

## CLINICAL REVIEW

### Clinical Review Section

	MEETING, SUBMISSION, OR ACTION	INDICATION, PROTOCOL, ISSUES	AGREEMENTS OR FDA RECOMMENDATIONS
		trial	<p>trial; conduct a Phase I trial with MTA + vitamins</p> <p>2. Stop current trial and open a new trial with a new protocol and new dose</p> <p>3. Continue current trial with addition of vitamins and recalculate sample size</p> <p>Lilly opted for #3</p> <p>After 150 patients are treated with vitamin supplementation, a survival analysis will be done polling the approx. 150 patient without vitamin supplementation</p> <p>FDA concern about ability to determine the benefit of adding vitamins to trial; no standard dose of vitamins</p> <p>Lilly to provide patient diary and pill count</p> <p>FDA not convinced that clinical benefit response data will warrant early filing</p>
March 8, 2000 (serial #212) and April 13, 2000 (serial #220)	Follow-up questions on EOP2	2 <sup>nd</sup> -line NSCLC trial as supporting trial for mesothelioma or Phase II data from mesothelioma trial(s) for support of mesothelioma	2 <sup>nd</sup> -line NSCLC trial as supporting trial for mesothelioma

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		early submission of the NDA based on an interim analysis of clinical benefit endpoints	FDA expects mature survival data
June 21, 2000	Follow-up to EOP2 re: mesothelioma indication	2 <sup>nd</sup> -line NSCLC trial to support mesothelioma indication  acceptance of an interim analysis secondary endpoints on the mesothelioma trial	2 <sup>nd</sup> -line NSCLC trial (superiority in survival) to support mesothelioma indication  no double-blinding of mesothelioma trial  demonstration of an improved survival associated with MTA would provide confidence that MTA is an effective agent providing clinical benefit
July 6, 2000	Serial #240 Special Protocol assessment of 2 <sup>nd</sup> -line NSCLC trial (JMEI: a Phase 3 trial of alimta vs docetaxel in patients with locally advanced or metastatic non-small cell lung cancer previously treated with chemotherapy)	As support for mesothelioma indication:  Demonstrate superiority assessment  Demonstrate non-inferiority assessment	8/24/2000:  Demonstrate superiority
July 12, 2000	Serial #242 Mesothelioma pivotal trial revisions	Statistical analysis issues, regarding the addition of vitamins to the treatment regimens after the study had accrued about 150 patients  Potential approval	

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		<p>strategies for MTA via an interim analysis or the final analysis</p> <p>430 (75 without vitamin-supplemented patients/arm) + (140 vitamin-supplemented patients/arm) Final analysis p-value 0.0236</p>	
July 12, 2000	A single-blind randomized phase 3 trial of MTA plus cisplatin vs. cisplatin in patients with malignant pleural mesothelioma	Revisions: statistical analysis issues, regarding the addition of vitamins to treatment regimens	
March 20, 2001	Special protocol assessment: a randomized Phase 3 trial comparing alimta plus best supportive care vs. best supportive care alone in previously treated patients with locally advanced or metastatic malignant pleural mesothelioma (JMEW)	JMEW to support the front-line mesothelioma claim	<p>Comments about strategy (5/7/2001):</p> <ul style="list-style-type: none"> <li>• Interim analysis of JMCH planned later in year</li> <li>• Pre-NDA meeting scheduled 8/2001</li> <li>• JMEW projected to accrue over 15-months plus 12-months of follow-up</li> </ul>
July 11, 2001	Interim database lock		
August 23, 2001	Orphan drug status granted		
October 29, 2001	Communication of data safety monitoring board conclusions	Indication: treatment of mesothelioma	Conclusion: follow the statistical analysis plan as stated in protocol and base

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			the final primary analysis on the mixed population of both supplemented and non-supplemented patients; final significance level of $p = 0.0476$
November 7, 2001	Last patient on-study visit		
January 30, 2002	Pre-NDA meeting	<p style="text-align: center;">/</p> <p>Lilly proposed to provide for electronic reader capability at the FDA and providing images for responders at baseline and at best response</p> <p>Proposal for Protocol for Treatment: alimta + cisplatin, alimta + carboplatin, alimta alone</p>	Alimta in combination with cisplatin is indicated for patients with advanced malignant pleural mesothelioma
March 19, 2002	Serial #394	Change in formulation (formulation → lyophilized product); CMC package and data delayed until 2 <sup>nd</sup> quarter 2003	
March 26, 2002	1 <sup>st</sup> single patient IND for compassionate and emergency use for malignant mesothelioma based on results from JMCH (JMCH to be		

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	presented at the plenary session of ASCO annual meeting)		
April 3, 2002	Protocol for treatment for chemo-naïve patients with malignant pleural mesothelioma	Regimens: alimta + cisplatin, alimta + carboplatin, alimta alone	FDA: alimta + cisplatin
April 10, 2002	Request for fast track designation	Supported by JMCH data in abstract submitted to ASCO for 2002 annual meeting	
May 20, 2002	Presentation of the results of JMCH at plenary session of ASCO annual meeting  Abstract was one of top five out of 3500 abstracts submitted		
June 10, 2002	Fast track designation granted for malignant pleural mesothelioma indication		
October 31, 2002	Rolling submission of NDA begins		

#### 4. Other Relevant Information

Alimta is not approved in the United States or in any other country

#### 5. Important Issues with Pharmacologically Related Agents

##### 5.1 Introduction of folic acid and vitamin B12 for safety reasons

The introduction of folic acid and B12 into the pivotal trial, JMCH, was based on a Lilly initiated multivariate analysis conducted in late 1997 to assess the relationship of vitamin metabolites, drug exposure, and other pre-specified baseline patient characteristics to toxicity following therapy with MTA. Data were examined from 139 Phase 2 patients

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with tumors of the colon, breast, pancreas, and esophagus who had been treated with MTA at 600 mg/m<sup>2</sup> intravenously over 10 minutes once every 21 days. These patients had homocysteine (Hcys), cystathionine, and methylmalonic acid levels measured at baseline and once each cycle thereafter. Stepwise regression modeling, multivariate analysis of variance and discriminant analysis were implemented to determine which predictors might correlate with severe toxicity, and to predict which patients were at high risk of experiencing such toxicity. Prognostic factors then considered were age, gender, prior therapy, baseline albumin, liver enzymes, ANC, platelets, vitamin metabolites, and AUC.

The findings from this investigation led to the following conclusions:

- Toxicity resulting from therapy with MTA appeared to be higher in patients with elevated pre-therapy homocysteine levels.
- Elevated baseline homocysteine levels ( $\geq 10 \mu\text{mol/L}$ , for the 139 patients included in this initial analysis) highly correlate with severe hematological and nonhematological toxicity following therapy with MTA.
- Homocysteine was found to be better than baseline albumin (another predictor of toxicity identified in the analysis) at predicting toxicity and was not altered with MTA therapy.

Because of the observation that pre-therapy homocysteine levels were critically important in predicting toxicity, the same multivariate analysis was repeated on data from 305 patients who had their baseline homocysteine levels measured and recorded using a single laboratory. To eliminate the confounding factor of the effect of folic acid supplementation on toxicity, patients on Study JMAS who received folic acid supplementation ( $n=38$ ) were removed from the analysis, leaving a final sample size of 267 patients. Prognostic factors considered in this second wave of analysis were age, gender, baseline albumin, liver enzymes, ANC, platelets, vitamin metabolites, pretherapy weight, AUC, tumor type, and prior treatment. Baseline homocysteine was identified as a highly statistically significant predictor of febrile neutropenia ( $p < 0.00001$ ), Grade 4 neutropenia ( $p = 0.0191$ ), Grade 4 thrombocytopenia ( $p < 0.00001$ ), and Grade 3 or 4 diarrhea ( $p < 0.00001$ ). According to Lilly, these results confirmed the original findings and supported the conclusion that homocysteine may provide an ideal prognostic variable for predicting toxicity during MTA therapy.

During the conduct of the JMCH trial, a programmatic change was made by Lilly in the clinical development of MTA whereby every patient treated with MTA must be supplemented with folic acid and vitamin B12 to improve patient safety. Initiation of vitamin supplementation in this study was done in both treatment arms and at the same time point to preserve study blinding at the patient level. By this time a total of 112 patients had been randomized in the study and received therapy without vitamin supplementation from the start, while a total of 40 patients received vitamin supplements

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after at least one cycle of study therapy. For the purpose of this study, a patient was classified as supplemented with vitamins if he/she received study vitamin supplement during his/her entire study participation. The two groups of patients described above were classified as not supplemented with vitamins in this study while those who received vitamin supplementation with all cycles of study therapy were be classified as supplemented with vitamins. As such, approximately 150 patients were considered treated without study vitamin supplementation (initial study cohort) while an anticipated 280 qualified patients were considered treated with vitamin supplementation on the revised protocol.

#### 5.2 The effect of folic acid and vitamin B12 on the efficacy of an antifolate

The narrative above does not take into account the potential negative effect on efficacy by the addition of folic acid + B12. The commentary below seeks to understand the enhanced efficacy from the addition of a folate to an antifolate.

Natural folates and antifolates have two important properties, such as: 1) the requirement for cellular uptake via a reduced folate carrier (RFC); and 2) the ability to be polyglutamylated. Increased extracellular folate concentrations and expanded intracellular folate pools may contribute to decreased antifolate sensitivity due to competition for transport and polyglutamylation, thus, decreasing the inhibitory effect on TS and GARFTase.<sup>6</sup>

#### 5.3 Transport

In comparison to all other transport routes identified in rodent and human neoplastic cell types, the basic kinetic properties and preferences among structurally related folates and their analogues as permeants for the one-carbon, reduced-folate system are remarkably similar.<sup>7</sup> Enhanced RFC activity promotes the efficient transport of RFC-dependent antifolates and thus, more potent TS inhibition.<sup>8</sup> Folic acid is a poor substrate for RFC1 and enters cells by other mechanisms.<sup>9</sup>

Carrier-mediated systems transporting folates have a variety of properties in common. The internalization (influx) of folates by these systems is saturable, conforming to Michaelis-Menten kinetics. However, they exhibit differences in preferences for structurally related folates and their analogues, which are *competitive* inhibitors.<sup>10</sup> The carrier was encoded by the RFC1 gene.<sup>11</sup> There is also a receptor-mediated process. The

<sup>6</sup> Bachus et al. Int J Cancer. 2000;87:771-778.

<sup>7</sup> Sirotnak FM. Annual Review of Nutrition. 1999;19: 91-122

<sup>8</sup> Bachus et al. Int J Cancer. 2000;87:771-778.

<sup>9</sup> Zao, Babani, Gao, Liu, Goldman. Clin Cancer Res. 2000; 6:3687-3695

<sup>10</sup> Sirotnak FM. Annual Review of Nutrition. 1999;19: 91-122

<sup>11</sup> Khokhar, Lam, Rusch, Sirotnak. J Thoracic Cardiovasc Surg. 2002; 123:862-868

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extent to which carrier- or receptor-mediated processes contribute to net translocation of folates in cell types where both processes are found is controversial, but it will depend on the level of expression of the corresponding gene in each cell type. Because the translocation efficiency of carrier-mediated processes is much greater than that of receptor-mediated processes, the relative level of expression required for the latter to contribute significantly to net translocation of folates is proportionally greater.<sup>12</sup> The exact mechanism of transport has not been established for MTA. MTA does have high affinity for RFC1 and folate receptor-alpha.<sup>13</sup>

In one cell type, L1210, free levels of folates and antifolates are governed by RFC1.<sup>14</sup> For mesothelioma cells, there are varying views on MTA transport. One reason for MTA activity in mesothelioma may be due to a highly expressed, high-affinity alpha folate receptor on mesothelioma cells of all histologic subtypes. This type of highly expressed receptor was thought to contribute to MTA transport into mesothelioma cells.<sup>15</sup> However, other evidence suggests that human mesothelioma cell lines predominately internalize tritiated methotrexate (MTX shares a transport route and is polyglutamylated in tumor cells in a manner similar to natural folate compounds<sup>16</sup>) by means of a carrier-mediated mechanism, with little transport by a receptor-mediated mechanism.<sup>17</sup> Recently, a high-affinity transport activity in three human mesothelioma cell lines was characterized. The researchers reported that the transport activity was specific for MTA and had low affinity for other antifolate inhibitors of dihydrofolate reductase (MTX, aminopterin, PT523) and thymidylate synthase (ZD1694, ZD9331); also, *this activity may be another transport route for mesothelioma cells of 5-methyl-tetrahydrofolate, the predominate folate in the plasma of man and rodents.*<sup>18</sup> The degree of expression of this transport activity in comparison to the RFC1 has not been elucidated.

#### 5.4 Polyglutamylation

Pharmacological activity of MTA depends on conversion to polyglutamylated derivatives inside the cell; polyglutamylation increases the affinity of the MTA derivative. Polyglutamylated forms also ensure cellular retention. Only inhibition of DHFR is not affected by the degree of polyglutamylation. The effect of polyglutamylation on the inhibitory activity of MTA is shown below.<sup>19</sup>

<sup>12</sup> Sirotnak FM. Annual Review of Nutrition. 1999;19: 91-122

<sup>13</sup> Zao, Babani, Gao, Liu, Goldman. Clin Cancer Res. 2000; 6:3687-3695

<sup>14</sup> Zao, Babani, Gao, Liu, Goldman. Clin Cancer Res. 2000; 6:3687-3695

<sup>15</sup> Scagliotti et al. J Clin Oncol. 2003;21:1556-1561

<sup>16</sup> Egan MG, Sirlin S, Rumberger BG, Garrow TA, Shane B, Sirotnak FM. J Biol Chem. 1995.270(10):5462-8.

<sup>17</sup> Khokhar NZ, Lam AF, Rusch VW, Sirotnak FM. J Thorac Cardiovasc Surg. 2002. 123(5):862-8.

<sup>18</sup> Wang, Zhao, Chattopadhyay, Goldman. Cancer Res. 2002;62:6434-6437

<sup>19</sup> Zao, Babani, Gao, Liu, Goldman. Clin Cancer Res. 2000; 6:3687-3695

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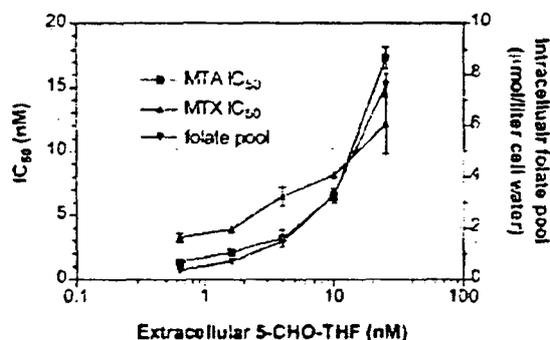
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	MTA MONOGLUTAMATE	MTA PENTAGLUTAMATE
Human TS, Ki	109 nM	1.3 nM
Murine GARFT, Ki	9.3 $\mu$ M	65 nM
DHFR, Ki	~ 7 nM	~ 7 nM

#### 5.5 The effect of increased folate levels

Antifolates, under conditions of increased extracellular folate levels, have decreased sensitivity due to *competition* for transport and polyglutamylation. This diminishes the effect on thymidylate synthase (TS) and GARFTase. Cells grown in low folate conditions are more sensitive to antifolates, including MTA, than cells grown in high folate conditions.<sup>20</sup>

Intracellular folates rise as extracellular 5-formyl-THF increased and MTA sensitivity decreased in an inverse relationship. Intracellular levels of THF cofactors modulate the growth-inhibitory activity of MTA (figure below). THF cofactor pool size plays a critical role in modulating the growth-inhibitory effects of MTA.<sup>21</sup> In this system, an increase in folate pool size required an increase in MTA concentration for comparable inhibition.



*Fig. 7* Relationships among MTA or MTX IC<sub>50</sub>, intracellular folate pool size, and extracellular 5-CHO-THF concentration in L1210 cells. L1210 cells were grown in folate-free RPMI 1640 supplemented with different concentrations of 5-CHO-THF for at least 1 week before MTA or MTX IC<sub>50</sub>s were determined. Intracellular folate pools were measured after cells were grown exponentially for 1 week in folate-free medium supplemented with different concentrations of [<sup>3</sup>H]5-CHO-THF. The data are the mean  $\pm$  SE from three separate experiments.

MTA activity is modulated within cells by natural folates that *compete* for polyglutamation at the level of folylpolyglutamate synthetase. Contraction of the cellular folate pool decreases suppression of MTA polyglutamation.<sup>22</sup>

<sup>20</sup> Bachus et al. Int J Cancer. 2000;87:771-778.

<sup>21</sup> Zao, Babani, Gao, Liu, Goldman. Clin Cancer Res. 2000; 6:3687-3695

<sup>22</sup> Goldman ID, Zhao R. Semin Oncol. 2002 Dec;29(6 Suppl 18):3-17.

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Changes in folate levels influence the competition between antifolates and natural folates. Below are processes that may be affected.

Natural folate pools within the cell may modulate MTA activity by:

- competing with and inhibit MTA polyglutamation at the level of folyl-poly-gamma-glutamate synthetase
- competing with antifolates at the level of target enzymes

For example, increased folate pools (*i.e.*, by *folic acid supplementation*) may prevent polyglutamylation, resulting in faster efflux and a decrease in sensitivity of MTA.

Below is an *in vitro* example of the biochemical perturbations on MTA activity, resulting from changing folate levels.

In the murine colon cancer cell lines (5-41x<sup>23</sup>), human colon cancer cell lines (1.2 x), and the human head and neck cancer lines (1.8-22x), IC50 values for MTA were higher in cells grown in standard folate media (8.8 uM folic acid and 2.2 uM folic acid, respectively) compared to cells grown in low folate media (2.5 nM leucovorin for murine colon cancer cells; 1 nM leucovorin for the human colon cancer cells; 0.5 nM leucovorin for head and neck cancer cell lines). FdUMP binding capacity and TS protein expression (by Western blotting) was lower in cells grown in low folate media. RFC activity was increased several fold (2-7x) in cells grown in low folate media compared to high folate media. In the case of lower activity of TS, lower concentrations of TS inhibitors are required for inhibition. No significant changes in polyglutamylation activity were found.<sup>24</sup>

**MEDICAL OFFICER NOTE:** It appears that in cell culture, MTA has biochemical advantages under low folate conditions. In marked contrast, in patients, *i.e.*, the randomized JMCH trial, the addition of folic acid to the regimens increased efficacy without increasing the dose of MTA.

Below is an *in vitro* example of the inhibitory activity of MTA, resulting from increasing folate levels. Again, note that for a comparable IC50, the concentration of MTA is increased as the folic acid concentration is increased.

The table below illustrates that a several fold increase in MTA is required to give comparable inhibition of the cancer cell lines (none are mesothelioma cell lines) when folic acid is added to the media.<sup>25</sup>

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<sup>23</sup> Refers to IC50

<sup>24</sup> Bachus et al. *Int J Cancer*. 2000;87:771-778.

<sup>25</sup> Worzalla et al. *Anticancer Research*. 1998; 18:3235-3240

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Table 1. *In vitro* protective effects of folic or isotonic acid on LY231514-induced cytotoxicity

Cell line <sup>a</sup>	IC <sub>50</sub> (nM) <sup>b</sup>	Relative (+/-SE) Change in IC <sub>50</sub>						
		Folic acid conc. in media <sup>c</sup>			Isotonic acid conc. in media			
		1 μM	10 μM	100 μM	0.1 μM	1 μM	10 μM	100 μM
IGROV1	44	1	14	25	26	370	>970	>970
NB	34	2	3	17		6	76	>1970
GCS	12	1	3	9		106	47	640
LX-1	4	1	3	6		6	12	1460
CCRF-CEM	4	1	4	22	2	22	130	460

<sup>a</sup> Cells were adapted to 24 week passages in low folate (2 nM folic acid) medium.

<sup>b</sup> IC<sub>50</sub> was determined by MTT assay with 72 h exposure to LY231514. Data represents mean of triplicate determinations.

<sup>c</sup> Folic or isotonic acid was added two hours prior to LY231514 addition.

It is known that the MTD of antifolates in folated-depleted mice is much lower (50x) compared to mice on a standard diet.<sup>26</sup> Below is an *in vivo* example of the changes in MTA lethality, resulting from changing folate in the diet.

In mouse strains, CD 1 nu/nu and DBA/2 (figure below), the MTA LD50s were 250x and 60x greater, respectively, in mice fed a standard diet (1-2 mg folate/kg/day) compared to a low folate diet (0.001-0.008 mg folate/kg/day) (figure below). Inspection of the figure shows that the two mouse strains had approximately the same MTA LD50 same on standard diet. On a low folate diet, the strains could be differentiated; there was a 10-fold difference in MTA LD50, i.e., DBA/2 > CD 1 nu/nu.<sup>27</sup> In view of the data in the next figure, a MTA LD50 study with low folate + folate supplement (15 mg folate/kg/day) would have been helpful.

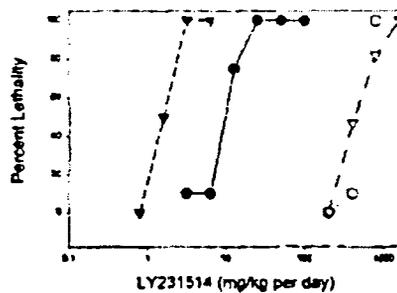


Figure 1. The toxicity of LY231514 in mice is increased by a folate-deficient diet. DBA/2 and CD1 mouse mice were fed either a standard laboratory diet (○ and △, respectively) or a folate-deficient diet for 2 weeks prior to the first dose of LY231514 (● and ▽, respectively) and for the duration of the study. Groups of mice (n = 10 animals/group) in each diet were given 10 daily doses of LY231514 at the indicated doses. The data present the percent lethality within 4 weeks after the last dose of LY231514.

<sup>26</sup> Bachus et al. Int J Cancer. 2000;87:771-778.

<sup>27</sup> Worzalla et al. Anticancer Research. 1998; 18:3235-3240

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In mouse strain DBA/2 on a low folate diet, there was 100% inhibition of L5178Y/TK-/HX- lymphoma (figure below), at a MTA dose of 0.3 and 1 mg/kg/day administered intraperitoneal for 10 days, starting the day after tumor transplant. In mice fed a low fat diet + folate supplementation, 100% inhibition of L5178Y/TK-/HX- lymphoma was achieved at MTA doses of 30 - 1000 mg/kg/day or *the dose of MTA had to be increased 30x to obtain comparable efficacy with folate supplementation*(figure below).

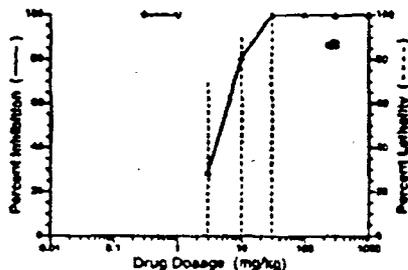


Figure 2. Antitumor activity of L5178Y/TK-/HX- lymphoma (10<sup>6</sup> cells, qd x 10) against L5178Y/TK-/HX- lymphoma for mice on low folate diet with no folate supplementation (---) and for mice on low folate diet that received 15 mg/kg/day folate supplementation (.....). Vertical dashed lines represent percent lethality in mice on low folate diet with no folate supplementation. No lethality was observed in mice that received folate supplementation.

**MEDICAL OFFICER NOTE:** These preclinical results are counterintuitive to the results of the pivotal clinical trial, JMCH. In JMCH, after accrual of 70 of patients to the trial, subsequent patients were supplemented with folic acid + B12 without an increase in the dose of MTA. In comparison to the never supplemented group, efficacy parameters appear to have improved with folic acid + B12 supplementation, *including in the cisplatin arm*. Similar clinical findings of increased efficacy with the addition of folic acid + B12 were reported from a Phase 2 trial of MTA alone in mesothelioma patients; i.e., in the non-supplemented patients the median survival was 8 months and in the supplemented patients the median survival was 13 months.<sup>28</sup>

In mice, folic acid supplementation required a significant increase in the dose of MTA to obtain comparable efficacy as the non-supplemented mice. In humans, the dose of MTA was not increased with folic acid + B12 supplementation and the efficacy increased in comparison to the non-supplemented group.

However, the in vivo experiment below appears to mimic the clinical data.

<sup>28</sup> Scagliotti et al. J Clin Oncol. 2003;21:1556-1561

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To assess the effect of vitamins involved in the folate pathway on the antitumor efficacy of LY231514 disodium in a human tumor xenograft model, female nude mice bearing human MX-1 breast carcinoma were treated with LY231514 disodium (MTA or alimta) alone or along with super physiologic doses of folic acid, vitamin B6 (pyridoxine), or vitamin B12 (cobalamin). The doses used in these growth delay experiments were: LY231514 (alimta, 100 or 150 mg/kg) administered by intraperitoneal injection on Days 7 through 11 and Days 14 through 18 post-tumor implantation alone or along with folic acid (6 or 60 mg/kg), vitamin B6 (100 mg/kg) or vitamin B12 (165 mg/kg).<sup>29</sup>

**MEDICAL OFFICER NOTE:** The schedule of vitamins is different in JMCH. In JMCH, the protocol indicated that patients should take oral folic acid (350 - 600 ug) daily beginning approximately 1 to 3 weeks before treatment with MTA plus cisplatin or cisplatin alone and continuing daily until 3 weeks after discontinuation from study therapy; in the animal study, folic acid was given by *intraperitoneal injection* (the METHODS section suggests IP and the figure indicates PO) concurrently with MTA, i.e., d 7-11 and d 14-18. In JMCH, the protocol indicated that a vitamin B12 (1000 ug) injection must be administered approximately 1 to 3 weeks before treatment with MTA plus cisplatin or cisplatin alone and should be repeated approximately every 9 weeks until the patient discontinues from study therapy; in the animal study, B12 was given by intraperitoneal injection concurrently with MTA, i.e., d 7-11 and d 14-18. In JMCH, patients received both folic acid and B12; in the animal study, only one of the vitamins was given. It is not stated why these doses of vitamins were used. For example, the folic acid doses were 6 mg/kg and 60 mg/kg by *intraperitoneal injection*; in another Lilly Research study, a standard mouse diet contained 1-2 mg/kg/day of folate and mice on a low folate diet received 15 mg/kg/day of oral folic acid.<sup>30</sup> The full dose response of these vitamins is not provided; i.e., the dose of the super physiological doses of vitamins may be on the inhibitory portion of a bell-shaped dose response curve.

Also, the schedule of MTA was different in another Lilly Research study. In this study, nude mice transplanted with MX-1 breast cancer were treated with MTA 100, 150, and 200 mg/kg/day on a day 7-11 schedule.<sup>31</sup> In the study described below, the mice were treated with MTA on a day 7-11 and day 14-18 schedule or twice the amount of MTA. In the other Lilly Research study, the definition of tumor growth delay was defined as the time taken by each individual tumor

<sup>29</sup> Lilly Research Laboratories: Nonclinical Pharmacology Report 30, March 2002

<sup>30</sup> Worzalla et al. *Anticancer Research*. 1998; 18:3235-3240

<sup>31</sup> Teicher et al. *Clin Cancer Res*. 2000; 6:1016-1023

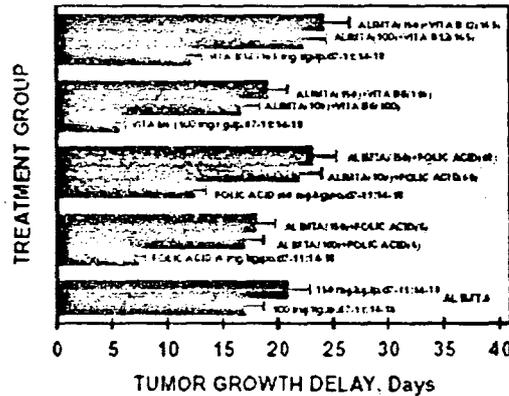
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to reach 500 mm<sup>3</sup> compared with the time in the untreated controls;  
in study described below, the goal for the tumor size was 1000 mm<sup>3</sup>.

A figure with the results is below.

RESPONSE OF THE HUMAN MX-1 BREAST CA  
TO ALIMTA ALONE & ALONG WITH VITAMIN SUPPLEMENTS



The table below illustrates the same data. MTA alone @ 100 mg/kg delayed tumor growth by 17 days. Although the addition of folate @ 6 mg/kg did not change tumor growth delay, folate @ 60 mg/kg increased the tumor growth delay to 22 days. The addition of B6 did not change tumor growth delay of MTA. The addition of B12 increased the tumor growth delay to 22 days. MTA alone @ 150 mg/kg delayed tumor growth by 21 days. Although the addition of folate @ 6 mg/kg did not change tumor growth delay, folate @ 60 mg/kg increased the tumor growth delay to 23 days. The addition of B6 did not change tumor growth delay of MTA. The addition of B12 increased the tumor growth delay to 24 days. With regard to folate *alone*, in a dose-response fashion, folate 6 and 60 mg/kg delayed tumor growth by 7 and 12 days, respectively. B6 alone delayed tumor growth by 5.7 days. B12 *alone* delayed tumor growth by 12 days. It appears that at these doses, in this tumor, folate (in a dose-response fashion) and B12 alone and in combination with MTA contribute to the delay of tumor growth without an increase in MTA dose. This is in marked contrast to another Lilly Research study.<sup>32</sup>

<sup>32</sup> Worzalla et al. Anticancer Research. 1998; 18:3235-3240

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REGIMEN, MG/KG	TUMOR GROWTH DELAY (DAYS)
MTA 100 alone	17
+ 6 folate	17
+ 60 folate	22
+ 100 B6	17
+ 165 B12	22
MTA 150 alone	21
+ 6 folate	21
+ 60 folate	23
+ 100 B6	21
+ 165 B12	24
Folate alone	
6	7
60	12
B6 alone	
100	5.7
B12 alone	
165	12

**MEDICAL OFFICER NOTE:** Although not a mesothelioma cell line, these results are consistent with the results in JMCH, i.e., the addition of folate or B12 to an antifolate enhances antineoplastic activity. In fact, high dose folate alone and B12 alone may have antineoplastic activity independent of the antifolate, MTA. These results also run counter to the other *in vitro* and *in vivo* models presented above.

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## II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

### 1. Statistical Review and Evaluation, completed and entered into DFS 12/10/2003

- Yong-Cheng Wang, Primary Reviewer  
Ming Li, Acting Team Leader

### 2. Clinical Pharmacology and Biopharmaceutics Review, completed and entered into DFS, 12/4/2003

- Brian Booth, Primary Reviewer/Pharmacometrics
  - Roshni Ramchandani, Atul Bhatram, Pharmacometrics  
Joga Gobburu, Pharmacometrics, Team Leader  
N.A.M. Atiqur Rahman, Team Leader

### 3. Pharmacology/Toxicology Review and Evaluation, completed and entered into DFS 12/19/2003

- Doo Y. Lee Ham, Primary Reviewer  
David Morse, Team Leader

There were three consultations (e.g., medical imaging, \_\_\_\_\_, and pulmonary). The medical imaging consultation is not shown below because the findings of the consultation were blended into the Medical Officer's evaluation of tumor response.

4.



# CLINICAL REVIEW

## Clinical Review Section

### 4.1 Recommendations for labeling:

- 1.
- 2.
- 3.

#### **BACKGROUND:**

The LCSS cannot be interpreted as a general measure of either

— ” The LCSS is based on a conceptual model in which the physical and functional dimensions are the main determinants of a patient’s health-related quality of life (HRQL), however, it specifically excludes items that focus on the psychological, social and spiritual domains.<sup>33</sup> The LCSS has been shown to explain only half the variability in overall HRQL.<sup>34</sup> In addition, the LCSS does not directly measure symptoms of treatment toxicity except in the situation where the symptoms of the condition are similar to the symptoms of treatment toxicity, e.g., fatigue.

The LCSS has been documented psychometrically to measure (as demonstrated by content, construct and criterion-related validity) the physical symptoms and function from the perspective of the lung cancer patient.<sup>35</sup> Patients with both NSCLC and SCLC have been tested. The extent that the same conclusions can be reached in malignant pleural mesothelioma would depend in part on whether the symptoms measured include all important symptoms specific to the mesothelioma experience. Symptoms measured by the LCSS are fatigue, decreased activity, cough, dyspnea, decreased appetite, pain and haemoptysis. The LCSS also includes a general symptom distress item a single-item global quality of life item.

Item 9 of the LCSS asks the broad question, “How would you rate the quality of your life today?” This broad question cannot be considered support for a broad claim, i.e., “improved QOL,” since the determinants of that broad concept are not captured and it cannot be ascertained what treatment or non-treatment related changes are impacting the broad concept.

<sup>33</sup> Hollen P, Gralla R, et al. Quality of life assessment in individuals with lung cancer: Testing the Lung Cancer Symptom Scale (LCSS). *Eur J Cancer* 29A: S51-S58, 1993.

<sup>34</sup> Hollen P, Gralla R, et al. Quality of life during clinical trials: Conceptual model for the Lung Cancer Symptom Scale (LCSS). *Supportive Care in Cancer* 2: 213-222, 1994.

<sup>35</sup> Hollen p, Gralla R, et al. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies: Psychometric assessment of the Lung Cancer Symptom Scale. *Cancer* 73: 2087-2098, 1994.

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Administration of the LCSS requires that the respondents adequately understand the visual analog scale (VAS) response options. However, the LCSS is rated at a Grade 2 level of comprehension and consists of only 9 VAS items. It asks about the patient's experience in the previous 24 hours. It takes only 3-5 minutes to complete. Some experts suggest that the VAS is the scale of choice when trying to reduce respondent burden and limit the attrition in ill patients. Nonetheless, evidence that patients were given standardized instructions and procedures for completing the questionnaire should be documented. The instrument developers recommend the LCSS be administered on a day of treatment, before the patient receives results from any clinical test, and before the patient receives chemotherapy.

In the literature I reviewed, the developers of the LCSS did not determine the minimum change that can be considered clinically important when interpreting clinical trial results. Other researchers have compared a variety of methods for estimating the smallest change that can be interpreted as clinically meaningful finding that 0.5 standard deviation has generally approximated those estimates.<sup>36</sup>

The LCSS has been translated into many languages, but status of the linguistic validation of those translations is unknown.

The following paragraph appears in Lilly's draft label for perimetrexed (Alimta).

[

]

Comments on Lilly's draft labeling language above:

The study results do not support a conclusion of a treatment impact as demonstrated by the LCSS. The LCSS total score was not statistically significant. It appears that the only scale item that showed a statistically significant difference is the pain scale, and there is no indication that there was adjustment for multiple comparisons. Furthermore, there is no evidence that the LCSS was developed for individual item analysis.

The LCSS is not a measure of — nor has the LCSS been shown to represent the global concept of ' — for reasons stated above. In addition, there is no evidence in the authors' published documentation of LCSS development that the LCSS is designed to be used as a measure of the individual symptoms of "dyspnea, pain, fatigue, symptom distress, or interference with activity" but rather as a measure of physical symptoms and function. In addition, if perimetrexed would have specific adverse

<sup>36</sup> Norman G, Sloan J, Wyrwich K. Interpretation of changes in health-related quality of life remarkable universality of half a standard deviation. *Med Care* 41:582-592, 2003.

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events associated with its treatment that have an impact on a patient's clinical benefit, those adverse effects on patients' clinical benefit may not be measured by this instrument.

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### MEDICAL OFFICER COMMENTS FORWARDED TO LILLY

Although changes in some of the in the components of the LCSS are statistically significant, none of the changes are clearly clinically significant.

### 5. Pulmonary Function Tests

The table below illustrates the number of patients randomized and treated, the number of patients eligible for response evaluation, and the number of patients providing data for each of the pulmonary function tests. In general, 23-43% of patients did not provide pulmonary function data on the alimta/cisplatin arm compared to 28-44% of patients on the cisplatin alone arm. With regard to FVC, 26-32% of patients did not provide pulmonary function data on the alimta/cisplatin arm compared to 30-37% of patients on the cisplatin alone arm. This is an excessive amount of missing data. In a single-blinded study, this may suggest bias in testing and reporting.

	TOTAL NUMBER OF PATIENTS	ALIMTA/CISPLATIN NUMBER OF PATIENTS	CISPLATIN NUMBER OF PATIENTS
Entered (consented) in NDA	574		
Enrolled (randomized)	456		
Randomized and treated	448		
Eligible for response evaluation	447	225	222
<b>PULMONARY FUNCTION</b>			
Slow vital capacity			
Liters		145	140
% predicted		143	140

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	TOTAL NUMBER OF PATIENTS	ALIMTA/CISPLATIN NUMBER OF PATIENTS	CISPLATIN NUMBER OF PATIENTS
change from baseline liters		131	125
% predicted		129	125
Force vital capacity liters		167	156
% predicted		167	155
change from baseline liters		152	141
% predicted		152	139
FEV1 liters		173	159
% predicted		173	159
change from baseline liters		158	145
% predicted		158	145

Consult from Division of Pulmonary and Allergy Drug Products (HFD-570)  
(Sally Seymour)

Below, in part, is the consult:

Table 1 and Table 2 summarize the results of the forced vital capacity for the Phase 3 clinical trial. Per the Sponsor's protocol, to be included in the analysis of a particular PFT parameter, a patient must have had data from the baseline period and data from at least one cycle among cycles 2, 4, and 6.

**Table 1**  
**Forced Vital Capacity**  
**(Liters, % predicted)**  
**RT Population \*\***

	ALIMTA/CISPLA TIN		CISPLATIN	
Cycle	N	LS Mean	N	LS Mean
Baseline	167	2.37 (61.52)	156/155	2.45 (62.12)
Cycle 2	152	2.51 (65.37)	141/139	2.44(63.21)
Cycle 4	117	2.57 (67.11) *	89/88	2.41 (63.44) *
Cycle 6	66	2.55 (67.12) *	54/53	2.33 (60.72) *
Average	167	2.54 (66.53) *	156/155	2.40 (62.45) *

\*\*Randomized & Treated      \* p < 0.05

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Table 2  
 Forced Vital Capacity - Change from Baseline  
 Liters (% predicted)  
 RT Population \*\*

	ALIMTA/CISPLATIN		CISPLATIN	
Cycle	N	LS Mean	N	LS Mean
Cycle 2	152	0.08 (2.90)	141/139	0 (0.67)
Cycle 4	117	0.14 (4.62) *	89/88	-0.03 (0.70) *
Cycle 6	66	0.12 (4.57) *	54/53	-0.11 (-2.01) *
Average	167	0.11 (4.03) *	156/155	-0.05 (-0.21) *

\*\*Randomized & Treated      \* p < 0.05

The Division of Oncology Drug Products asked three questions. Below are the questions and answers.

5.1      What are the appropriate pulmonary function tests to demonstrate benefit in this disease?

Malignant mesothelioma causes a loss of lung volume and therefore would be expected to produce a restrictive pattern on pulmonary function tests. Measurement of lung volumes such as total lung capacity and vital capacity would be the most appropriate variables to monitor a restrictive disease, while FEV1 is less useful. Unless a significant amount of obstruction and/or air trapping is present, the FVC and SVC should be similar and performing analysis on both is redundant. Although the FVC can suggest restriction, it is effort dependent and lung volumes are necessary to confirm the restrictive defect. Therefore, the ideal parameter for assessing restrictive physiology would be lung volume measurements, which can be performed using helium dilution or body plethysmography. However, of the variables the Sponsor measured, the FVC could reasonably be used to monitor and analyze trends. Therefore, the remainder of this consult will focus on the FVC results.

5.2      What degree of improvement in pulmonary function is clinically important?

The degree of improvement in pulmonary function that is clinically important is not well defined. Therefore even though the data shows a

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statistically significant difference between groups in FVC, the clinical relevance of the magnitude of change is unclear.

When measuring FVC, several acceptable maneuvers are recorded to show reproducibility. According to the American Thoracic Society, the two largest FVCs from acceptable maneuvers can vary up to 200 mL.<sup>37</sup> In addition, serial measurement of FVC is subject to a certain amount of variability often termed the coefficient of variation. The amount of within subject variability is not well defined but is often estimated to be around 5% over the course of day-to-day measurement.<sup>38</sup>

The Sponsor's data for FVC reported in Table JMCH.11.69 and Table JMCH.11.70 is summarized in Table 1 and Table 2, above. The average mean increase in FVC from baseline in the alimta/cisplatin arm was 110mL while the average mean decrease from baseline in the cisplatin arm was 50mL. Thus, the difference between groups in average mean change in FVC totals 160mL.

Because the difference between groups in mean change from baseline FVC in this trial is less than the range of variability allowed by the ATS in a single test session and less than generally accepted day-to-day variability, it is the opinion of this Reviewer that the difference in FVC is not clinically significant.

If the effects of multiple cycles of alimta are felt to be cumulative, one could argue that it would be more appropriate to base conclusions on the Cycle 6 data, rather than the data representing the average values over multiple cycles. One difficulty with this approach is that the numbers of patients for which data are available become quite small with successive cycles. That said, the largest change in FVC was in cycle 6 in which the alimta/cisplatin arm showed a mean increase from baseline FVC of 120mL while the cisplatin arm showed a mean decrease from baseline FVC of 110mL. The difference between groups in mean change from baseline FVC was 230mL. Although this is a larger increase in FVC, the value is only slightly out of the range of variability allowed by the ATS in a single test session. In addition, as mentioned above, the significant decline in patient data available during the course of the trial makes any interpretation of the data very difficult. Therefore, it remains the opinion of this Reviewer that the difference in FVC is not clinically significant.

#### 5.3 Does the data on pulmonary function support the label claims of improvement in pulmonary function and clinical benefit?

<sup>37</sup> Am J Respir Crit Care Med 1995; 152:1107-1136.

<sup>38</sup> Am Rev Respir Dis 1991; 144:1202-1218.

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It doesn't appear that appropriate statistical methods were specified to account for multiplicity among the various secondary endpoints. DPADP defers to DODP in regards to whether this alone would preclude inclusion of the proposed claims in the label.

Although the data on pulmonary function does support a statistically significant difference between the two treatment groups (issues of multiplicity aside), the effect size is not considered clinically meaningful

The observation that we see in this study is interesting. To support a specific labeling claim of an improvement in lung function which is clinically meaningful, the Sponsor should do a 'second' trial where assessment of lung function is declared as the primary variable. A 'second' trial is recommended because of the secondary nature of the observation in this trial as well as lack of control of multiplicity. Furthermore, the choice of variables to be measured would need further explanation with a detailed discussion in the protocol of what would constitute a favorable response. Finally, in the design of the 'second' trial, the Sponsor would need to address the significant decline in the numbers

#### MEDICAL OFFICER COMMENTS FORWARDED TO LILLY

Although changes in pulmonary function evaluations are statistically significant, the changes are within the variability range for these tests (i.e., FVC) allowed by the American Thoracic Society and thus, the changes are not clinically significant. Also, over 20% of the patients did not contribute data to the pulmonary function evaluations; in a single-blinded study, this may suggest bias in testing and reporting.

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### III. Human Pharmacokinetics and Pharmacodynamics

#### 1. Pharmacokinetics

Refer to:

Clinical Pharmacology and Biopharmaceutics Review, completed and entered into DFS, 12/4/2003

- Brian Booth, Primary Reviewer/Pharmacometrics
  - Roshni Ramchandani, Atul Bhatram, Pharmacometrics
  - Joga Gobburu, Pharmacometrics, Team Leader
  - N.A.M. Atiqur Rahman, Team Leader

#### 2. Pharmacodynamics

Refer to:

Clinical Pharmacology and Biopharmaceutics Review, completed and entered into DFS, 12/4/2003

- Brian Booth, Primary Reviewer/Pharmacometrics
  - Roshni Ramchandani, Atul Bhatram, Pharmacometrics
  - Joga Gobburu, Pharmacometrics, Team Leader
  - N.A.M. Atiqur Rahman, Team Leader

### IV. Description of Clinical Data and Sources

#### 1. Overall Data

##### 1.1 Sources used in review:

- Literature
- Study reports
- For Financial disclosure: data tabulations and source documents
- Electronic datasets: "SURVLOCK" (Date "24-OCT-2002" and "6-DEC-2002"), "LABRESLT.XPT"
- \_\_\_\_\_ the independent review database of CT scans and the independent review findings
- Laptop containing the \_\_\_\_\_ database ( \_\_\_\_\_ /BASE) of the independent reviewers' evaluations
- Pre-NDA meeting Briefing Documents

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- Documents reviewed: 10/24/2002 (Rolling Submission), 11/22/2002, 11/26/2002, 1/10/2003, 2/13/2003, 3/24/2003 (financial disclosure), 5/9/2003, 5/29/2003, 7/23/2003 (Safety Update), 7/30/2003, 8/8/2003, 8/15/2003, 8/21/2003, 8/28/2003, 9/2/2003, 9/12/2003, 9/15/2003, 9/19/2003, 9/22/2003, 9/29/2003, 10/6/2003 (labeling), 10/20/2003, 11/4/2003 (labeling), 11/5/2003, 11/14/2003 (labeling), 11/14A/2003, 11/18/2003, 11/24/2003 (labeling), 11/26/2003, 12/4/2003 (financial disclosure), 12/4A/2003, 12/5/2003 (labeling), 12/10/2003 (financial disclosure), 12/15A/2003 (labeling), 12/16/2003.

### 2. Tables Listing the Clinical Trials

Protocol H3E-MC-JMCH(g): A Single-blind Randomized Phase 3 Trial of MTA<sup>39</sup> plus Cisplatin versus Cisplatin in Patients with Malignant Pleural Mesothelioma (Pivotal trial; reviewed by FDA)

Enrolled: 226 alimta plus cisplatin arm (168 folic acid + Vitamin B12 supplemented 168; 58 partially supplemented or never supplemented); 222 cisplatin alone arm (163 folic acid + Vitamin B12 supplemented, 59 partially supplemented or never supplemented).

Protocol H3E-MC-JMDR Phase 2: A Phase 2 Trial of LY231514 Administered Intravenously Every 21 Days in Patients with Malignant Pleural Mesothelioma (Supported trial; not reviewed by FDA)

Enrolled: 64 (43 folic acid + Vitamin B12 supplemented; 21 never supplemented)

### 3. Postmarketing Experience

N/A

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<sup>39</sup> alimta

## CLINICAL REVIEW

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#### 4. Literature Review

##### 4.1 The FDA's Background on Malignant Pleural Mesothelioma

###### Introduction

In the last two decades, there has been remarkable progress in understanding the clinical and biological manifestations and treatment of mesothelioma. The first edition of Cancer. Principles and Practice of Oncology (1982)<sup>40</sup> mentioned mesothelioma in one paragraph (5 lines) in the chapter Neoplasms of the Mediastinum, and in two separate paragraphs (7 and 6 lines, respectively) in the chapter Sarcomas of the Soft Tissue and Bone. In comparison, lung cancer had a dedicated chapter, Cancer of the Lung, with 78 pages. In the latest edition of Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition (2001)<sup>41</sup>, there is a chapter dedicated to mesothelioma, Benign and Malignant Mesothelioma, with 35 pages. Again, in comparison, lung cancer also had a dedicated chapter, Cancer of the Lung, with 103 pages.

The bulk of this background material on mesothelioma (and given credit in serial footnotes) is from two textbooks of oncology.<sup>42, 43</sup> This material is important because it may provide insight into the state-of-the-art knowledge and judgement of investigators entering and enrolling patients into the alimta pivotal mesothelioma trial.

In the United States, an estimated 2000 to 3000 new cases of mesothelioma are diagnosed each year or approximately 12.1 per million white men.<sup>44</sup> Males are affected by this malignancy five times more than females. The median age at the time of diagnosis is 60 years; incidence rises steadily with age and is approximately tenfold higher in men aged 60 to 64 years as compared with those aged 30 to 34. Asbestos exposure is the risk factor with an interval between exposure and malignancy of 3-4 decades. Median survival is about 10 to 17 months from onset of symptoms and 9 to 13 months from diagnosis. The 3- and 5-year survival probabilities are 10 and 3%, respectively, in one review of 92 cases, and 5.6% for 5-year survival in another review of 123 patients.<sup>45</sup> Mesotheliomas contain both epithelial and sarcomatoid elements; the designation of pathological type is dependent on the relative abundance of each component; 50% are epithelial, 34% are mixed, and 16% are sarcomatoid. This is important because the survival is influenced by the pathological type. Depending on the series cited, median survival for epithelial type is 22 months compared to 6 months for

<sup>40</sup> Edited by DeVita VT, Hellman S, Rosenberg SA. JB Lippincott Co., Philadelphia.

<sup>41</sup> Edited by DeVita VT, Hellman S, Rosenberg SA. JB Lippincott Co., Philadelphia.

<sup>42</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943  
Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

<sup>43</sup> Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine, edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London

<sup>44</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943  
Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

<sup>45</sup> Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine, edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London

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the other types.<sup>46</sup> The majority of patients who survive for 2 years have the epithelial histology.<sup>47</sup> Variations in prognostic factors may, in part, explain variations in survival in Phase II and III trials in malignant mesothelioma.<sup>48</sup> In contrast to lung cancer, this is a disease of local progression and rare hematogenous spread, including in the late stages of untreated disease.<sup>49</sup> In patients, who are considered completely resectable by surgery, clinical symptoms and radiographic studies are not sensitive enough to accurately diagnose early recurrence, making survival the major endpoint of interest.<sup>50</sup>

### Asbestos Risk

Because of local asbestos industries, some locations in the U.S. have incidences as high as 636 male cases and 96 female cases per year per million population. Whether risk in such communities extends to the population at large who are not employed in the asbestos industry remains controversial. The standardized incidence of mesothelioma in Wittenoom, Australia, was 260 per million for both men and women once residents employed in the crocidolite industry were excluded. Purely residential exposure accounted for only 3% of incident cases in Yorkshire, England, but at least 18% of the cases in South Africa.<sup>51</sup>

The incidence of mesothelioma appeared to be increasing perhaps by as much as 50% in the last decade. Projections of incidence for the U.S. suggested that the numbers of cases would peak at the turn of the twentieth century or rise moderately in the twenty-first century, and then decline as a result of legislation to reduce asbestos exposure in the workplace and the ambient environment. In the Netherlands, the peak in annual male mesothelioma deaths is expected later, in approximately the year 2018. Pleural mesothelioma may account for 0.87% of all deaths in the 1943 to 1947 birth cohort of Dutch men. There are projections that the risk of dying of mesothelioma in Western Europe will double over the next 20 years, with the highest risk of approximately 1 in 150 men in the 1945 to 1950 birth cohort.<sup>52</sup>

Despite the obstacles to quantifying risk of mesothelioma, several consistent observations have emerged from studies worldwide. Crocidolite is associated with high risk of mesothelioma in miners, manufacturers, and workers who install asbestos products. Another amphibole, amosite, appears to carry an intermediate risk. Chrysotile, currently the major form of asbestos in production, shows the weakest association with mesothelioma.

<sup>46</sup> Lee JS et al. Non-small-cell lung cancer, mesothelioma, and thymoma. In: *Cancer Management: A Multidisciplinary Approach*. Edited by Pazdur R et al. New York: PRR, Inc., 2001. P. 117-120

<sup>47</sup> Jett JR. Malignant pleural mesothelioma. A proposed new staging system. *Chest*. 1995;108:895-897)

<sup>48</sup> Steele JPC, Rudd RM. *Thorax* 2000;55:725-726

<sup>49</sup> Sugarbaker et al. *J Thorac Cardiovasc Surg* 1999;117:54-65

<sup>50</sup> Sugarbaker et al. *J Thorac Cardiovasc Surg* 1999;117:54-65

<sup>51</sup> Antman KH, Pass HI, Schiff PB. *Management of Mesothelioma*. P. 1943

*Epidemiology In: Cancer. Principles and Practice of Oncology*, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

<sup>52</sup> Antman KH, Pass HI, Schiff PB. *Management of Mesothelioma*. P. 1943  
*Epidemiology In: Cancer. Principles and Practice of Oncology*, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

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Occupations with highest risk appear to be insulators, asbestos producers and manufacturers, and heating and construction tradespeople. The projected lifetime risk among these workers exposed from early adulthood ranges up to 20%. Working in proximity to these occupational groups in construction sites confers a relatively lower risk. In addition, some patients with mesothelioma have reported only isolated or brief occupational exposures to asbestos.<sup>53</sup>

Antman and co-authors write that malignant mesothelioma is rarely curable at present, so screening of asbestos workers for mesothelioma is inappropriate. However, smoking greatly increases the risk of lung cancer (but not mesothelioma) in asbestos workers and smoking cessation efforts are needed in this high-risk group. Practicing physicians considering the diagnosis of malignant mesothelioma should take a detailed exposure history emphasizing the period 20 to 50 years before diagnosis and including possible household contact exposure. Brief exposures may be long forgotten.<sup>54</sup>

### Presentation and Evaluation of the Patient

Malignant pleural mesothelioma most commonly develops in the fifth to seventh decade (median age, 60 years), typically 20 to 50 or more years since first documented asbestos exposure. The risk has been estimated to be linearly proportional to the intensity and duration of exposure, and to the time since first exposure to a power of between 3 and 4.

Latency periods between first exposure to asbestos and a diagnosis of mesothelioma may vary by occupation, with shorter latencies for insulators and dock workers and longer intervals for shipyard and maritime workers, as well as domestic exposures. A significant proportion of patients with mesothelioma diagnosed between the ages of 20 and 40 report household or neighborhood exposure during childhood. Children who present with the disease generally have no apparent asbestos exposure.<sup>55</sup>

Dyspnea, nonpleuritic chest wall pain, or both bring 90% of patients to medical attention. Examination is generally remarkable for dullness at one base, and chest radiography reveals a large freely movable unilateral pleural effusion. Occasional patients are asymptomatic, an effusion found incidentally on chest radiography. Five patients in one series presented with spontaneous pneumothorax with the unsuspected diagnosis of mesothelioma made at pleurectomy. Sixty percent have right-sided lesions, and less than 5% have bilateral involvement at the time of diagnosis.<sup>56</sup>

<sup>53</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943  
Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

<sup>54</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943  
Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

<sup>55</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943  
Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

<sup>56</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943

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Pulmonary function test results may document restrictive lung disease resulting from encasement of the lung and assess the potential tolerance for pneumonectomy. Obstructive spirometric changes are unrelated to mesothelioma or asbestosis. Laboratory evaluation is otherwise generally unremarkable except for an elevated platelet count and erythrocyte sedimentation rate.<sup>57</sup>

Bronchoscopy is usually normal or reveals extrinsic pressure. Thoracentesis yields a serous to viscous, glutinous fluid, which is occasionally bloody. The fluid is an exudate, and pleural fluid glucose can be low, but this finding is nonspecific. The best positive marker for malignant mesothelioma is the detection of a high level of hyaluronic acid in the fluid. However, the diagnostic yield by cytology is disappointing. Cytologic studies in large series reveal malignant cells in 16 to 38% of patients, but their exact nature is often undetermined or misclassified, and they are diagnostic in only 3 to 16% of patients with mesothelioma. Greater awareness of the disease, increasing expertise, and use of special stains or electron microscopy may improve these disappointing results. Pleural needle biopsy shows malignant disease in 13 to 48% of cases, and a diagnosis of mesothelioma in 10 to 36%. Use of Tru-cut needles or CT-guided pleural biopsies need more evaluation. Thoracoscopy is a useful technique in cases where it is technically possible, yielding a diagnosis of mesothelioma in 70 to 80% of cases and false-negative results in up to 20% of cases, although it was diagnostic in virtually all patients in another study. Otherwise, thoracotomy with open surgical biopsy remains the best diagnostic procedure, yielding the diagnosis in 77 to 100% of patients.<sup>58</sup>

### Pathology

#### Histopathology

The annual incidence of mesothelioma is not known with certainty because this malignancy is difficult to diagnose, even by expert pathologists. Initial misdiagnosis is common. Data from death certificates are unreliable for estimating disease frequency despite the usually rapidly fatal outcome of malignant mesothelioma. Cancer deaths are not coded by morphology (mesothelioma). The cause of mortality is assigned by primary site of the neoplasm (primary neoplasms of pleura and peritoneum). In a study of the Surveillance, Epidemiology, and End Results program of the National Cancer Institute, only 274 of 1130 white decedents with mesothelioma (approximately 95% diagnosed by microscopy) were recorded as having died of a primary neoplasm of pleura or peritoneum. The majority of

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Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

<sup>57</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943

Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

<sup>58</sup> Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine, edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London

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these mesothelioma cases were coded as having malignant neoplasm of the lung or unknown site.<sup>59</sup>

In the past, expert panels have been set up to review suspected malignant pleural mesothelioma cases. Pathologic opinion appeared particularly diverse when litigation is involved. Because a substantial percentage of mesotheliomas developed in patients with no known asbestos exposure and other malignancies were common in asbestos workers, asbestos exposure should not influence the diagnosis of mesothelioma. Because of the poor current prognosis of pleural mesothelioma, a major role of establishing the diagnosis was to exclude the possibility of a more treatable illness.<sup>60, 61</sup> Accurate diagnosis is also important in the event of subsequent litigation and for epidemiologic and therapeutic studies.<sup>62</sup> Again, one editorialist wrote about the need for a panel of experts to review pathological material to guarantee the accuracy of diagnosis.<sup>63</sup>

The histopathologic types of malignant pleural mesothelioma include: 1) epithelial or tubulopapillary (50 to 70% of cases), 2) mesenchymal or fibrosarcomatous (7 to 20% of cases), and 3) mixed or biphasic (20 to 35% of cases) (the mixed type contains both epithelial and mesenchymal elements).<sup>64</sup>

It is important to differentiate mesothelioma from adenocarcinoma--tumors with histologic similarities--since it may influence the treatment and avoid an extensive and expensive search for another primary lesion (see table below). Electron microscopy and immunohistochemistry are important adjuncts to routine microscopic evaluation in the diagnosis and classification of malignant mesothelioma.<sup>65</sup> Electron microscopy is a method to aid in differentiation with typical microvilli on epithelial mesothelioma cells (the fibrosarcomatous cells lack them) which are longer and thinner than in adenocarcinomas, as well as tonofilaments and cell junctions. Another method is through immunochemistry. A property of the mesothelial cell is the production of hyaluronic acid, a glycosaminoglycan which stains weakly with mucicarmine and strongly with colloidal iron or Alcian blue and disappears after preincubation with hyaluronidase.<sup>66, 67</sup>

<sup>59</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943

Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

<sup>60</sup> Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine. Edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London

<sup>61</sup> Jett JR. Malignant pleural mesothelioma. A proposed new staging system. Chest. 1995;108:895-897)

<sup>62</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943. Epidemiology. In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

<sup>63</sup> Jett JR. Malignant pleural mesothelioma. A proposed new staging system. Chest. 1995;108:895-897)

<sup>64</sup> Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine, edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London

<sup>65</sup> Nash G, Otis CN. Protocol for the examination of specimens from patients with malignant pleural mesothelioma. A basis for checklists. Arch Pathol Lab Med. 1999;123:39-44

<sup>66</sup> Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine, edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London

<sup>67</sup> The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)

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Hyaluronic acid has been reported to be useful in diagnosis or for following response but is relatively nonspecific. The level of hyaluronic acid was studied in the pleural fluid of 19 patients with malignant mesothelioma, 27 with lung cancer, 1 with breast cancer, 1 with mediastinal tumor, and 51 with benign diseases. The pleural fluid concentration of hyaluronic acid was greater than 100 ug/mL in 37% of (7 of 19) mesotheliomas and 1.3% of (1 of 80) lung cancers and other malignant and benign diseases. A markedly elevated serum or pleural fluid carcinoembryonic antigen, however, suggests a diagnosis other than mesothelioma.<sup>68</sup>

Hematopoietic growth factors and blood group antigens have been produced by normal and malignant mesothelial cell lines. Serum levels of interleukin-6 (IL-6), C-reactive protein, alpha(1)-acid glycoprotein, and fibrinogen were significantly higher in 25 mesothelioma patients than in patients with lung adenocarcinoma with cytology-positive pleural effusions. Serum IL-6 levels correlated with the levels of the acute-phase proteins and significantly with platelet counts. The level of IL-6 in the pleural fluid of patients with mesothelioma was approximately 60 to 1400 times higher than in the serum. Even higher levels of IL-6 in the pleural fluid and of thrombocytosis were found in patients with tuberculous pleurisy. High cytokine levels were not specific to mesothelioma (similar profiles were found in patients with tuberculous pleurisy).<sup>69</sup> However, the detection of a markedly increased level of IL-6 in pleural fluid argues against a diagnosis of adenocarcinoma.<sup>70</sup>

Pulmonary adenocarcinoma tend to express CEA, LeuM1, B72.3, and BerEP4; malignant mesotheliomas, in general, do not express these markers.<sup>71</sup> Monoclonal antibodies against keratin proteins tend to be expressed in mesotheliomas.<sup>72</sup> The table below from Chahinian and Pass<sup>73</sup> compares mesothelioma and adenocarcinoma of the lung immunochemistry.

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<sup>68</sup> Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine. Edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London

<sup>69</sup> Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine. Edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London

<sup>70</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943. Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

<sup>71</sup> DeVita VT, Hellman S, Rosenberg SA. Cancer. Principles and Practice of Oncology, 2001, p. 2731

<sup>72</sup> DeVita VT, Hellman S, Rosenberg SA. Cancer. Principles and Practice of Oncology, 2001, p. 1947

<sup>73</sup> Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine. Edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London

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**Table #9.1. Special Stains Useful in Differentiating Malignant Mesothelioma from Metastatic Adenocarcinoma**

STAIN	Mesothelioma	Adenocarcinoma
Hyaluronic acid*	+	-
Mucicarmine*	-	+
PAS	++	-
D-PAS*	-	+
CEA*	-	+
Leu M1*	-	+
Keratin	-	+
Vimentin	+	-
HMFG	++	-
EMA	-	+

PAS - periodic acid-Schiff; D-PAS - with diastase digestion; CEA - carcinoembryonic antigen; Leu M1 - human myelomonocytic antigen; HMFG - human milk lipoglobulin; EMA - epithelial membrane antigen.  
 \* Most discriminating stains.

Benign inflammatory and reactive processes producing mesothelial hyperplasia or other malignant tumors may mimic mesothelioma but do not invade normal tissues and lack cytologic atypia and hyperchromatism. Repeated cytologic examination or biopsy results may be negative despite active tumor. When tumor tissue is obtained, light microscopy often provides documentation of malignancy, but usually does not distinguish adenocarcinoma from mesothelioma. Electron microscopy of either needle biopsy or cytocentrifuge specimens from pleural fluid may establish the mesothelial origin of the malignant tumor. Sputum cytology and bronchoscopy may be helpful in documenting an occult bronchogenic adenocarcinoma. The Cancer Committee of the College of American Pathologists has established a checklist protocol for the examination of specimens from patients with malignant pleural mesothelioma.<sup>74</sup>

Adenocarcinomas from primary lung, breast, ovary, stomach, kidney, or prostate cancer frequently metastasize to the pleura and can be extremely difficult to distinguish from epithelial mesothelioma cytologically or histologically. Metastatic adenocarcinoma with extensive pleural involvement may grossly resemble mesothelioma and has been called pseudomesothelioma. Sarcomatous mesotheliomas must be distinguished from fibrosarcoma, malignant fibrous histiocytoma, malignant schwannoma, and hemangiopericytoma. Synovial sarcoma and carcinosarcomas, which may also have mixed sarcomatous and epithelial components, usually present as a localized mass in the lung. In one series, of 82 malignant localized tumors, 45% were cured by simple excision. If the nature of a lesion was ambiguous, involvement of the pleura on random biopsy would establish a diagnosis of diffuse (malignant) disease.

Autopsy requires skilled performance and experienced interpretation to reliably exclude other occult primary carcinomas. Advanced malignant mesothelioma tends to form

<sup>74</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943  
 Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

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peripheral visceral masses mimicking primary carcinomas. Asbestos counts and postmortem examinations may have legal as well as epidemiologic value.<sup>75</sup>

#### Cytology

In one study of 21 cases of epithelial malignant mesothelioma (15 pleural, 6 peritoneal) diagnosed by effusion cytology, 13 were of the cohesive cell type and 8 were of the noncohesive cell type. Because of its resemblance to florid reactive mesothelial hyperplasia and the general lack of awareness of the existence of the single-cell pattern of mesothelioma, the noncohesive cell type can often be missed. For 29 patients with at least one cytologic pleural fluid examination, cytology was positive for mesothelioma in 32%. The median time from initial symptoms to the diagnosis of mesothelioma was 8 weeks (4 weeks for patients with positive or suspicious cytology results, and 12 weeks for those with negative cytology results). Cytogenetic analysis of pleural fluid had a sensitivity of 56% and was positive in one case in which results of cytologic examination were negative.<sup>76</sup>

Patients in whom the time from presentation to diagnosis was greater than 1 year all had negative cytologic results followed by long periods without further workup, despite a history of exposure to asbestos. Because the sensitivity of cytologic examination for mesothelioma is so low, patients in whom mesothelioma is suspected should undergo immediate pleural biopsy if the pleural fluid cytology result is negative.<sup>77</sup>

Below is a table of malignant pleural mesothelioma and adenocarcinoma of the lung.

APPEARS THIS WAY  
ON ORIGINAL

<sup>75</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943  
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<sup>76</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943  
Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

<sup>77</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943  
Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

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#### Comparison of Malignant Pleural Mesothelioma and Adenocarcinoma of the Lung

	MALIGNANT PLEURAL MESOTHELIOMA	ADENOCARCINOMA OF THE LUNG
Incidence, per year U.S.	2000 - 3000	66,000 <sup>75</sup>
Sex, male:female	5:1	1.2:1 for lung cancer; adeno- common in women
Age, years (median)	60	60
Etiology, latency	Asbestos, 3 - 4 decades	Smoking, asbestos, asbestos + smoking
Pathology	Epithelial>mixed>sarco matoid	<p>Adenocarcinomas from primary lung, breast, ovary, stomach, kidney, or prostate cancer frequently metastasize to the pleura and can be extremely difficult to distinguish from epithelial mesothelioma cytologically or histologically.</p> <p>Metastatic adenocarcinoma with extensive pleural involvement may grossly resemble mesothelioma and has been called pseudo-mesothelioma.</p> <p>Synovial sarcoma and carcinosarcomas, which may also have mixed sarcomatous and epithelial components, usually present as a localized mass in the lung.</p> <p>Sarcomatous mesotheliomas must be distinguished from fibrosarcoma, malignant fibrous histiocytoma, malignant schwannoma, and hemangiopericytoma.</p>
Immunohistochemistry	Positive: hyaluronic acid, keratin, vimentin	Positive: CEA, LeuM1, B72.3, BerEP4, D-PAS
Electron microscopy	Typical long microvilli on epithelial cells (the fibrosarcomatous cells	Microvilli are shorter and thicker than on mesothelioma cells

<sup>75</sup> Based on year 2000 numbers: 164,100 lung cancer cases x 40% adenocarcinoma: 65,640

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	MALIGNANT PLEURAL MESOTHELIOMA	ADENOCARCINOMA OF THE LUNG
	lack them), as well as tonofilaments and cell junctions.	
Pleural effusion	Hyaluronic acid positive Increased IL-6 level (non-specific: also high with TB)	CEA positive
Staging		
Earliest stage with malignant pleural effusion/surgical candidate	T1 (median: 27 mo.)/yes	T4 (<10% 5-yr. Surv.)/no
Ipsilateral supraclavicular node	N3 (Stage IV)	N2 (Stage III)
Stage IV	T4, N3, or M1	M1
Natural history: metastatic disease pattern vs. locoregional disease	Local progression; rare hematogenous spread	Hematogenous spread common

### Other Variants of Mesothelioma

#### Benign Fibrous Tumors of the Pleura

Benign fibrous tumors of the pleura are approximately one-third as common as diffuse malignant mesotheliomas and are most common from age 40 to 70 years. Because they appear to arise from subsurface fibrous tissue, rather than from the mesothelial lining, they have also been called submesothelial fibromas, localized fibrous mesothelioma, or solitary fibrous tumor of the pleura. Few patients have been exposed to asbestos, approximating the incidence of exposure in the general population. CT scan and MRI are useful but nonspecific. The differential diagnosis between benign and malignant lesions is based on histologic study. Lesions have ranged in size from 1 to 36 cm. Associated effusions can be serosanguineous. Hypertrophic pulmonary osteoarthropathy has occurred in approximately one-third of patients, particularly associated with lesions more than 10 cm in size. Hypoglycemia has also been associated with large lesions,

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associated in some cases with tumor production of insulin-like growth factor. Mesotheliomas are often pedunculated and 80% arise from but usually do not invade the visceral pleura. Thus, benign pleural mesotheliomas usually have a sharp separation between tumor and compressed lung, and resection can be performed without pulmonary resection. Others may require a limited chest wall resection. While generally cured if completely resected, recurrences have occurred after several decades and 12% of patients eventually die of extensive local tumor. Localized malignant fibrous tumors of the pleura have also been described. Of 82 malignant localized tumors, 45% were cured by simple excision. If the nature of the lesion is ambiguous, involvement of the pleura on random biopsy would establish a diagnosis of diffuse (i.e., malignant) disease.<sup>79</sup>

### Malignant Peritoneal Mesothelioma

Patients usually present with symptoms and signs of advanced disease including pain, ascites, weight loss, or an abdominal mass. A cake of tumor in the omentum may be palpable as an epigastric mass. No satisfactory staging system has been proposed for peritoneal mesotheliomas, which are usually confined to the abdomen at diagnosis. Chest radiography reveals pleural plaques in approximately 50% of patients with peritoneal primaries, compared with 20% in patients with pleural mesothelioma, reflecting the higher level of asbestos exposure in patients with peritoneal disease. Classic findings on CT scan include mesenteric thickening, peritoneal studding, hemorrhage within the tumor mass, and ascites; however, patients may have advanced disease with relatively normal CTs. MRI offers the possibility of improved resolution. Given the low incidence of bone, brain, or liver metastasis at presentation, extensive evaluation for metastatic disease is inappropriate in the absence of laboratory abnormalities. Adrenal, intrapulmonary, or bony metastasis should raise the possibility of an alternative diagnosis.<sup>80</sup>

Peritoneal fluid from malignant ascites may be a watery transudate or a viscous fluid rich in mucopolysaccharides. No diagnostic significance has been attached to the character of the fluid, although a viscous ascites (with high fluid hyaluronidase levels) may suggest the diagnosis. Massive ascites may result in confusion of mesothelioma with severe cirrhosis. Cytology establishes the diagnosis in only 5% to 10% of cases. Ultimately, definitive diagnosis requires adequate tissue sampling, preferably from peritoneoscopy or an open directed

<sup>79</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943  
Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

<sup>80</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943  
Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

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biopsy. A generous biopsy specimen is required to perform immunohistochemical stains, as well as electron microscopy. Open biopsy also permits inspection of the abdominal cavity for extent of disease with particular attention to the bowel and ovaries to distinguish mesothelioma from other more common causes of peritoneal carcinomatosis. Peritoneal mesotheliomas can be confused with adenocarcinomas arising from any abdominal organ, but the pattern of spread and tendency to accumulate in the pelvis readily leads to confusion with adenocarcinoma of the ovary or carcinoma arising from Mullerian duct remnants in the peritoneum. The tumor generally remains confined to the abdomen until late in the course and even then is more likely to spread to one or both pleural cavities than to disseminate hematogenously. Thrombocytosis is common and associated with high levels of IL-6 and a poor prognosis. Other common clotting abnormalities include phlebitis, emboli, hemolytic anemia, and disseminated intravascular coagulation. Most patients die without metastases or involvement of the chest. Esophageal achalasia, secondary amyloidosis, and dermatomyositis have been reported. The median survival of untreated patients in most series is short, 4 to 12 months.<sup>81</sup>

#### Well-Differentiated Papillary Mesothelioma or Cystic Mesotheliomas of the Peritoneum

Rare, well-differentiated papillary variants and a syndrome of recurrent peritoneal mesothelial cysts have both been found predominantly in younger women associated with a prolonged survival despite bulky disease. Rarely, the disease progresses over time to a typical malignant mesothelioma. Approximately 130 cases of multiloculated peritoneal inclusion cysts (also called benign cystic peritoneal mesotheliomas) have been described, mainly in the pathologic and surgical literature. Some authors have advocated classifying this lesion as reactive proliferation rather than as malignant. The radiologic differential diagnosis has been reviewed. Frequently associated with prior surgery, endometriosis, or pelvic inflammatory disease, they occur predominantly in women, but can occur in men. Treatment should be provided for palliation of symptoms or for clearly documented progression. Despite initial surgical resection, approximately one-half recur locally. Neither lesion size nor proliferation correlates with outcome. Tamoxifen resulted in a prolonged response in a 19-year-old woman. Permanent transvaginal catheter drainage in a patient with recurrent cysts resulted in infection and obliteration of the cyst. The potassium titanyl phosphate laser has also been used in treatment of benign multicystic peritoneal mesothelioma.<sup>82</sup>

<sup>81</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943  
Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

<sup>82</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943  
Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

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#### Surgery for Peritoneal Mesothelioma

Surgical and autopsy series have shown that peritoneal mesothelioma involves all peritoneal surfaces, often with masses of 5 cm or more. Sites of local invasion included the liver, abdominal wall, diaphragm, retroperitoneum, gastrointestinal tract, and bladder. Seeding of laparotomy scars and biopsy tracts has also been observed. The tumor is most often confined to the peritoneal cavity at the time of initial diagnosis and remains there for much or all of the subsequent clinical course. Hence, effective local therapy may have a substantial effect on the survival of patients with this disease. Complete surgical resection is rarely, if ever, feasible, and has not been shown to afford survival benefit in the absence of additional therapy. Nevertheless, surgical intervention can provide palliation for small bowel obstruction and relief of massive ascites by peritovenous shunting or paracentesis via Tenckhoff's catheter.<sup>83</sup>

#### Prognostic Factors for Malignant Pleural Mesothelioma

Performance status has been one of the most reliable prognostic factors, in addition to the stage, which is discussed below. Epithelial cell type has been associated with a more favorable prognosis in most large series; the fibrosarcomatous type carries the worst prognosis, and the mixed type is intermediate. Younger age at diagnosis has also been reported as a favorable feature, whereas no prognostic differences were found between men and women, particularly after adjustment for cell type. Absence of weight loss, lack of involvement of the visceral pleura, early stage, and epithelial cell type were shown to be favorable prognostic factors in a large group of 188 patients with pleural mesothelioma. The negative prognostic impact of thrombocytosis first reported by Chahinian and colleagues has been confirmed in three other series. The prognostic role of other factors (asbestos exposure or not, duration of symptoms, side of pleural disease, and pleural versus peritoneal involvement) is more contradictory at this time.<sup>84</sup> The EORTC system of prognostic factors for malignant pleural mesothelioma defined high risk as: poor performance status, high WBC at diagnosis, probable or possible (uncertain) histology, male sex, and sarcomatous cell type;<sup>85</sup> in their experience in 204 adults with malignant pleural mesothelioma on five consecutive phase II clinical trials, the median survival was 13 months from diagnosis and 8 months from trial entry.<sup>86</sup> Epidermal

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<sup>83</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943  
Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

<sup>84</sup> Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine. Edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London

<sup>85</sup> Steele JPC, Rudd RM. Thorax 2000;55:725-726

<sup>86</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943

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growth factor-positive cells have been found in 68% of mesotheliomas examined and correlate with improved survival.<sup>87</sup>

The table below summarizes specific articles, which analyzed data for prognostic factors in malignant pleural mesothelioma.

AUTHOR JOURNAL DATE	DATES OF DATA	POPULATION	FACTORS	RESULTS OF PROGNOSTIC FACTORS
Curran J Clin Oncol 1998 <sup>88</sup>	1984-1994	204 patients from 5 European Phase II trials  drugs studied: mitoxantrone, epidoxirubicin, VP- 16, taxol	Poor prognosis: Poor performance (PS) status High WBC Probable/possible histological dx Male Sarcomatous subtype	Good prognosis group: 1 yr. surv. 40% (95% CI:30%, 50%)  Bad prognosis: 1 yr. Surv. 20% (95% CI:4%, 20%)
Herndon Chest 1998 <sup>89</sup>	1984-1994	337 Patients from CALGB trials  Drugs studied: MMC, adriamycin, carboplatin, DHAC, trimetrexate, edatrexate, taxol	<b>Median survival in bold</b> PS=0, age<49 yr Or PS=0, age≥49 yrs, Hgb ≥14.6: <b>13.9 mo.</b>  PS=1/2, WBC < 8.7, no chest pain: <b>9.5 mo.</b>  PS=0, age ≥ 49 yrs, Hgb < 14.6 Or P/S=1/2, WBC < 15.6, chest pain, no weight loss, Hgb ≥ 12.3 Or	Best median survival, 13.9 months: PS=0 & age < 49 yrs and PS=0, age > 49 yrs., Hbgf ≥14.6  Worse median survival, 1.4 months: PS=1/2 and WBC ≥ 15.6 uL

Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

<sup>87</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943

Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

<sup>88</sup> J Clin Oncol. 1998;16:145-152

<sup>89</sup> Chest 1998; 113:723-731

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AUTHOR JOURNAL DATE	DATES OF DATA	POPULATION	FACTORS	RESULTS OF PROGNOSTIC FACTORS
			<p>PS=1/2, 9.8 ≤ WBC&lt;15.6, chest pain, weight loss, Hgb ≥ 11.2: <b>9.2 mo.</b></p> <p>PS=1/2, 8.7 ≤ WBC&lt;15.6, no chest pain: <b>6.5 mo.</b></p> <p>PS=1/2, WBC &lt;15.6, chest pain, no weight loss, Hgb&lt;12.3 Or PS=1/2, 9.8 ≤ WBC&lt;15.6, chest pain, weight loss, Hgb &lt; 11.2 Or PS=1/2, WBC&lt;9.8, chest pain, weight loss: <b>4.4 mo.</b></p> <p>PS=1/2, WBC&gt;15.6: <b>1.4 mo.</b></p>	
Pass J Thorac Cardiovasc Surg 1998 <sup>90</sup>	1993-1996	Analysis of impact of preoperative and postresection solid tumor volumes 47 of 48 malignant pleural mesothelioma patients resected and randomized to +/- photodynamic therapy @ the NCI		<p><b>Preoperative volume</b></p> <p>&lt; 100 cc: median, 22 months &gt;100 cc: 11 months; p =0.03</p> <p><b>Postoperative volume</b></p> <p>&lt; 9 cc: median, 25 months &gt; 9 cc: 9 months; p=0.0002</p>

<sup>90</sup> Pass HI, Temeck BK, Kranda K, Steinberg SM, Feuerstein IR. J Thorac Cardiovasc Surg 1998; 115:310-318

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AUTHOR JOURNAL DATE	DATES OF DATA	POPULATION	FACTORS	RESULTS OF PROGNOSTIC FACTORS
				<p><b>Extrapleural pneumonectomy:</b> median, 11 months</p> <p><b>Pleurectomy/decortication:</b> 22 months; p = 0.07</p>

### Stage and Staging

Accurate staging and identifying significant prognostic factors is important and accepted in the study and treatment of other malignancies.<sup>91</sup> As an example, in another thorax tumor, precise staging of NSCLC has defined homogenous groups of patients according to prognosis;<sup>92</sup> a large surgical-pathological database supports the TNM staging system for NSCLC.<sup>93</sup> The International Mesothelioma Interest Group (IMIG) is a collection of pulmonary medicine physicians, thoracic surgeons, medical and radiation oncologists, epidemiologists, radiologists, pathologists, and laboratory scientists interested in research in malignant pleural mesothelioma.<sup>94</sup> The data to devise this staging system can be applied to radiographic, surgical, and pathological staging of this disease; it is the latter two that are primarily the basis of the staging system.<sup>95</sup>

Before the IMIG staging system, there were five other staging systems--three with stages I through IV and two with TNM stages; there was little prospective data to support these staging systems as derived from meticulously staged patients based on surgical-pathological data.<sup>96, 97</sup> None of these staging systems have been fully validated or consistently used for survival analyses.<sup>98</sup>

The IMIG is a surgically-based TNM staging system that takes into consideration information about the impact of T and N status on survival. The IMIG staging system

<sup>91</sup> Rusch VW, Venkatraman, E. J Thorac Cardiovasc Sug 1996; 111:815-826.

<sup>92</sup> The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)

<sup>93</sup> Jett JR. Malignant pleural mesothelioma. A proposed new staging system. Chest. 1995;108:895-897)

<sup>94</sup> The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)

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<sup>97</sup> The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)

<sup>98</sup> Rusch VW, Venkatraman, E. J Thorac Cardiovasc Sug 1996; 111:815-826.

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improves upon other staging systems and provides precise TNM descriptors that can be used for radiographic, surgical, and pathologic staging.<sup>99</sup>

The staging system differentiates between T1a and T1b; based on thoracoscopy data, T1a tumors had a median survival of 32.7 months and T1b tumors had a median survival of 7 months; this degree of differentiation between tumors is difficult noninvasively. This is also true about differentiating T1b and T2 tumors—i.e., diaphragmatic muscle involvement or tumor penetrating the pulmonary parenchyma is obvious at thoracotomy but not as obvious at thoracoscopy.<sup>100</sup> In one series, T3 tumors had a median survival of 13 months and T4 tumors had a median survival of 6.5 months.<sup>101</sup> Nodal staging in the IMIG is virtually identical to the staging system for NSCLC. N1 is involvement of the ipsilateral bronchopulmonary and hilar lymph nodes. N2 is subcarinal or ipsilateral mediastinal lymph nodes and ipsilateral internal mammary nodes. N3 is metastasis to nodes in the contralateral mediastinal, contralateral internal mammary, or the ipsilateral or contralateral supraclavicular areas,<sup>102</sup> in general, N3 is nodal involvement outside same hemithorax as the primary tumor. One study demonstrates a median survival of 18.3 months for N0 and 9.4 months for any nodal involvement.<sup>103</sup>

The IMIG staging system has been validated in two series of patients; it has not been prospectively evaluated with regard to clinical vs. operative stage.<sup>104 105</sup>

In one validation study,<sup>106</sup> from October 1983 to July 1994, 131 consecutive patients with malignant pleural mesothelioma underwent exploratory thoracotomy (108 men; 23 women; median age 63 years [range 32-80 years]). In this series, the pathological diagnosis was always based on both histologic tumor type and immunohistochemistry; when necessary, electron microscopy was added to confirm the diagnosis. There were 101 resections (71%), including 50 extrapleural pneumonectomies and 51 pleurectomy/decortications. The IMIG staging system was applied retrospectively to each patient to determine the TN status and corresponding tumor stage. Staging was based on precise information about tumor extent in the operative summary dictated by the surgeon

<sup>99</sup> Rusch VW, Venkatraman, E. *J Thorac Cardiovasc Sug* 1996; 111:815-826.

<sup>100</sup> The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. *Chest*. 1995;108:1122-1128)

<sup>101</sup> The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. *Chest*. 1995;108:1122-1128)

<sup>102</sup> The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. *Chest*. 1995;108:1122-1128)

<sup>103</sup> The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. *Chest*. 1995;108:1122-1128)

<sup>104</sup> Pass HI, Temeck BK, Kranda K, Steinberg SM, Feuerstein IR. *J Thorac Cardiovasc Surg* 1998; 115:310-318

<sup>105</sup> Rusch VW, Venkatraman, E. *J Thorac Cardiovasc Sug* 1996; 111:815-826.

<sup>106</sup> Rusch VW, Venkatraman, E. *J Thorac Cardiovasc Sug* 1996; 111:815-826.

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and on nodal involvement as recorded in the pathology report. The figure and table below summarizes much of the data.

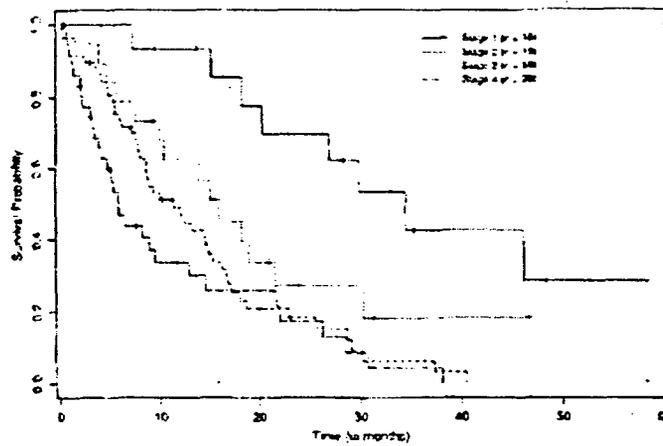


Fig. 5. Univariate analysis of overall survival by stage. When stage I/II was compared with stage III/IV,  $p$  was 0.0001. When all four stage groups were compared simultaneously,  $p$  was also 0.0001.

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Table III. Median survival for all 151 patients according to TN status, stage, and histologic type

	Median survival (mo)
Operation	
Extrapleural pneumorectomy	9.0
Pleurectomy/decortication	18.3
T status	
T1	27
T2	12
T3	13
T4	6.3
N status	
N0	18.3
N1-3	5.4
Stage	
I	34
II	16
III	11.5
IV	5.9
Histologic type	
Epithelial	15.1
Mesothelial	6

The median survival for the 101 patients who had either a pleurectomy/decortication or extrapleural pneumorectomy is shown according to which operation was performed.

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As shown in the table above, this surgical series correlated survival with stage, type of surgical resection, and histological type of cancer.

Based on this data, surgical decisions may be made. The primary tumor is considered potentially resectable if preoperative CT scans of the chest and abdomen did not show extrathoracic disease, clear invasion of the mediastinal organs or chest wall, or extension through the diaphragm. The decision to perform an extrapleural pneumorectomy as opposed to a pleurectomy/decortication for resection was based on the extent of visceral pleural tumor at thoracotomy. Extrapleural pneumorectomy, defined as an en-bloc resection of the pleura, lung, ipsilateral diaphragm, and pericardium was performed for locally advanced disease, usually in patients with confluent visceral pleural tumor not separable from the lung and a partially or totally fused pleural space. Pleuroectomy/decortication, which removed all gross tumor without removing the underlying lung, was performed in patients who had minimal visceral pleural tumor. Partial parietal pleurectomy was sometimes performed for control of a pleural effusion if incompletely resectable tumor was found at exploration, but all pleurectomy/decortications and extrapleural pneumorectomies were performed only if it was thought that all gross tumor could be removed. Resection was defined as incomplete if any visible gross tumor remained at the completion of thoracotomy, even if only a few scattered tumor foci < 5 mm in size were present.<sup>107</sup>

Below is the IMIG staging system.

#### International Mesothelioma Interest Group Staging Criteria for Mesothelioma

##### Primary Tumor (T):

T1

<sup>107</sup> Rusch VW, Venkatraman, E. J Thorac Cardiovasc Sug 1996; 111:815-826.

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T1a Tumor limited to the ipsilateral parietal including mediastinal and diaphragmatic pleura, no involvement of the visceral pleura mediastinal and diaphragmatic pleura, scattered foci of tumor also involving the visceral pleura

T2

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

T3

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

T4

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

#### Lymph Nodes (N):

NX

Regional Lymph nodes cannot be assessed

N0

No regional lymph node metastases

N1

Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes

N2

Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes including the ipsilateral internal mammary nodes

N3

Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes

#### Metastases (M):

MX

Presence of distant metastases cannot be assessed

M0

No distant metastasis

M1

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Distant Metastasis present

#### Staging:

Stage Ia T1aN0M0

Stage Ib T1bN0M0

Stage II T2N0M0

Stage III Any T3M0, AnyN1M0, AnyN2M0

Stage IV AnyT4, AnyN3, AnyM1

#### Evaluation of the Patient for Staging

##### Noninvasive Studies to Determine Stage

Although CT scans and MRIs are important in the staging of malignant pleural mesothelioma, these noninvasive techniques are not as accurate as surgical and pathologic staging.<sup>108</sup> For example, Rusch and Venkatramen report in their surgical series that more than 50% of malignant pleural mesothelioma cases are clinically understaged in comparison to their surgically documented pathologic nodal status.<sup>109</sup>

The major role of noninvasive procedures is to determine isolated hemithorax disease. Despite a history of asbestos contact in 50% to 70% of patients, pleural plaques or interstitial fibrosis are apparent on chest radiography in only approximately 20%, but pleural calcifications are evident on almost one-half of computed tomographic (CT) scans and in up to 87% at autopsy. Scoliosis with contracture of the ipsilateral hemithorax is visible even on chest radiography with advanced disease. A CT scan or magnetic resonance imaging (MRI) of the primary tumor to assess the extent of disease is indicated if treatment is contemplated. Characteristic CT findings in almost 100 patients are pleural thickening in 92% (and of the intralobar fissures in 86%), effusions in 74%, and pleural calcifications in 20% to 50%. CT scan is helpful in differentiating benign from malignant pleural thickening, but does not reliably distinguish primary from metastatic malignancy. Coronal MRI is particularly helpful to evaluate the diaphragm. In a study of 26 mesothelioma patients evaluated with sequential paired CT and MRI scans, MRI showed tumor spread into the interlobar fissures, tumor invasion of and through the diaphragm, and invasion of bony structures better than CT. Invasion of the chest wall and mediastinal soft tissue and tumor growth into the lung parenchyma were equally well seen on both imaging methods. CT was better for detecting pleural calcifications. Twenty-eight consecutive patients referred for the evaluation of suspected malignant

<sup>108</sup> The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. *Chest*. 1995;108:1122-1128)

<sup>109</sup> Rusch VW, Venkatraman, E. *J Thorac Cardiovasc Sug* 1996; 111:815-826.

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mesothelioma were evaluated by positron emission tomography (PET) with 2-fluoro-2-deoxy-d-glucose (FDG) imaging. Video-assisted thoracoscopy or surgical biopsies provided a malignant diagnosis in 24 patients (22 with mesothelioma) and benign processes in the remaining four. The uptake of FDG was significantly higher in malignant than in benign lesions ( $P = .0001$ ). FDG-PET images identified active tumor sites. Hypermetabolic lymph nodes were noted on FDG-PET images in 12 patients, 9 of which appeared normal on CT scans. Histologic examination in six patients confirmed malignant nodal disease in five cases and granulomatous lymphadenitis in one. Standardized uptake values were inversely correlated with duration of survival after the PET study ( $P = .05$ ). These data could be useful in deciding which patient may be a candidate for an aggressive approach since a high FDG uptake in these tumors may indicate a shorter patient survival. Mesotheliomas are reported to take up gallium 67. Gallium 67 scans in seven cases obtained before resection were compared with pathology. When the involved pleural thickness was over 6 mm, gallium 67 uptake correlated with the macroscopic thickness of mesothelioma in resected specimens. Thickness of the pleura on CT images was only reliable for thick involvement. No definite correlation was found between gallium 67 uptake and the histologic type, extent of tumor parenchyma, interstitial volume, and tumor vascularity. Planar  $^{201}\text{Tl}$  scintigraphy in a single mesothelioma patient revealed diffuse pleural tumor accumulation. Single photon emission CT demonstrated exact tumor location. Brain, bone, and liver metastases or extension into other serosal surfaces, although present in more than one-half of patients at autopsy, are sufficiently uncommon at presentation to obviate the need for extensive baseline studies in the absence of symptoms or laboratory abnormalities. However, such studies may identify an occult adenocarcinoma of the lung, a pattern of widespread metastases, or a markedly elevated serum or pleural fluid carcinoembryonic antigen suggesting a diagnosis other than mesothelioma. Although there are no definitive biomarkers for mesothelioma, future studies investigating serial serum levels of tissue polypeptide antigen or thrombomodulin may be of interest.<sup>110</sup>

### Invasive Studies to Determine Stage

Although obtaining an accurate histologic confirmation of mesothelioma from pleural fluid cytology or needle biopsy specimens is often difficult, the diagnosis of mesothelioma has such a poor prognosis that an unequivocal tissue diagnosis is mandatory. Surgical intervention is usually required, either a thoracoscopy or thoracotomy, despite the risk of seeding the biopsy site or surgical scar with tumor. In any evaluation for the patient with mesothelioma, careful attention must be paid to the diaphragmatic extent of the tumor with suspicious scans

<sup>110</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943  
Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

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confirmed by laparoscopic evaluation for transdiaphragmatic extension. For patients who are not candidates for radical surgery, thoracoscopy usually obtains sufficient tissue for histochemical analysis. The later development of chest wall masses from seeding of the biopsy site or surgical scar is an uncommon complication (approximately 10%) of any diagnostic procedure, but can usually be avoided by radiotherapy to the scar if appropriate. Tumor nodules seeded from fluids rich in tumor cells may develop in the subcutaneous tissue surrounding Denver shunts and intrapleural ports. If preoperative studies suggest stage I mesothelioma in good-risk patients with asbestos exposure, most surgeons combine the diagnostic and therapeutic surgical interventions in one stage. Generous biopsies can be performed at the inception of the exploration, using frozen sections to differentiate mesothelioma from adenocarcinoma. A sample of uninvaded lung should be obtained for counting asbestos fibers. Bronchoscopy should be performed in all patients suspected of mesothelioma to rule out endobronchial disease, rare in mesothelioma. The role of mediastinoscopy in patients with suspected mesothelioma is undefined. Some surgeons believe it is unnecessary because nodes can be removed with the lung. Other surgeons believe that, because positive nodes indicate stage III disease, surgery would be contraindicated. Nevertheless, if radical extrapleural pneumonectomy (EPP) is contemplated, mediastinoscopy is recommended, because 20% of patients with mesothelioma have mediastinal lymph node involvement.<sup>111</sup>

### Natural History

The natural history of malignant mesothelioma is important because it provides insights into the development of treatment strategies. Investigators have described the initial presentation as variable in symptoms and duration, and disease progression as initially being local. Systemic disease has been underemphasized. At least 50% of all patients have distant metastatic disease at autopsy and systemic disease is the most common form of relapse in patients who have achieved local control of their disease via extrapleural pneumonectomy.<sup>112</sup>

Before the 1990s, with few exceptions, there was little effort to precisely stage malignant pleural mesothelioma. The disease was thought of as a tumor that involved all the pleural surfaces, encased the lung, and led to death within 2 years of diagnosis due to cardiopulmonary failure from local progression of disease.<sup>113</sup>

<sup>111</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943  
Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

<sup>112</sup> Rusch VW. Oncology 1999;13:931-932

<sup>113</sup> The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)

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Mesotheliomas spread over the parietal and visceral serosal surfaces. Pleural mesothelioma extends over the diaphragm, mediastinum, pericardium, and, eventually, the peritoneum. It also extends into the interlobar fissures and into the lung itself by contiguity or by interstitial and alveolar spread. Seeding along the track of needle biopsy channels occurs in 10 to 20% of cases. Lymphatic dissemination is common and mediastinal nodes are involved in about 50% of cases of pleural mesothelioma.<sup>114</sup> Distant blood-borne metastases are more common than was previously thought and are seen at autopsy in 50 to 80% of cases. They can occur in any organ, including the brain. A peculiar pattern of massive hepatic calcifications, attributed to degenerative and necrotic liver metastases, has been described.<sup>115</sup>

Based on thorascopic studies, investigators suggest that malignant pleural mesothelioma arise in the parietal and diaphragmatic pleura, and then spreads to the visceral pleura. Patients with T1 disease usually have a free pleural space and present with a large pleural effusion.<sup>116</sup> T2 disease has confluent involvement of the visceral pleura and/or extension of the pulmonary parenchyma; the pleural tumor cannot be fully removed without resecting the underlying lung. In T2 disease, there is still free pleural space with an effusion but the parietal and visceral pleural surfaces have begun to fuse; the pleural effusion may have resolved or become loculated.<sup>117</sup> T3 disease is an advanced tumor that has the potential for resection. In T3 disease there is involvement of all the pleural surfaces; there may be tumor extension into the endothoracic fascia or the mediastinal fat; the surface of the pericardium may be involved; a focus of resectable tumor invading the chest wall is also considered T3.<sup>118</sup> T4 disease is locally advanced and not amenable to resection; there is involvement of all the pleural surfaces, diffuse extension into the chest wall, direct extension through the diaphragm to the underlying peritoneum; there may also be direct extension to the contralateral pleura, mediastinal organs, the spine, the myocardium, or the internal surface of the pericardium. Interestingly, malignant pleural mesothelioma may progress to T4 disease before distant metastasis is present.<sup>119</sup>

Shortness of breath and chest pain can be controlled initially by repeated thoracenteses and minor narcotics. Although chest tube drainage and sclerosis is

<sup>114</sup> Note for comparison: Peritoneal mesothelioma involves mainly the parietal and visceral serosal surfaces, the omentum, and the mesentery with tumor nodules and/or infiltration causing thickening. Involvement of the serosa overlying the small and large bowel, the liver, the spleen, and other organs leads to encasement of these organs in tumor tissue.

<sup>115</sup> Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine, edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London

<sup>116</sup> The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)

<sup>117</sup> The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)

<sup>118</sup> The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)

<sup>119</sup> The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)

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generally unsuccessful, pleural fluid eventually becomes loculated as the tumor obliterates the pleural space. With advanced disease, fatigue and dyspnea increase out of proportion to radiographic findings or pulmonary function values. Because hypoxia results from shunting of desaturated blood through a poorly aerated lung, therapeutic oxygen provides little symptomatic relief.<sup>120</sup>

Mesothelioma tends to be locally invasive. Chest wall masses develop in approximately 10% of patients, generally over thoracentesis, chest tube drainage, or thoracotomy tracts. Direct involvement of esophagus, ribs, vertebrae, nerves, and the superior vena cava cause dysphagia, pain, cord compression, brachial plexopathy, Homer's syndrome, or superior vena cava syndromes, respectively. Fevers and sweats with no documented source of infection are common and often accompanied by significant weight loss, poor performance status, and an early death. Thrombocytosis and other clotting abnormalities occur in 10% to 20% (more frequently in peritoneal mesothelioma). Disseminated intravascular coagulation, thrombophlebitis, pulmonary emboli, and Coombs' positive hemolytic anemia have been reported, as well as hypercalcemia associated with elevated levels of a parathyroid hormone-like peptide.<sup>121</sup>

Patients generally die of respiratory failure or pneumonia. Small bowel obstruction from direct extension through the diaphragm develops in approximately one-third, and 10% die of pericardial or myocardial involvement.<sup>122</sup>

### Surgical Treatment

According to one group of authors, the role of surgery in managing diffuse pleural mesothelioma remains controversial, but there are an increasing number of thoracic oncologic surgeons who are operating for this disease. Nevertheless, overwhelming pessimism for curative surgical options continues in most centers that do not routinely deal with the disease since the combination of effusive disease and bulky tumor renders surgical eradication virtually impossible. The disappointing long-term overall survival results, the historically high morbidity and mortality, as well as the propensity for local recurrences have forced many centers to abandon radical operations except for the rare localized situation. The arguments regarding appropriate management of mesothelioma can have geographic differences. In a United Kingdom poll of chest physicians, only 46% of the physicians surveyed would consider referral to a thoracic surgeon for radical resection. The French approach to the disease has been a concentration on detection of

<sup>120</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943  
Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

<sup>121</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943  
Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

<sup>122</sup> Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943  
Epidemiology In: Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.