC	**15**	**18.5**
Numbers of cycles		
Min. – Max.	1.0 – 10.0	
Mean ± SD.	4.43 ± 1.87	

This table showed that the most common used 1st line chemotherapiotic regimens among included patients was Gem\Cis in 66.7% of patients with mean number of cycles was 4.43,18.5% of the patients had only best supportive care.

Table 7: distribution of the studied cases according to first line chemotherapy response (n=81)

Response to 1st line chemotherapy	No.	%
CR	2	2.5
PD	37	45.7
PR	26	32
SD	16	19.8

This table showed that after receiving first line chemotherapy only 2.5% of patients showed complete remission after receiving complete 6 cycles gem/cis, 45.7%showed PD, 32% showed PR and 19.8% showed SD.

Table 8: distribution of the studied cases according to chemotherapy 2ndline(n=14)

Chemotherapy2ndline regimen	No.	%
ALEMTA/CIS+3rd	5	35.7
GEM/CIS	1	7.1
Navilbine	7	50.0
VIP/CIS	1	7.1
Numbers of cycles		
Min. – Max.	2.0 – 6.0	
Mean ± SD.	4.14 ± 1.56	

This table showed that the most common chemotherapy used as second line among included 14 patients was navelbine in 50% followed by alemta\cis 3rd in 35.7% with mean number of cycles 4.14.

Table 9: distribution of the studied cases according to response to 2nd line(n=14)

Response to 2nd line chemotherapy	No.	%
Progressive	7	50
PR	4	28.6
SD	3	21.4

This table showed that among 14 patients had second line chemotherapy 50% showed progressive course and 28.6% had PR,21.4% had SD.

Table 10: distribution of the studied cases according to chemotherapy 3rdline(n=5)

Chemotherapy3rdline	No.	%
Alemta	1	20.0
Alemta/carb	1	20.0
Alemta/CIS	3	60.0
Numbers of cycles		
Min. – Max.	5.0 – 6.0	
Mean ± SD.	5.80 ± 0.45	

This table showed that only (60%) of patients who received 3rd line chemotherapy in the form of alemta\cis and(20%)recieved alemta\carb, another(20%) patients received alemta alone with mean number of cycles 5.80.

Table 11: distribution of the studied cases according to response to 3rdline(n=5)

Response to 3rd line	No.	%
PD	1	20.0
PR	1	20.0
SD	3	60.0

This table showed that after receiving 3rd line chemotherapy 60% of patients showed SD,20% showed PR and PD.

Table 12: distribution of the studied cases according to treatment modality (n=81)

Treatment modality	No.	%
Surgery + CTX	20	24.7
Surgery + CTX + RTX	8	9.9
BSC	15	18.5
CTX only	27	33.3
CTX + RTX	11	13.6

This table showed the different treatment modality given to patients: 20 patients(24.7%) received combined surgery&chemotherapy,8 patients (9.9%) received trimodality therapy, while 27 patients(33.3%) received chemotherapy alone,11 patients(13.6%) received radiotherapy in combination with chemotherapy, on the other hand15 patients(18.5%) were on BSC.

Table 13: distribution of the studied cases according to chemotherapy toxicity (n=81)

Chemotherapy toxicity	No.	%
No	61	75.3
Yes	20	24.7

As regard chemotherapy toxicity among included patients 75.3% had no toxicity but 24.7% had toxicity.

Table 14: distribution of the studied cases according to chemotherapy toxicity (n=81)

Chemotherapy toxicity	G1-G2	G3	G4	No.	%
Anemia	4	6		10	12
Diarrhea	1			1	1.2
Thrombocytopenia	4	2		6	4.9
Impaired KFT				3	3.6
Elevated liver enzymes				1	1.2
Melena				1	1.2
Neuropayhy	2			1	1.2
Neutropenia		1		1	1.2
Rectal bleeding				1	1.2
Vomiting	4	1	1	6	4.9

Survival outcomes (Several analysis for OS and PFS)

Table 15 : progression free and overall survival curve

	Mean	Median	% 2 years	% 5 years	End of study
Progression free survival	4.2	2.0	-	-	0.0
Overall survival	10.4	6.1	12.3	1.2	0.0

This table showed that the median PFS among included patients was 2 months. Median OAS was 6.1 months.

Table 16: descriptive analysis of the studied cases according to follow up period (n=81)

	Min. – Max.	Mean ± SD	Median
Follow up period (months)	0.0 – 62.93	10.39 ± 10.94	6.10

This table showed that the median follow –up time was 6.10 months.

Table 17: Kaplan-Meier survival curve for progression free survival

		Mean	Median	% 2 years	% 5 years	% End of study	Log rank	
							□□	p
Chemotherapy toxicity	No	4.9	2.0	-	-	0.0	2.693	0.101
	Yes	2.6	1.0	-	-	0.0		
Age	<50	0.6	1.0	-	-	0.0	8.407	0.078
	50 – 59	4.6	2.0	-	-	0.0		
	60 – 69	5.3	3.0	-	-	0.0		
	70 – 79	3.4	1.0	-	-	0.0		
	≥80	1.0	1.0	-	-	0.0		
ECOG performance	PS1	5.7	3.1	-	-	0.0	3.935	0.140
	PS2	3.6	1.0	-	-	0.0		
	PS3	1.6	0.9	-	-	0.0		
Comorbidity	Non	4.2	2.0	-	-	0.0	0.015	0.903
	Yes	4.2	1.0	-	-	0.0		
Stage	I	1.0	1.0	-	-	0.0	2.944	0.567
	Ib	3.3	0.9	-	-	0.0		
	II	4.7	1.0	-	-	0.0		
	III	4.8	3.0	-	-	0.0		
	IV	2.1	1.0	-	-	0.0		
Histopathologial type	Epithelial	4.7	2.0	2.5	-	0.0	4.718	0.095
	Biphasic	1.8	1.0	-	-	0.0		
	Sarcomatoid	1.2	1.0	-	-	0.0		
Chemotherapy 1st line	Alemta	5.1	0.9	-	-	0.0	1.236	0.539
	Gem/CIS	4.4	2.0	-	-	0.0		
	Other regimen	2.2	2.0	-	-	0.0		
Chemotherapy 2nd and 3rd line	Alemta	2.4	1.0	-	-	0.0	1.245	0.536
	Other regimen	3.6	2.0	-	-	0.0		
	No 2nd line	4.6	2.0	-	-	0.0		
Surgery	No	3.8	2.0	-	-	0.0	2.976	0.226
	Curative	-	-	-	-	100.0		
	Palliative	4.1	1.0	-	-	0.0		

All the insignificant variables found with PFS: chemotherapy toxicity**(p valu =0.101)**, age**(p valu=0.078)**, ECOG performance**(p valu =o.140),** co morbidity**(p valu= 0.903**), stage**(valu= 0.567)**, histopathologial type**(p valu= 0.095)**, chemotherapy 1st line**(pvalu= 0.539)**, chemotherapy 2nd and 3rd line**(p valu= 0.536)** and surgery had insignificant effect on progression free survival**(p valu= 0.226**).

Table 18:Kaplan-Meier survival curve for Overall survival

		Mean	Median	%2 years	%5 years	% End of study	Log rank	
							□□	p
Chemotherapy toxicity	No	10.7	6.1	13.1	1.6	0.0	0.346	0.556
	Yes+ Death+ DVT	9.3	6.0	10.0	-	0.0		
Age	<50	10.3	12.2	-	-	0.0	4.247	0.374
	50 – 59	11.9	6.1	17.6	2.9	0.0		
	60 – 69	10.0	7.1	13.0	-	0.0		
	70 – 79	8.7	6.0	5.9	-	0.0		
	≥80	3.5	2.0	-	-	0.0		
Comorbidity	Non	11.4	6.1	17.0	2.1	0.0	0.586	0.444
	Yes	9.0	7.1	5.9	-	0.0		
Chemotherapy 1st line	Alemta	8.5	5.1	-	-	0.0	0.844	0.656
	Gem/CIS	12.6	7.2	16.7	1.9	0.0		
	Other regimen	10.1	6.0	14.3	-	0.0		
Surgery	No	8.9	5.1	8.5	2.1	0.0	2.661	0.264
	Curative	23.3	23.3	-	-	0.0		
	Palliative	12.1	7.2	18.2	-	0.0		
Radiotherapy	No	9.4	6.1	3.9	-	0.0	2.598	0.273
	Adjuvant radiotherapy	26.4	23.3	50.0	-	0.0		
	Palliative radiotherapy	11.9	5.1	15.8	5.3	0.0		

All the insignificant variables found with OS: chemotherapy toxicity**(p valu= 0.556),** age**(p valu= 0.374),** Comorbidity**(p valu= 0.444)**, Chemotherapy 1st line **(p valu =0.656),** surgery**(p valu= 0.264)** and radiotherapy(**p valu= 0.273**).

Table 19: ECOG performance(as a significant variable on OS)

	ECOG performance	Mean	Median	% 2 years	% 5 years	% End of study	Log rank	
							□□	p
Overall survival	PS1	13.3	11.1	21.7	-	0.0	18.519*	<0.001*
	PS2	11.1	7.1	11.6	2.3	0.0		
	PS3	3.9	2.0	-	-	0.0		

This table showed that there was a significant difference between overall survival and performance status with **p-value(<0.001**).

Table 20: stage(as a significant variable on OS)

	Stage	Mean	Median	% 2 years	% 5 years	% End of study	Log rank	
							□□	p
Overall survival	I	4.1	4.1	-	-	0.0	10.328*	0.035*
	Ib	8.3	5.1	-	-	0.0		
	II	13.2	8.2	19.4	-	0.0		
	III	10.3	4.0	10.0	5.0	0.0		
	IV	5.5	4.0	-	-	0.0		

This table showed that there was significant differences between tumor stage and overall survival (**p-value 0.035)**

Table 21: histopathological type(as a significant variable on OS)

	Histopathological type	Mean	Median	% 2 years	% 5 years	% End of study	Log rank	
							□□	p
Overall survival	Epithelial	10.5	7.1	13.4	-	0.0	6.624*	0.036*
	Biphasic	21.6	9.1	25.0	25.0	0.0		
	Sarcomatoid	5.0	4.1	-	-	0.0		

This table showed that there was a significant difference between overall survival and histopathological type with**(p-value 0.036**).

Table 22:BSC(as a significant variable on OS

	BSC	Mean	Median	% 2 years	% 5 years	% End of study	Log rank	
							□□	p
Overall survival	No Yes	12.0 3.3	7.1 2.0	15.2 -	1.5 -	0.0 0.0	24.899*	<0.001*
		-	-	- -	- -	-	-	-

This table showed that there were significant differences between overall survival and best supportive care **(p-value <0.001)**

Table 23: chemotherapy 2nd and 3rd line (as a significant variable on OS

	Chemotherapy 2nd and 3rd line	Mean	Median	%2 years	%5 years	% End of study	Log rank	
							□□	p
Overall survival	Alemta Other regimen No 2nd line	20.7 23.6 8.1	15.2 27.3 5.1	30.0 75.0 6.0	10.0 - -	0.0 0.0 0.0	10.762*	0.005*

This table showed that there was significant differences between overall survival and Chemotherapy 2nd and 3rd line **(p-value 0.005)**

Table 24: radiotherapy(as a significant variable on OS

	Radiotherapy	Mean	Median	% 2 years	% 5 years	% End of study	Log rank	
							□□	p
Overall survival	No Adjuvant radiotherapy Palliative radiotherapy	4.2 19.3 2.2	2.0 19.3 1.0	- - -	- - -	0.0 0.0 0.0	7.792*	0.020*

This table showed that there was significant differences between overall survival and radiotherapy (**p-value 0.020).**

Table25: treatment modality: (as a significant variable on OS

	Treatment modality	Mean	Median	% 2 years	% 5 years	% End of study	Log rank	
							□□	P
Overall survival	**Surgery + CTX**	12.1	8.2	15.0	-	0.0	26.336*	<0.001*
	Surgery + CTX + RTX	16.7	7.2	37.5	-	0.0		
	BSC	3.3	2.0	-	-	0.0		
	CTX only	10.3	7.1	11.1	-	0.0		
	CTX + RTX	12.7	6.0	9.1	9.1	0.0		

This table showed how different treatment modalities affect OS,it shows that trimodality therapy improved OS with**(p-value less than 0.001**)

DISCUSSION

Karabulut *et al.* [24] found that malignant pleural mesothelioma (MPM) is a relatively rare and highly lethal tumor induced by asbestos exposure, with a growing incidence over the last decades. As it has a highly aggressive behavior; there have been some studies to identify more accurate prognostic factors and staging systems and to investigate novel treatment regimens. However, the relative rarity of this neoplasm has limited research opportunities, and only a few clinical trials have been done or are on-going.

Billé *et al.* [25] found that chemotherapy alone for advanced stages, or in combination with surgery and/or radiotherapy for resectable disease, is the mainstay of treatment. For many patients with locally advanced disease that is not surgically resectable because of tumor invading the chest wall or the mediastinal structures, treatment options are limited to palliative chemotherapy, radiotherapy or best supportive care alone .The same authors found that various prognostic factors for survival in MPM have been described. The most significant prognostic factor remains the histology; epithelioid mesothelioma is the subtype with the best prognosis. The tumor, node and metastasis staging system has been validated in several large series, but the radiological assessment of tumor extension is limited and can underestimate the real extent of the tumor.

In the present study, we retrospectively analyzed the clinic pathological criteria, the various prognostic factors and treatment response of malignant mesothelioma patients presented from 1 Jan 2011 to 31 Dec 2014 at the Department of Clinical Oncology, Ain Shams Hospital in terms of overall survival and progression free survival,81 patients were included. We found that the mean age of the included patients was 61.04 years with male predominance 50.6% and female 49.4%. Occupational risk was documented in only 11.1% of included patients, most of the patients (67.9%) lives in the industrial environment, in Shobra, Helwan. Kalyobia and Elsowais and the rest in non industrial environment (32.1%).

All patients had negative family history of cancer and had negative surgical history. Positive family history of asbestos exposure was recorded in 66.7% of patients. the commonest co morbidity among the studied patients were HTN as it accounted for 24.7% of the included patients followed by diabetes mellitus IN(16%) of patients. On the other hand, only 3.7% of patients had no co morbidity as regarding to performance status (28.4%) of included patients had P.S 1 and 53.1% had P.S 2 the rest of patients (18.5%) had P.S 3.

Similarly, **Labby *et al.*** [26] found that of the 78 MPM patients included in this study, 66 were men and 12 were women. The median patient age at study entry was 66 years (range, 41–80 years).

While, **Akl *et al.*** [27] demonstrated after full analyzing demographic data of the 165 patient study population and they showed that the mean age cases was 50.78 ±13.5 years, ranging from 15 to 83 years, 94 were males (57%) and 71 were females (43%), male/female ratio was 1.3/1. These results are similar to study done by **Billé *et al.*** [25] as they concluded that among the 413 patients with MPM who were treated between January 2000 and December 2013 that the patient's median age was 71 years and 147 (77%) were men.

In addition, **Ceresoli *et al.*** [28] in their study they found that among the 715 MPM cases diagnosed at the six participating Hospitals in the study period median age was 75 years, with a range from 70 to 92. Forty-eight cases (20%) were 80 years or older. Patients were mainly males (64%), with ECOG-PS of 0–1 (94%).

This is supported by the findings of **Adel *et al.*** [4] who showed that out of the 165 cases, 45 (27.3%) cases were reported from Helwan, followed by 34 (20.6%) cases from Shobra and in the neighbouring areas of both, 25 (15.2%) cases in Giza, and 11 (6.7%) cases in Kaliobeya. From Upper Egypt 21 (12.7%) cases were reported and 29 (17.5%) cases were from other parts of Egypt including Alexandria, Alesmaeleia, Alseweis, Algharbeia, Alsharqeia and areas in Cairo other than Helwan and Shobra.

This is in coincidence with results of **Akl *et al.*** [27] who found that occupational risk factors account for only 23 (13.9%) patients as they were working in asbestos industries, while 142 (86.1%) patients were not exposed to this hazard during working hours.

As regarding major comorbiditied **Ceresoli *et al.*** [28] found that no major co morbidity was found in 145 patients (60%), whereas at least one comorbid condition was reported in 92 (38%). Main reported co morbidities were peripheral vascular disease, diabetes and chronic liver disease**.**

However, **Karabulut *et al.*** [24] in their retrospective study on 53 patients with MPM they found that the performance status on admission was ECOG 0 in four patients (7.5%), ECOG 1 in 44 patients (83%) and ECOG 2 in five patients (9.4%)**.**

In the present study we found that dyspnea was the commonest symptoms among the included patients (77.8%) followed by cough (33.3%) patients and chest pain in 12.3% patients the other symptoms with lower presentation included hemoptysis and anemia.

This is partially in agreement with results of **Brims *et al.*** [29], they showed that 80.9% of patients presented with dyspnea, 58.5% presented with chest pain and 47.5% presented with weight loss.

In the present study the cases were diagnosed with CT chest, pleural biobsy either ultrasound guided or CT guided also thoracoscopic biopsy used for diagnosis and FNAC from effusion. Chest X- ray was the initial tool of diagnosis in almost all the cases.

This is matched with the study of **Akl *et al.*** [27] who found that thoracoscopy was done in 70 (42.4%)cases, open pleural biopsy in 56 (33.9%) cases, fine needle aspiration cytology (FNAC) in 10.3% (17 cases), CT-guided biopsy in 9.1% (15 cases), a single case was diagnosed by thoracocentesis (0.6%) .

In the present study as regarding pathological type 82.7% of patients had epithelial type mesothelioma,12.3% had sarcomatoid type and (5%) had biphasic.

These results coincide with the study done by **Genestreti *et al.*** [30] where the histologic examination revealed an epitheliod subtype in 7 (88%) cases and a mixed subtype in 1 (12%).

In addition **Akl *et al.*** [27] found that epithelioid mesothelioma represents the most common histopathological subtype of MPM diagnosed in 114 (69.1%) cases, followed by biphasic subtype in 43 (26.1%) and sarcomatoid type in 8 (4.8%) cases. No case was diagnosed as desmoplastic.

Ceresoli *et al.* [28] found that more than two thirds of patients had an epithelioid histological subtype.

In addition, **Karabulut *et al.*** [24] found that histological subtypes, 35 patients (66%) were epithelial, 3 patients (5.7%) were sarcomatous, 7 patients (13.2%) were mixed type and 8 patients (15.1%) had undefined pathology.

In the present study regarding TNM staging, stage II was the commonest stage in the included patients(44.44%) followed by stage III in 24.7% ,IV in 18.5%,Ib in 11.1% and I in 1.2%.

However, **Genestreti *et al.*** [30] found that 7 patients (88%) had stage I and 1 (12%) had stage II diseases**.**

This is partially in agreement with results of **Ceresoli *et al.*** [28] who reported stage I&II in 149 patients (62%), while stage III–IV in 92 (38%) patients.

While, **Karabulut *et al.*** [24] found that in terms of stages, 17 patients (32.1%) were stage 1,18 (34%) patients were stage 2, 7 (13.2%) patients were stage 3 and 11 (20.8%) were stage 4

Moreover **Liu *et al.*** [31] found that thirteen patients with low radiologic TNM stage (stage I, n= 3; stage II, n =10) ; whereas seventeen patients with high radiologic TNM stage (stage III, n = 12; stage IV, n = 5)

On the other hand, another study done by **Labby *et al.*** [26] showed that CT staging identified 11 patients as stage I, 3 patients as stage II, 34 patients as stage III, and 30 patients as stage IV.

In the present study, we found that 58% of patients had no surgical interference due to advanced disease and 40.7% had palliative surgical interference either before or after receiving chemotherapy with or without radiotherapy, but only 1.2% patients had curative debulking surgical interference. The surgical interference included extrapleural pneumonectomy in 2 patients,decortication in 6 patients, palliative insertion of intercostal chest tube in 17 patients and pleurodysis in 8 patients.

Akl *et al.* [27] showed that surgery was performed in 58 cases either alone or combined with chemotherapy, extrapleural pneumonectomy in 49 cases, out of which in addition pericardiectomy was performed in 3 cases and excision of extrathoracic swelling in another 3 cases. Pleurectomy was the choice in 8 cases and metastasectomy in a single case.

While, **Adel *et al.*** [4] showed that seven patients (2.3%) underwent surgery in the form of extrapleural pneumonectomy or pleurectomy/decortication and were excluded from this analysis due to incomplete data. Those patients did not receive neo- or adjuvant chemotherapy and did not return for follow up.

This is partially in agreement with results of **Billé *et al.*** [25] who found that at the time of surgery, all 52 patients were found to have unresectable disease due to chest wall involvement (n= 47) patients or mediastinal invasion (n= 5) patients.

However **Karabulut *et al.*,** [24] study, they found that a total of 19 patients were referred to the clinic after surgery. Twenty- six patients combined treatment with radiotherapy plus

chemotherapy and trimodality were performed in 12 patients, respectively.

Regarding radiotherapy, the present study showed that 74.1% of patients had no radiotherapy on the other hand 2.5% had adjuvant radiotherapy and 23.5% had palliative radiotherapy either to areas of bony metastasis or to the site of biopsy.

In **Adel *et al.*** [4] study they recorded that palliative radiotherapy was given to 42 patients (13.8%), either as hemithoracic irradiation or localized radiotherapy to the biopsy site

In the present study, as regard chemotherapy given the most common used chemotherapy regimens among included patients was Gem\Cis in(66.7%) of patients with mean number of cycles was 4.43 and the most common chemotherapy used as second line among 14 patients was navelbine in 50% followed by alemta\cis as 3rd in 35.7% , 5 patients with mean number of cycles 4.14. While, 60 % of patients had received alemta\carb and alemta/cis as 3rd line and alemta alone in 20% with mean number of cycles 5.80. in the present study patients received chemotherapy either as a monomdality therapy in 33,3% or as a part of multimodality therapy combined with surgery and radiotherapy in 9,9%. 18.5% of patients had only best supportive care due to bad performance and old age.

This is in accordance with the study done by **Adel *et al.*** [4] who showed that one hundred and sixty-nine patients (55.6%) received chemotherapy. The majority of patients (150 patients, 91.7%) received platinum-based chemotherapeutic regimens (etoposide/cisplatin, gemcitabine/cisplatin, vinorelbine/ cisplatin) while 19 patients (11.2%) received non-platinumbased chemotherapy (ifosfamide/doxorubicin, or high-dose methotrexate). Elderly patients older than 70 years old and/or patients with a bad PS who could not tolerate chemotherapy were offered best supportive care (BSC)

Similarly, **Ceresoli *et al.*** [28] showed that overall, 198 patients (82%) underwent an active treatment, whereas 43 (18%) received best supportive care (BSC) only. Active treatment was given in 18 patients who consisted of multimodality therapy (including any kind of surgery, chemotherapy and in some cases radiotherapy) and chemotherapy as single modality therapy was given in 180 patients. In patients more than75 years (n = 122), 3 cases were treated with multimodality therapy, 86 with chemotherapy, and 33 received BSC. The respective numbers for patients more than 80 years (n = 48) were 0, 30 and 18 cases.

However **Billé *et al.*** [25] study showed that chemotherapy was given in all study patients (177 patients) and 90% of patients received pemetrexed.

After receiving first line chemotherapy in the present study we found that only 2.5% of patients showed complete remission, 45.7%showed PD, 30.9% showed PR and 19.8% showed SD among 14 patients who had second line chemotherapy; 50% patients showed progressive disease and 28.6% had PR and,21.4% had SD.and after receiving 3rd line chemotherapy 60% of patients showed SD, while 20% showed PR and PD.

This is partially in agreement with results of **Ceresoli *et al.*** [28], they showed that first-line chemotherapy (as single treatment or as a part of multimodality therapy) was mainly pemetrexed based, most patients treated with the combination of pemetrexed and carboplatin. Overall, 178 patients (74% of the study population) received a pemetrexed-based regimen. Response was not assessed or not reported in 23 cases; a complete or partial response was achieved in 1 and 45 patients, respectively, for a response rate of 23%; 75 patients had stable disease (38%) and 54 patients progressed; therefore, A second-line treatment was administered to 87 patients

About a quarter of patients were re-challenged with pemetrexed; the remaining received a gemcitabine or vinorelbine based regimen. Overall, response to second-line therapy was observed in 4 cases (28.6%) in form of PR, with 3 patients having stable disease.

This coincides with results of **Karabulut *et al.*** [24] who showed that the number of patients who responded to treatment was 29 (54.7%). Complete response was achieved in two patients (3.8%) and partial response in 12 patients (22.6%). 34 patients (64.2%) had stable disease. Post-treatment progression was detected in 5 patients as locoregional relapse (9.4%).

Also, this is partially in agreement with results of **Adel *et al.*** [4] who showed that 152 of the patients who received chemotherapy (89.9%) were assessable for response (after at least two courses of chemotherapy). Four patients (2.6%) attained complete response (CR), 33 patients (21.7%) had partial response (PR) and 68 patients (44.7%) had stable disease (SD), while, 47 patients (30.9%) progressed PD. For analysis in this study, patients were categorized into two groups according to response. Responders comprised CR+PR+SD (105 patients) while, non-responders comprised PD (47 patients). Sixty-nine patients received 2 lines of chemotherapy. The range of

cycles was 2–8 cycles per regimen, median 4 cycles.

As regard chemotherapy toxicity generally almost all lines of treatment were well tolerated, among included patients we found that 75.3% had no toxicity but 22.2% had toxicity in the form of meylosuppresion; neutropania G3 was recorded in 1 patients, as neutrophils less than 1000(n= 1), anemia G2 in 4 patients was recorded while G3 in 6 patients, thrombocytopenia G2 was recorded in (n= 4) patients while G3 was recorded in 2 patients, vomiting G2 was recorded in 4 patients, while G3 was recorded in 1 patients &G4 in 1 patients ,neuropathy was recorded in 1 patients, elevated serum creatinin was recorded in 3 patients and diarrhea was recorded in 1 patients.also melena was reported in one patient, in addition to rectal bleeding which was recorded in 1 patients and elevated liver enzymes was also recorded in one patients.

This is in coincidence with results of **Karabulut *et al.*** [24] , they showed that all treatments were in general well tolerated, but the serious adverse events were observed, including grade III–IV myelosuppression and radiation pneumonia determined by physical examination and confirmed radiologically in 4 and 6 patients, respectively.

In the present study we have found that the median PFS among included patients was 2 months, median OS was 6.1 months and median follow-up time was 6.1 moths (range 0.0-62.9 months) .

Also, **Ceresoli *et al.*** [28] study showed a median follow-up of 40.1 months (range 0.2–80.8 months), the median OS was 11.4 months.

However in the study done by **Karabulut *et al.*** [24] they showed that progression-free survival of 11 months and overall survival of 14 months.

This is supported by the finding of **Adel *et al.*** [4] who showed that the follow-up period of the study patients population ranged from 3–36 months. Survival data was available for 181 patients. The median overall survival (OS) was 8.00 months. Whil, the median overall survival was 16 months in **Liu *et al.*** [31] study.

Domen *et al.* [32] study included a total of 101 patients and they recorded overall median survival as 18.3 months.

This coincides with another study of **Papadatos-Pastos *et al.*** [33] who found that in a total of 65 patients with advanced MPM. The PFS was 2.5 months and OS was 8 months**.**

Moreover **Wang *et al.*** [34] showed that the median PFS for all patients was 3.0 months and the median OS was 7.2 months.

Also, **Linton *et al.*** [35] in their study recorded 910 patients as median overall survival of 10.0 months**.**

In the present study, we found that chemotherapy toxicity, age, ECOG performance, comorbidity, stage, histopathologial type, chemotherapy 1st line, chemotherapy 2nd and 3rd lines and surgery had insignificant effect on progression free survival as well as overall survival. However as regard prognostic factors that affect survival we have found that good performance status(PS 1&2) improved the OS with (pvalue less than 0.001),tumor stage(stage 2 improved OS rather than stage 3 &4) with (pvalue=0.035) but the improvement of PFS was not significant (pvalue 0.567) .Regarding tumor pathological type, patients with sarcomatoid subtype,showed decreased OS with no significant effect on PFS, in comparison with epithelial &biphasic subtypes(pvalue =0.036),We have found that in patients who recieved best supportive care a prolonged OS was recorded with no significant effect on PFS, while in patients who had received Chemotherapy 2nd and 3rd line and in patients who had received adjuvant radiotherapy a significant overall survival was recorded of p-value 0.005, 0.020, respectively , without any effect on PFS,patients who received trimodality therapy significantly affect OS P-VALUE less than o.oo1 with improvement of PFS but it was not significant.

However, **Montanaro *et al.*** [36] in a large, population-based study, they found that younger age at diagnosis, female gender and epithelioid histotype were all associated with better prognosis. while, asbestos exposure and treatment offered were not associated with a statistically significant improvement in survival.

Currently, **Akl *et al.*** [27] showed that when comparing the overall survival to the modality of treatment, they have found that the survival time for cases subjected to surgery was about 4 months, for cases receiving only supportive treatment was about 9 months, for cases receiving only chemotherapy was about 10 months, while for cases subjected to combined treatment was 13 months. These differences in survival time were statistically significant, being the best for patients receiving chemotherapy. These results match those obtained by **Cicenas *et al.*** [37] whostudied the effect of treatment on MPM survival, they

have found that mean survival time after combined treatment (chemotherapy and surgery) was 12 ±2 months, compared with conservative treatment alone, which was only 6.0 ±2 months.

In another study carried out by **Thieke *et al.*** [38] who showed that multivariate analysis demonstrated that with respect to OS among all the variables tested, the male gender tended to result in worse prognosis although not reaching significance (Hazard Ratio (HR) 1.7; 95 % Confidence Interval (CI95) 0.7–4.9; p = 0.2). The only two significant variables were the postoperative resection status R (per higher status HR 3.9; CI95 1.3–12.2; p = 0.01 and biphasic histology (HR 2.2;CI95 1.2–5. 4; p = 0.03). With respect to locoregional control, no variable tested reached significance in multivariate analysis.

Thieke *et al.* [38] studied a higher PS status and biphasic histology tended to result in reduced local control. With respect to distant control, both higher PS Status and biphasic histology were significantly associated with worse outcome. Other variables, clinical factors such as lymph node involvement (N status), and patient factors such as age had no influence on OS, LRC and DC.

Leuzzi *et al*. [39] showed that the only prognostic factors that significantly affected survival were age, asbestos exposure, ratio between metastatic and resected lymph nodes and histological type (p-value 0.006, 0.028, 0.002, 0.011 respectively).Probably the lower results obtained in our study in comparison with other studies done by **Karabulut *et al*.**[24], **Akl *et al*.**[27], **Ceresoli *et al*.** [28] were due to, the smaller sample size, the predominance of low performance statuse (PS 2-3) (71.6% patients),the associated comorbidities (96.3% patients) and the predominance of exposure to risk factor (prolonged exposure to asbestos) (66.7% patients) among the study population.

CONCLUSION AND RECOMMENDATION

Best survival data in patients with MPM were currently reported from groups using multimodality treatment including MCR achieved either by EPP or extrapleural decortication for patients qualifying as far as tumor stage and functional reserve were concerned. In general, several treatment combinations have been applied ranging from systemic (neo- or adjuvant) to localized chemotherapy, neo- or adjuvant radiotherapy and others. The choice of the surgical procedure should be tailored according to tumor stage, performance status, and institutional experience. Morbidity and mortality of these treatment approaches have been reduced at experienced centres indicating that this complex treatment should be performed at dedicated high volume mesothelioma centers.

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