# Quick Review: Mesothelioma

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**Citation**

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**Abstract**

This article reviews briefly the main points of mesotheliomas.

## DEFINITION AND HISTORY

The term was first used in 1921 by Eastwood & Martin to describe primary tumors of the pleura

- At that time, the diagnosis was extremely controversial (required autopsy examination)
- Today, the diagnosis is still problematic
    - 15 % of cases can not be differentiated from adenocarcinoma
- Wagner, South African miners [Br J Ind Med]
    - first evidence implicating asbestos in the pathogenesis
    - landmark paper, began widespread investigation
- Incidence has reached “Epidemic”
    - European Experience: Expected Peak, 2010 - 2020 (2,700 - 9,000 deaths/yr.)
    - U.S. Experience: Peaked in the 1970's & since 1980 the incidence has been decreasing

The increase in general incidence has been attributed to the widespread use of asbestos in the post-World War II period [McDonald 1987]

- Precautions were first taken in the U.S.
- Europe was “slow” to respond
- Effect on third-world countries
- Industrialized Countries
    - 2 per million in females
    - 10 - 30 per million in males regional differences are due to the level of industrial activity
- Areas with shipyards are at the highest risk
- Type is also a Factor: Crocidolite & Amosite > Chrysotile

The occurrence of mesothelioma is related to an Occupational Exposure to Asbestos.

Non-occupational environmental exposure leading to it's development is uncommon

- Only 7.2 % of asbestos workers, will develop the disease
- Up to 50 % of patients, do not have any history of exposure

Cases due to exposure in buildings with asbestos insulation are extremely rare !

## THE RISK

[Hughes et al. 1986: “quantitative risk”]

[Lilienfield 1991: “four cases in school teachers”]

There has never been prospective evidence to support the widespread removal of asbestos insulation...

3 Main Groups:

- Benign Localized Mesothelioma
    - “pleural fibroma”

- Unassociated with asbestos exposure
- Paraneoplastic syndromes occur in 1/3
    - Migrating Thrombitis
    - Thrombocytosis
    - Hemolytic Anemia
    - Hypoglycemia
    - Hypercalcemia
    - Pulmonary Hypertrophic Osteoarthropathy [Boutin 1998]
- Arise from the visceral pleura
- Unless incomplete, surgical resection is curative

- Malignant Localized Mesothelioma
    - 20 % of all primary malignant pleural tumors are localized
    - Present as Symptomatic Masses
    - Difficult to differentiate from Chest Wall Neoplasms
    - Treatment
        - Wide enbloc excision of all involved tissue
        - Lung, Chest Wall, Soft Tissues, & Skin
        - With incomplete excision, the prognosis approaches MDM
        - External beam radiation is of little benefit

- Malignant Diffuse Mesothelioma
    - Classical form
    - Related to exposure
    - Latent Period of 20 years
    - Smoking is an associated factor
        - not for mesothelioma, but for overall survival rate

## TYPICAL SCENARIO

Middle-aged man with pleuritic chest pain, shortness of breath, & a clear history of asbestos exposure

## 3 CELL TYPES:

- Epithelial Type : 50 % of cases
    - most often confused with adenocarcinoma
- Mesenchymal Type : 16 % of cases
- Mixed Type : 34 % of cases

## PATHOGENECITY:

Benign pleural plaques are the most common manifestation of asbestos exposure

- usually develop on the parietal or diaphragmatic pleura
- malignant mesothelioma is thought to originate from the parietal pleura
- high concentrations of asbestos fibers in the lung are associated with bronchial carcinoma [Antilla 1993]

## CLINICAL POINTS:

- Mean Age of Patients: 60
    - has been reported in children (unrelated to asbestos) [Fraire 1988]
- Clinical signs/symptoms depend on the stage
    - TNM Classification
    - Early-Stage Disease: Symptoms are Rare
    - Late-Stage Disease: Pain, Dyspnea, Moderate Effusion

The initial chest radiograph leading to a diagnosis of mesothelioma reveals a pleural effusion 92 % of the time

- 7 % of the time, a Multinodular Pleural Tumor was found
- 0.5 % of the time, an Empyema

- 0.5 % of the time, a Spontaneous Pneumothorax [Boutin 1993]

On thoracentesis, the pleural fluid is an Exudate with little evidence of inflammation & a high number of mesothelial cells

- Cytology of the fluid is 30 % sensitive![Renshaw 1997]
- Removal of the pleural fluid improves the possibility of establishing the diagnosis

## DIAGNOSTIC WORK-UP

- CXR (with thoracentesis)
- Chest C.T.
    - irregular, nodular pleural thickening
    - spread into the diaphragm, pericardium, chest wall, or mediastinal lymph nodes is difficult to assess [Masilta 1991]
- Thoracoscopy with Biopsy
- MRI

## STAGING

- Stage I : tumor isolated to ipsilateral pleura or lung
- Stage II: tumor invades chest wall, mediastinum, pericardium, or contralateral pleura
- Stage III: tumor involves both thorax & abdomen
- Stage IV: distant blood-borne metastases

## EXPECTED SURVIVAL:

- Stage I: 16 months
- Stage II: 9 months
- Stage III: 5 months[Cohen 1995]

## ESTABLISHING THE DIAGNOSIS

Thoracoscopy is indicated in any patient without a precise histopathological diagnosis in whom clinical & laboratory findings raise the suspicion of mesothelioma

- Cardinal Characteristics
    - Age between 55 – 65
    - Previous occupational exposure to asbestos
    - Pleural Effusion
    - C.T. / MRI (with nodular lesions of the parietal pleura) [Boutin 1998]
- VATS
    - Mesothelioma takes on a “grape-like” appearance
        - patches of closely-spaced, smooth, translucid, poorly-vascularized nodules with a clear to yellowish color
            - not unique to mesothelioma
            - also seen with metastatic cancer of the pleura Unlike benign inflammation (pleurisy), the pleura becomes hard & non-elastic - with biopsy, the cut edges do not bleed
    - 10 - 15 % of cases, the observed lesions are nonspecific
        - path report: “benign pleural inflammation”
    - The more unimpressive the picture, the more biopsies should be taken (up to 20)
    - Look for involvement of the Lung or Visceral Pleura
    - 98 % sensitive in establishing the diagnosis
    - Mortality is 1:8000
    - Complications are minimal
        - Subcutaneous Emphysema
        - Localized Infection

        - Minor Bleeding (< 100 cc)[Viallat 1991]
    - 1 Problem with VATS: Seeding of the Trocar Path
        - unknown incidence but can occur
        - has been documented after thoracentesis & blind pleural biopsy

Can be prevented by performing Prophylactic Radiotherapy after healing to the point of entry [Rey 1995]

## NATURAL HISTORY

- Median Survival : 12 - 17 months
- 5-year Survival : < 5 %
- Mesothelioma is a Local Disease
    - Invasion usually first involves the Lung & Diaphragm
        - Progressive Retraction of the hemithorax leading to a “trapped lung”
        - Peritoneal Infiltration - through the diaphragm or it's posterior openings with secondary ascites
- Spread to the Endothoracic Fascia (T2) or Intercostal Spaces (T3) is common
    - Found in 30 - 50 % of patients at the time of biopsy[Chahinian 1983]
    - Parietal involvement can be “massive”
    - UNCOMMON:
        - Clinically-detectable lesions in bone, tissue, or brain
        - Involvement of the contralateral lung

However, at the time of autopsy, 50 % of patients will have metastatic spread [Antman 1981]. Death is usually due to progressive dyspnea & respiratory insuffiency with extensive weight loss & muscle wasting

## THERE IS NO SINGLE TREATMENT WHICH HAS PROVEN EFFECTIVE...

## TREATMENT: SURGERY

To ensure that surgery will be as curative as possible, resection must include:

- the Pleura: Stage Ia
- the Lung: Stages Ib, II, and III

Many cases will require resection of the diaphragm, pericardium, & chest wall; but does surgery improve survival?

- Worn 1974, 248 Patients
    - 62 Patients with Radical Pneumonectomy
        - 2-yr. Survival, 37 % 5-yr. Survival, 10 %
    - Conservative Treatment
        - 2-yr. Survival, 12.5 % 5-yr. Survival, 0 %
- Probst 1990, 111 cases
    - Median survival was longer after pneumonectomy than any other method (1.4 months)

Operative mortality for radical pneumonectomy, across the board, is 25 %

A current review of all surgical series suggests that treatment protocols including surgery do extend survival...

- Pleurectomy(2-yr. Survival): 11- 35 %
- Radical Pneumonectomy: 10 - 37 % [Boutin 1998]Aisner 1995
    - The only prospective study
    - Pneumonectomy, w/o post-operative treatment
        - 2-yr. Survival: 33 %
        - Median Survival: 10 months

A prospective, randomized, phase III trial is required to find the appropriate role of surgery.

### TREATMENT: RADIATION

Despite in-vivo success against mesothelial cells, this mode has not been proven successful in the clinical setting

- Problem: size of the target area
- Post-radiation fibrosis can further aggravate pain
    - via compression of the chest wall & intercostal nerves
- Is effective to prevent “seeding”

### TREATMENT: CHEMOTHERAPY

### RESPONSES SEEN IN 20 -30 % OF PATIENTS, BUT WITHOUT IMPROVEMENT IN OVERALL MORTALITY

- Doxorubicin
- Cisplatin
- Methotrexate
- Combined Protocols : 33 - 66 % response

### TREATMENT: IMMUNOTHERAPY

- Intrapleural delivery of cytokines are currently being tested
    - Interferon-Gamma
    - Interleukin-2
- Studies began in 1987 (150 patients)
    - Response Rates: 6 - 44 %
    - Effect on Survival is unknown at present [Dreisen 1992]

### TREATMENT: GENE THERAPY

trials have begun to evaluate the genetic transfer of thymidine kinase (from herpes virus to adenovirus)

** too early to judge effect or outcome...[Smythe 1995]

### SUMMARY

Mesothelioma kills - slowly & effectively...

- Early-stage disease: most important predictor of outcome
- To find “early-stage disease”, remember the risk factors
    - Age between 55 – 65
    - Previous occupational exposure to asbestos
    - Pleural Effusion
    - C.T. / MRI (with nodular lesions of the parietal pleura)
- Diagnosis is best established by V.A.T.S.
    - Following invasive procedures, “seeding” will occur & should be treated by radiotherapy
- Treatment: “it is currently, the clinician's choice”
    - Multimodal approach including radical surgery
    - “Limited-Role for Limited-Surgery”
        - Palliative
        - Relief of symptoms

south african miners -

european industrialists -

american manufacturers -

slowly but effectively...

### References

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