

ΕΜΒΡΥΟΛΟΓΙΑ – ΙΣΤΟΛΟΓΙΑ – ΠΑΘΟΛΟΓΙΚΗ ΑΝΑΤΟΜΙΚΗ ΜΕΣΟΘΗΛΙΟΥ

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ΕΜΒΡΥΟΛΟΓΙΑ

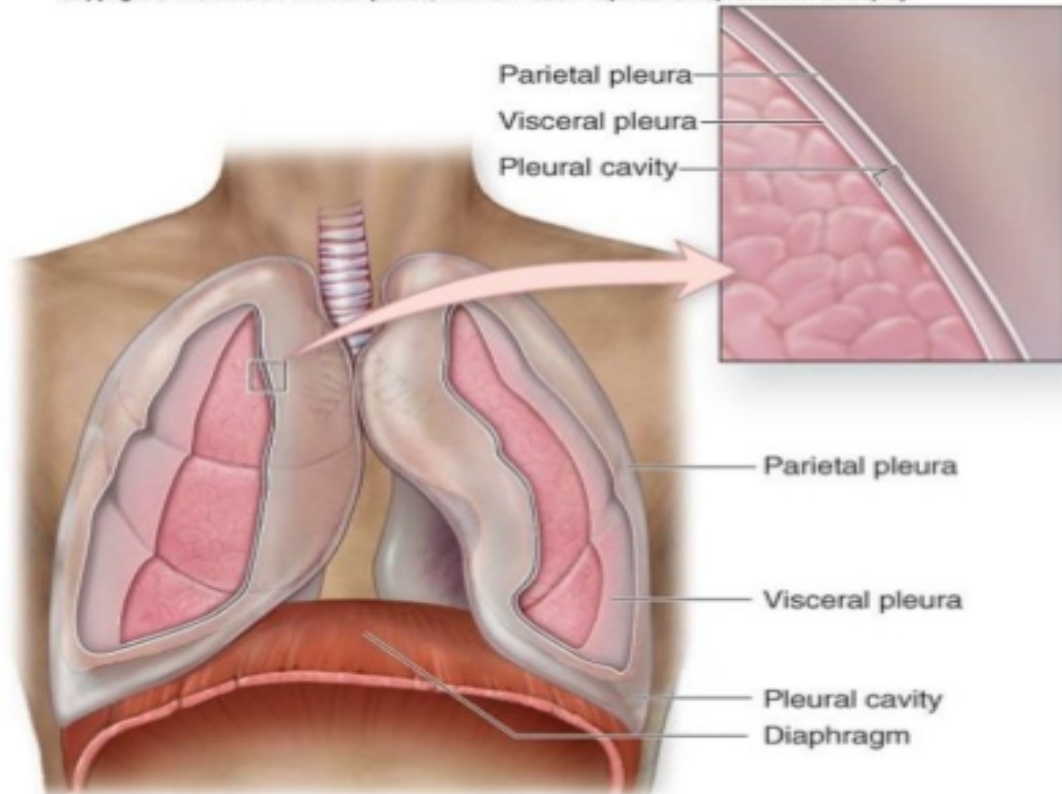
- τέλος 3^{ης} εβδομάδας: πλάγιο πέταλο μεσοδέρματος → σωματική και σπλαγχνική μεσοδερμική στιβάδα → ενδοεμβρυϊκό κοίλωμα
- σωματική μεσοδερμική στιβάδα → περίτονο/τοιχωματικό πέταλο υπεζωκότος/περιτοναίου
- σπλαγχνική μεσοδερμική στιβάδα → περισπλάγγνιο πέταλο υπεζωκότος/περιτοναίου
- εμβρυϊκό εγκάρσιο διάφραγμα → ανάπτυξη πνευμόνων → διαχωρισμός υπεζωκοτικής από περικαρδιακή κοιλότητα → διάπλαση οριστικού διαφράγματος → διαχωρισμός υπεζωκοτικής από περιτοναϊκή κοιλότητα

ΙΣΤΟΛΟΓΙΑ

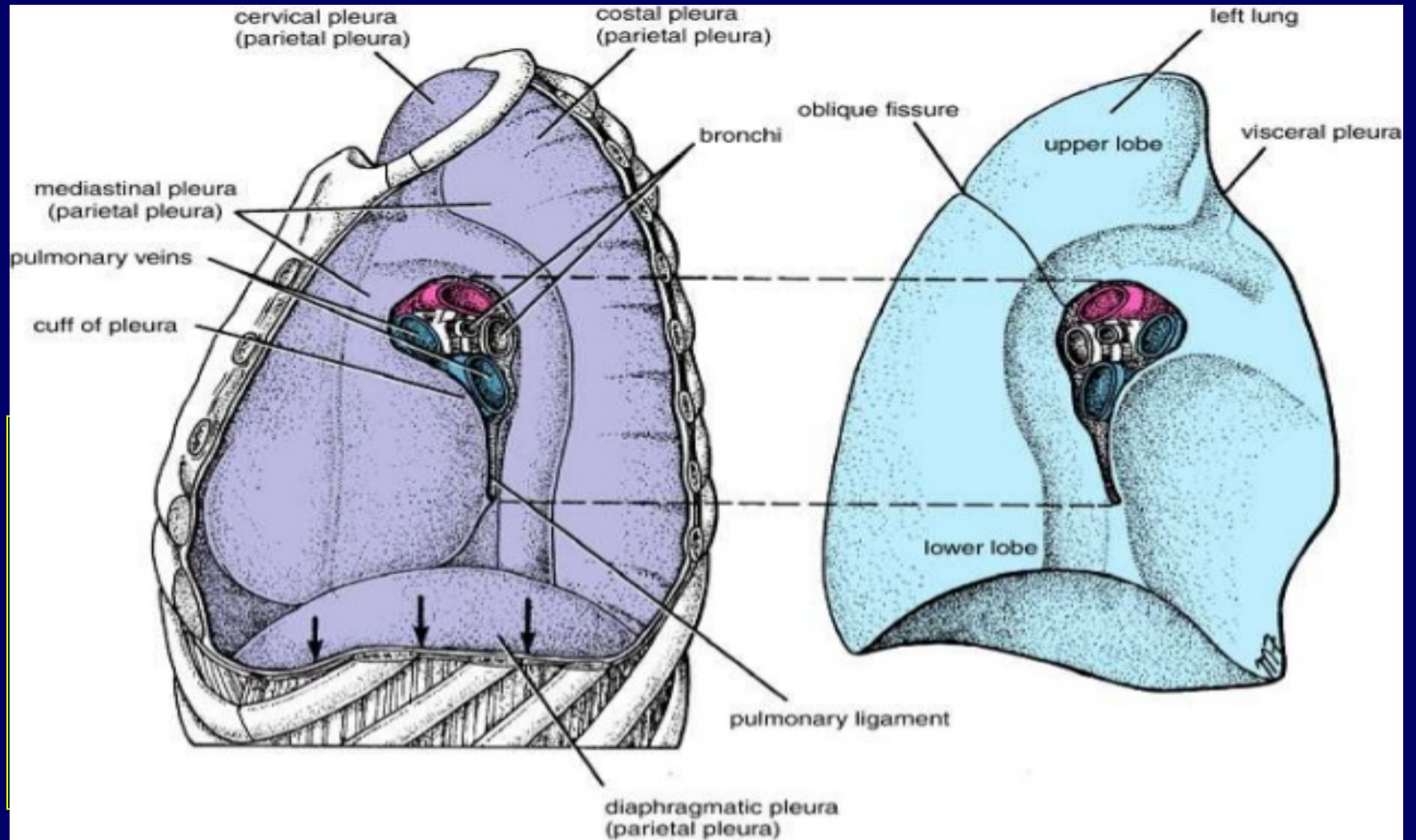
- μεσοθήλιο / μεσοθηλιακά κύτταρα ($\approx$ μονόστιβο πλακώδες)
- βασική μεμβράνη
- υποκείμενος χαλαρός συνδετικός ιστός

ΥΠΕΖΩΚΩΣ - ΑΝΑΤΟΜΙΚΗ

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ΥΠΕΖΩΚΩΣ - ΑΝΑΤΟΜΙΚΗ



ΥΠΕΖΩΚΩΣ - ΝΕΥΡΩΣΗ

Nerve Supply

- Parietal pleura:::
- The parietal pleura is sensitive to pain, temperature, touch and pressure, and is supplied as follows:
- The costal pleura is segmentally supplied by the intercostal nerves
- The mediastinal pleura is supplied by the phrenic nerve
- The diaphragmatic pleura is supplied over the domes by the phrenic nerve and around the periphery by the lower six intercostal nerves
- Visceral pleura:::
- The visceral pleura covering the lungs is sensitive to stretch
- It is insensitive to common sensations such as pain and touch
- It receives an autonomic nerve supply from the pulmonary plexus

ΥΠΕΖΩΚΩΣ - ΦΥΣΙΟΛΟΓΙΑ

Pleural Fluid

- The pleural space normally contains 5 to 10 ml of clear fluid
- It lubricates the opposing surfaces of the visceral and parietal pleurae during respiration
- The formation of the fluid results from hydrostatic and osmotic pressures between the capillaries
- The pleural fluid is normally absorbed into the capillaries of the visceral pleura
- Any condition that increases the production of the fluid or impairs the drainage of the fluid results in the abnormal accumulation of fluid, called pleural effusion
- The presence of 300 ml of fluid in the costodiaphragmatic recess in an adult is sufficient to enable its clinical detection
- The clinical signs include decreased lung expansion on the side of the effusion, with decreased breath sounds and dullness on percussion over the effusion

ΥΠΕΖΩΚΩΣ - ΜΗ ΝΕΟΠΛΑΣΜΑΤΙΚΕΣ ΝΟΣΟΙ (1)

- **Pleura**

- a) usually secondary complication of underlying disease
- b) primary disorders include:
 - i) intrapleural infections
 - ii) neoplasias → mesothelioma

- **Pleural effusion**

- a) normally ~ 15 ml serous fluid
- b) increased pleural fluid occurs:
 - i) CHF (i.e., ↑ hydrostatic pressure)
 - ii) ↑ permeability → pneumonia
 - iii) ↓ oncotic pressure → nephrotic
 - iv) ↑ (-) intrapleural press → atelectasis
 - v) ↓ lymph drainage → mediastinal

ΥΠΕΖΩΚΩΣ - ΜΗ ΝΕΟΠΛΑΣΜΑΤΙΚΕΣ ΝΟΣΟΙ (2)

c) inflammatory or noninflammatory effusions

1) inflammatory (serous or serofibrinous pleuritis)

- TB
- abscess
- pneumonia
- bronchiectasis
- RA
- SLE
- uremia
- diffuse systemic infections
- metastases (pleural)
- radiation therapy

ΥΠΕΖΩΚΩΣ - ΜΗ ΝΕΟΠΛΑΣΜΑΤΙΚΕΣ ΝΟΣΟΙ (3)

- i) purulent pleural exudate (empyema)
 - bacterial or mycotic seeding usually resulting from pulmonary infection
 - lymphatic or hematogenous
 - subdiaphragmatic or liver abscess bulging into pleura; usually occurring on the right side
- ii) hemorrhagic pleuritis (sanguineous)
 - differentiate → hemothorax
 - presence of tumor cells !!

ΥΠΕΖΩΚΩΣ - ΜΗ ΝΕΟΠΛΑΣΜΑΤΙΚΕΣ ΝΟΣΟΙ (4)

2. Noninflammatory pleuritis

i) hydrothorax

- CHF most common cause; usually collects at the base; causing compression and atelectasis of surrounding lung

ii) hemothorax (blood in pleura)

- fatal complication of ruptured aortic aneurysm / vascular trauma
- rare to find inflammatory milieu

iii) chylothorax

- accumulation of milky lymph
- more often confined to left side

ΥΠΕΖΩΚΩΣ - ΜΗ ΝΕΟΠΛΑΣΜΑΤΙΚΕΣ ΝΟΣΟΙ (5)

- Lymphatic obstruction, trauma, lymphoma
- distant metastases may grow in right lymphatic or thoracic duct

- c) pleural effusion may be associated with ascites of any cause
 - i) pressure difference favors movement of fluid into pleura via lymphatics or across diaphragmatic defects

- Pneumothorax

- a) air/gas in pleural space
 - i) spontaneous
 - ii) traumatic
 - iii) therapeutic

ΥΠΕΖΩΚΩΣ - ΜΗ ΝΕΟΠΛΑΣΜΑΤΙΚΕΣ ΝΟΣΟΙ (6)

- b) more often associated with:
 - i) emphysema
 - ii) asthma
 - iii) TB
- c) spontaneous idiopathic pneumothorax
 - i) young people
 - ii) rupture of apical blebs
 - iii) recurrent attack common
 - iv) flap valve
 - when defect allows air to enter but not to escape
 - results in increasing pressure
 - "tension pneumothorax"
 - may compress contralateral lung

ΥΠΕΖΩΚΩΣ - ΝΕΟΠΛΑΣΜΑΤΑ (ΓΕΝΙΚΑ)

- Pleural tumors
 - a) primary or secondary tumors
 - i) secondary → metastatic
 - more common vs. primary
 - arise from primary CA of lungs and breast
 - can arise from any organ (i.e., ovarian CA implant in thorax and abdomen)
 - ii) tumors produce serous / serosanguineous fluid
 - fluid good marker of tumor type

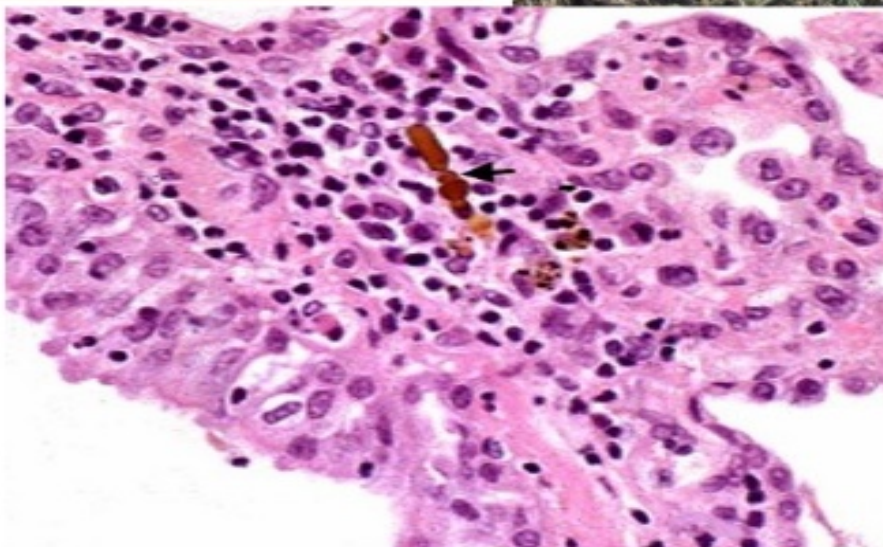
ΥΠΕΖΩΚΩΣ - ΜΟΝΗΡΗΣ ΙΝΩΔΗΣ ΟΓΚΟΣ

b) solitary (localized) fibrous tumors

i) "benign mesothelioma"

- soft fibrous tumors mainly in pleura and rarely in lung
- remains confined to surface of lung
- do not produce pleural effusions
- usually benign
- tumor cells → CD34+; keratin negative staining (good differential from malignant mesotheliomas)
- NO relationship to asbestos exposure !!

AMIANTOΣ (1)



AMIANTOΣ (2)

Asbestos in the developing world



ΝΟΣΟΙ ΠΡΟΚΑΛΟΥΜΕΝΕΣ ΑΠΟ ΕΚΘΕΣΗ ΣΕ AMIANTO (1)

Asbestos-Related Lung Disease

Pleural Lesions

Benign pleural effusion

Parietal pleural plaques

Diffuse pleural fibrosis

Rounded atelectasis

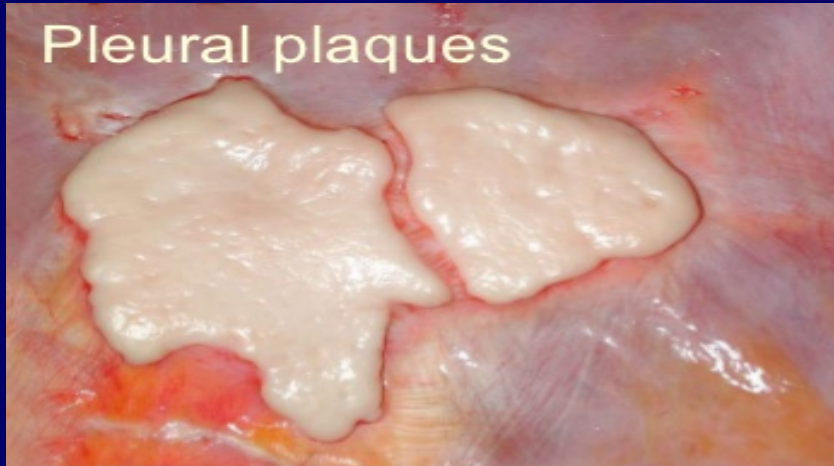
Interstitial Lung Disease

Asbestosis

Malignant Mesothelioma

Carcinoma of the lung (in smokers)

ΝΟΣΟΙ ΠΡΟΚΑΛΟΥΜΕΝΕΣ ΑΠΟ ΕΚΘΕΣΗ ΣΕ ΑΜΙΑΝΤΟ (2)



AMIANTΩΣΗ (1)

Asbestosis

Asbestos

- ❖ **Causing fibrosis** by interacting with lung macrophages
- ❖ **also functions as both a tumor initiator and a promoter**

AMIANTΩΣΗ (2)

Asbestosis

Morphology

Asbestosis is marked by diffuse pulmonary interstitial fibrosis

Characterized by

the presence of **asbestos bodies**

which are seen as **golden brown, fusiform or beaded rods with a translucent center**

coated with an iron-containing proteinaceous material

ΑΜΙΑΝΤΩΣΗ (3) - ΣΩΜΑΤΙΑ ΑΜΙΑΝΤΟΥ



Asbestos bodies

These ferruginous bodies are golden brown and beaded, with a central, colorless, nonbirefringent core fiber

ΙΝΩΔΕΙΣ ΥΠΕΖΩΚΟΤΙΚΕΣ ΠΛΑΚΕΣ ΑΠΟ ΑΜΙΑΝΤΟ



Pleural plaque. The dome of the diaphragm is covered by a smooth, pearly white, nodular plaque



Asbestos-related pleural plaques
Large, discrete fibrocalcific plaques are seen on the pleural surface of the diaphragm

ΥΠΕΖΩΚΩΣ - ΜΕΣΟΘΗΛΙΩΜΑ (ΓΕΝΙΚΑ)

c) Malignant mesothelioma

- i) arise from either pleura
- ii) asbestos exposure related
- iii) long latent period (25-50 yrs)
- iv) smoking does NOT increase risk
 - smoking ↑ risk of lung CA in asbestos workers !!
- v) produces pleural effusions
- vi) diffuse and covers lung; invades thoracic cavity and structures
- vii) S & S
 - chest pain, dyspnea and recurrent pleural effusions
- viii) outcome poor → death w/in 2 yrs

Epidemiology and tumorigenesis

- The incidence of mesothelioma in Europe will increase and peak between 2015 and 2020
- The median latency period from first exposure to clinical manifestation is over 40 years
- Asbestos continues to be used in many countries outside North America and Europe without any laws on worker protection
- Frequent inactivation of tumor suppressor genes include p16^{INK4A}/p14^{ARF} and neurofibromatosis type 2 (NF2) which encodes merlin

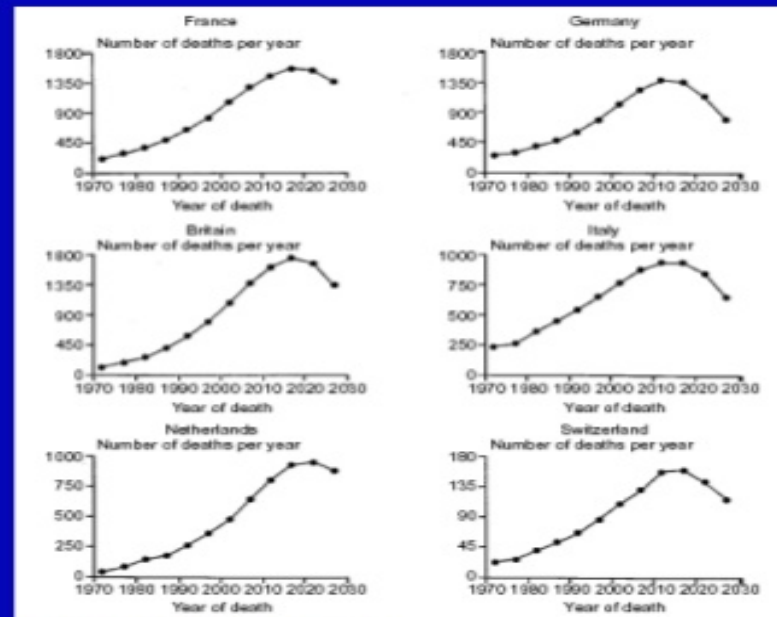
ΥΠΕΖΩΚΩΣ - ΜΕΣΟΘΗΛΙΩΜΑ (ΕΠΙΔΗΜΙΟΛΟΓΙΑ 2)

Mesothelioma in Europe

Peak incidence
around 2020

- British mesothelioma register and male death rates for cancer of the pleura from 6 European countries
- Statistical modeling taking into account asbestos legislation and the long latency period

Peto, BJC 1999



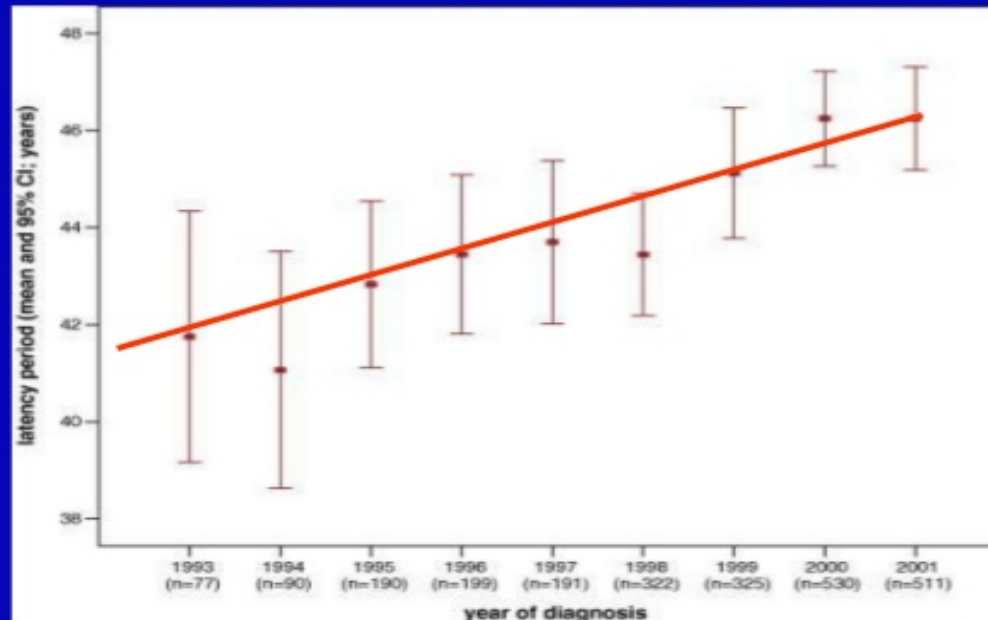
Peak leveling off between 2010 and 2015

Perlucchi, BJC 2004; Hodgson BJC 2005:

ΥΠΕΖΩΚΩΣ - ΜΕΣΟΘΗΛΙΩΜΑ (ΕΠΙΔΗΜΙΟΛΟΓΙΑ 3)

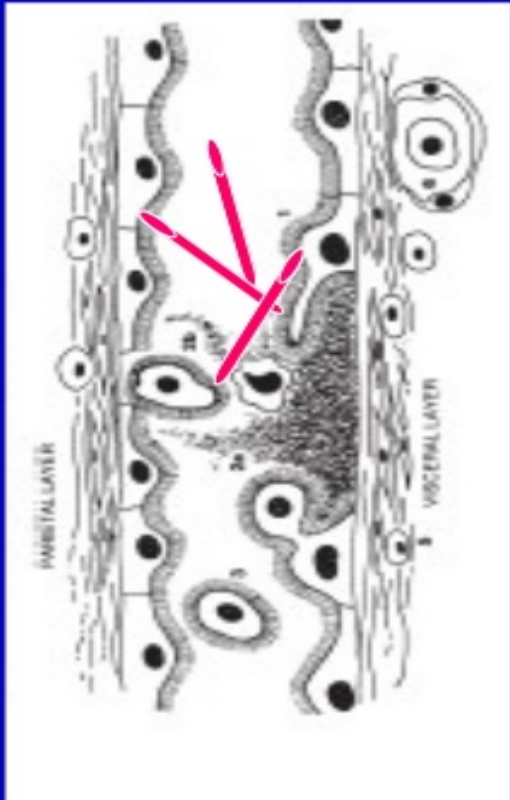
Latency period in pleural mesothelioma after asbestos-exposure

Data collected by the Italian mesothelioma registry in the period 1993-2000: median latency 44.6 years



ΥΠΕΖΩΚΩΣ - ΜΕΣΟΘΗΛΙΩΜΑ (ΟΓΚΟΓΕΝΕΣΗ - 1)

Multistep carcinogenesis in pleural mesothelioma



- Accumulation of asbestos fibers and chronic tissue injury
- Persistent stimulation of tissue repair program (mesothelium stem cells) leading to:
 - Epigenetic silencing or deletion of « caretaker » Ink4a locus (9p21)
 - Loss of « gatekeeper » NF2 function (22q12)
- Loss of contact-dependent growth inhibition and tumor progression

Alterations of NF2 in mesothelioma

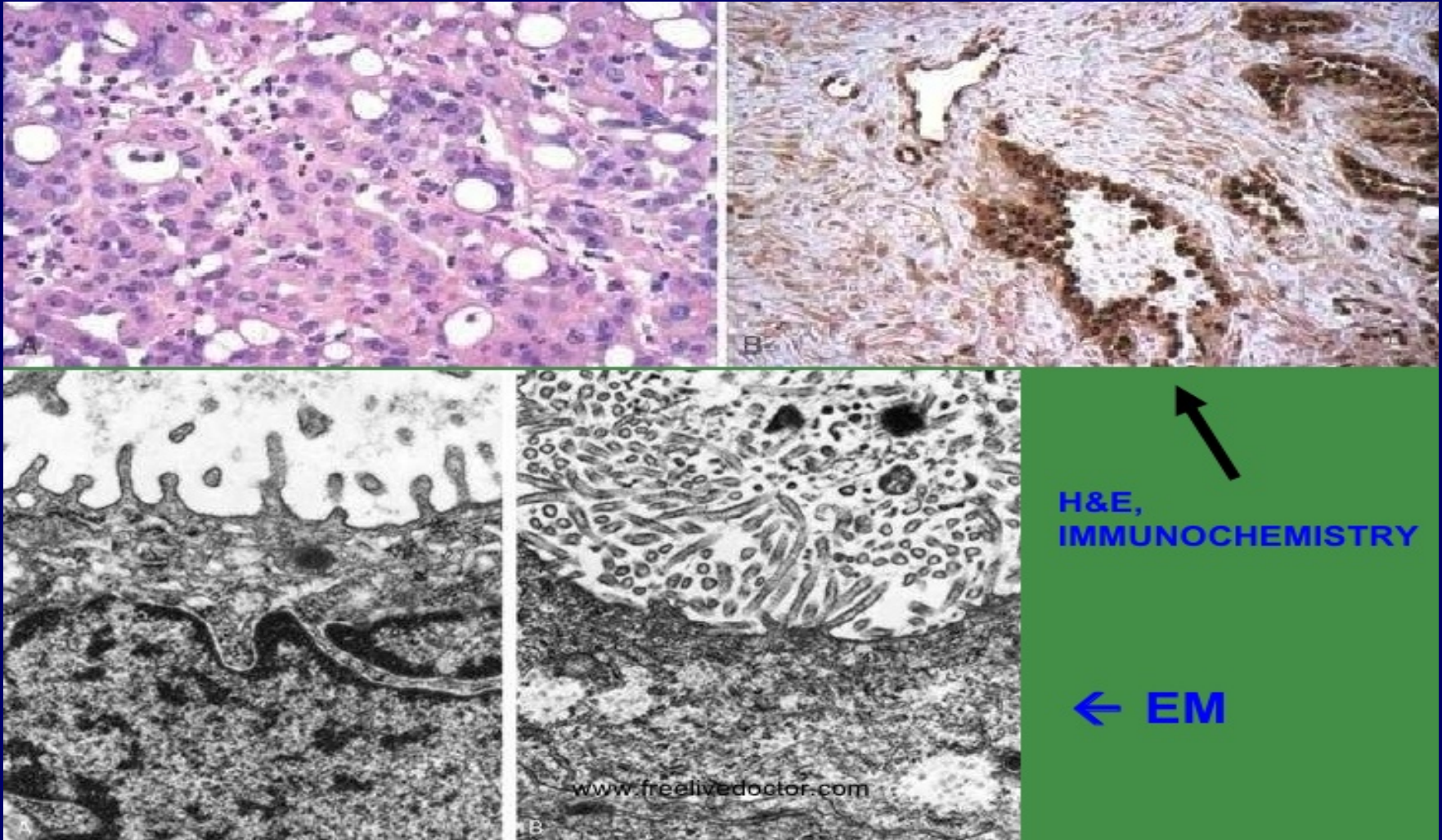
- **Mutations in NF2 have been described in 40% of mesothelioma**
Bianchi, PNAS 1995; Sekido, CR 1995; Deguen, IJC 1998
- **In an experimental model, targeted inactivation of NF2 in mesothelial cells lining of the thoracic cavity rarely results in mesothelioma. However, concomitant loss of *INK4a/ARF* strongly accelerates mesothelioma development**
Jongsma, Cancer Cell 2008
- **In tumors without NF2 truncation, NF2 activity is inhibited by phosphorylation, for example by increased expression of CPI-17**
Thurneysen, Lung Cancer 2009

ΥΠΕΖΩΚΩΣ - ΜΕΣΟΘΗΛΙΩΜΑ (ΜΑΚΡΟ-)



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ΥΠΕΖΩΚΩΣ - ΜΕΣΟΘΗΛΙΩΜΑ (ΙΣΤΟ-1)



ΥΠΕΖΩΚΩΣ - ΜΕΣΟΘΗΛΙΩΜΑ (ΙΣΤΟ-2)

Types of Mesothelioma

- Mesothelioma can be divided into three different types.
- Epithelioid- which has the best prognosis out of the three types.
- Sarcomatoid- which has about a 7 – 20% survival rate.
- Mixed/biphasic- which has about a 20 – 35% survival rate.

ΥΠΕΖΩΚΩΣ - ΜΕΣΟΘΗΛΙΩΜΑ (ΙΣΤΟ-3)

ΕΠΙΘΗΛΙΟΕΙΔΕΣ

- CK5/6, calretinin, thrombomodulin (μεμβρανικό πρότυπο), WT-1
- βρογχογενές αδеноκαρκίνωμα: mCEA, CD15, BerEp4, B72.3, MOC31, TTF-1,...
(**ΤΟΥΛΑΧΙΣΤΟΝ 2 [+] μεσοθηλιακοί vs 2[-] καρκινικών δεικτών**)
- αδеноκαρκίνωμα άλλης προελεύσεως: κατά περίπτωση
- κακόηθες μελάνωμα: S100, mgp100 (HMB-45), Melan-A/MART-1, MITF, ...
- αναπλαστικό λέμφωμα: ALK, CD30, EMA, ...
- επιθηλιοειδές αιμαγγειοενδοθηλίωμα: CD31
-

ΥΠΕΖΩΚΩΣ - ΜΕΣΟΘΗΛΙΩΜΑ (ΙΣΤΟ-4)

ΣΑΡΚΩΜΑΤΟΕΙΔΕΣ

- CKAE1/AE3, vimentin, S100, desmin, σπανίως calretinin
- σαρκωματοειδές (πολύμορφο) βρογχογενές καρκίνωμα, σαρκωματοειδές καρκίνωμα εκ νεφρικών κυττάρων: ΔΕΝ ΥΠΑΡΧΕΙ ΔΕΙΚΤΗΣ (ιστορικό, κλινικά στοιχεία, μορφολογία,...)

ΔΕΣΜΟΠΛΑΣΤΙΚΟ

- CKAE1/AE3 (εντός γραμμωτών μυών ή λιπώδους ιστού!), γιατί στον υπεζωκότα δ/δ από ινωτική πλευρίτιδα.

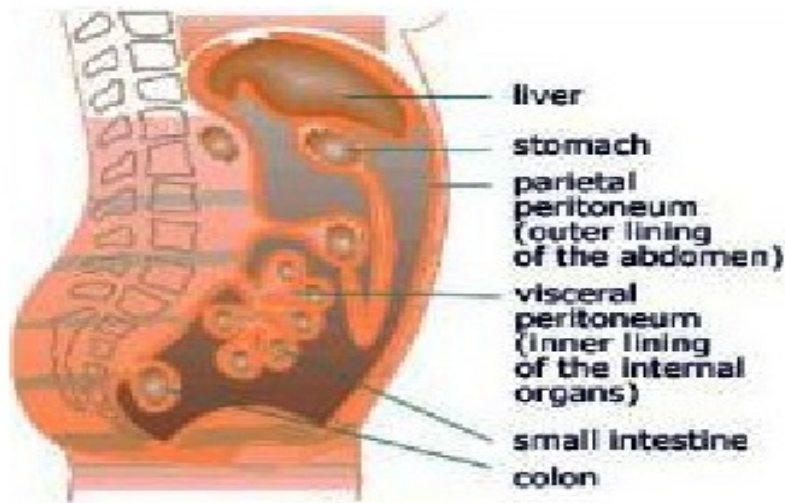
ΥΠΕΖΩΚΩΣ - ΠΡΩΤΟΠΑΘΕΣ ΛΕΜΦΩΜΑ (PRIMARY EFFUSION LYMPHOMA)

- συνήθως HIV(+), σπανιότατα σε ανοσοκαταστολή λόγω μεταμοσχεύσεως καρδιάς ή σε ανοσοεπαρκή ηλικιωμένα άτομα
- ♂ > ♀, MWM, ενίοτε με πολυκεντρική νόσο Castleman
- υπεζωκώς, περιτόναιο ή περικάρδιο (μόνον μία κοιλότης κάθε φορά!)
- HHV-8, συχνά συλλοίμωξη (αλλά όχι παθογενετικός ρόλος!) με EBV
- LCA/CD45, MUM-1/IRF4, CD30, CD38, CD138, HHV-8(+), σπανίως T φαινότ.
- CD19, CD20, CD79α, CD10, bcl-6, s/cIg(-)
- κακίστη πρόγνωση (< 1 έτος)

ΥΠΕΖΩΚΩΣ - ΛΕΜΦΩΜΑ ΕΠΙ ΠΥΘΩΡΑΚΟΣ (PYOTHORAX-ASSOCIATED LYMPHOMA)

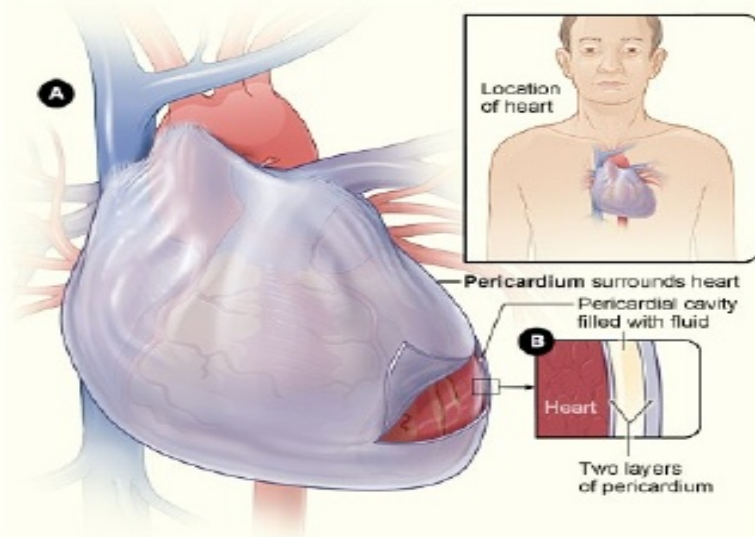
- ιστορικό πυοθώρακος, συνήθως λόγω τεχνητού πνευμοθώρακος για Tb ή Tb πλευρίτιδος
- ♂ > ♀, 65-70 ετών
- ογκόμορφη εξεργασία
- EBV
- CD20, CD79α, CD38, EBVish(+), σπανίως T φαινότ.
- CD10, bcl-6, MUM-1/IRF4(-)
- κακίστη πρόγνωση (< 1 έτος)

ΠΕΡΙΤΟΝΑΙΟ - ΜΕΣΟΘΗΛΙΩΜΑ



Peritoneal mesothelioma effects the organs in the abdomen and symptoms include abdominal swelling, nausea, vomiting, and bowel obstruction.

ΠΕΡΙΚΑΡΔΙΟ - ΜΕΣΟΘΗΛΙΩΜΑ



The rarest form of mesothelioma is pericardial mesothelioma, which involves the sac surrounding the heart.

ΣΥΜΒΟΛΗ ΤΟΥ ΠΑΘΟΛΟΓΟΑΝΑΤΟΜΟΥ

«Κακοὶ μάρτυρες ἀνθρώποισιν ὀφθαλμοὶ καὶ ὦτα, βαρβάρους
νόας ἔχόντων»

Ἡράκλειτος, *Περὶ τοῦ παντὸς*, IV