

Lung Cancer in Women: A Different Disease?

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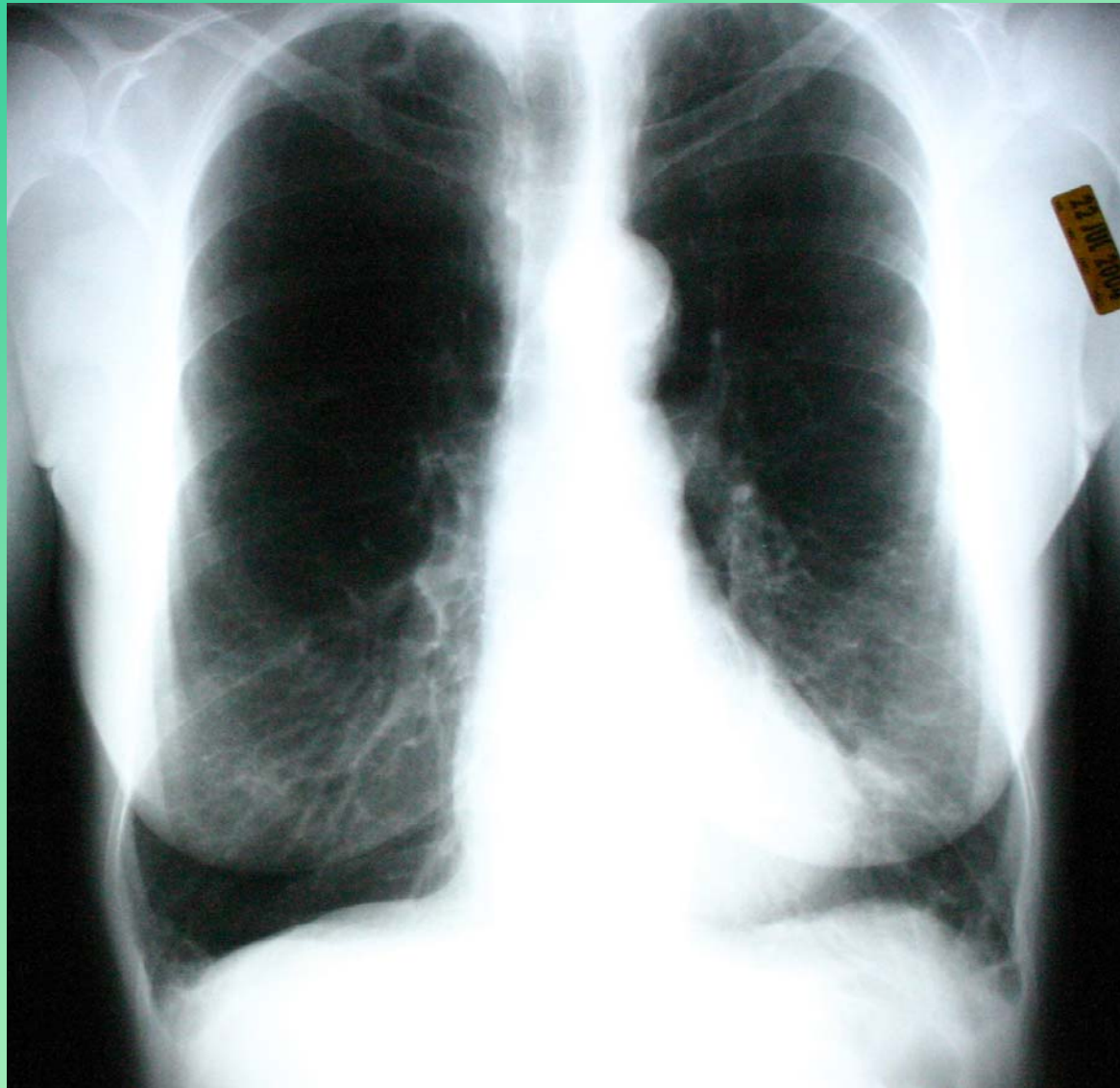


Case Presentation

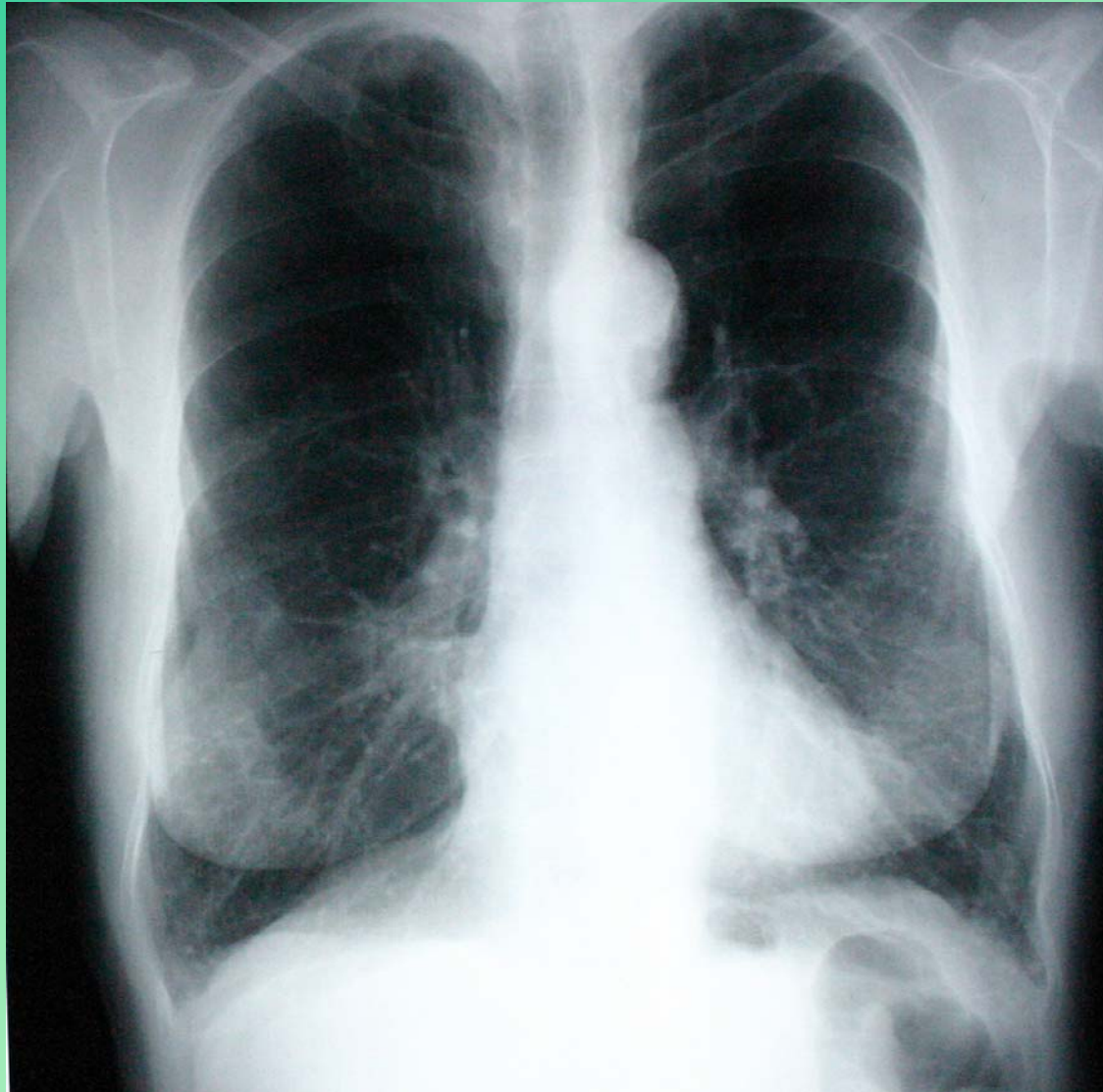
- 71 yo woman presented in November, 2005, with abnormal chest X-ray, changed from that of a year earlier...



Chest X-ray July 2004



Chest X-ray October, 2005

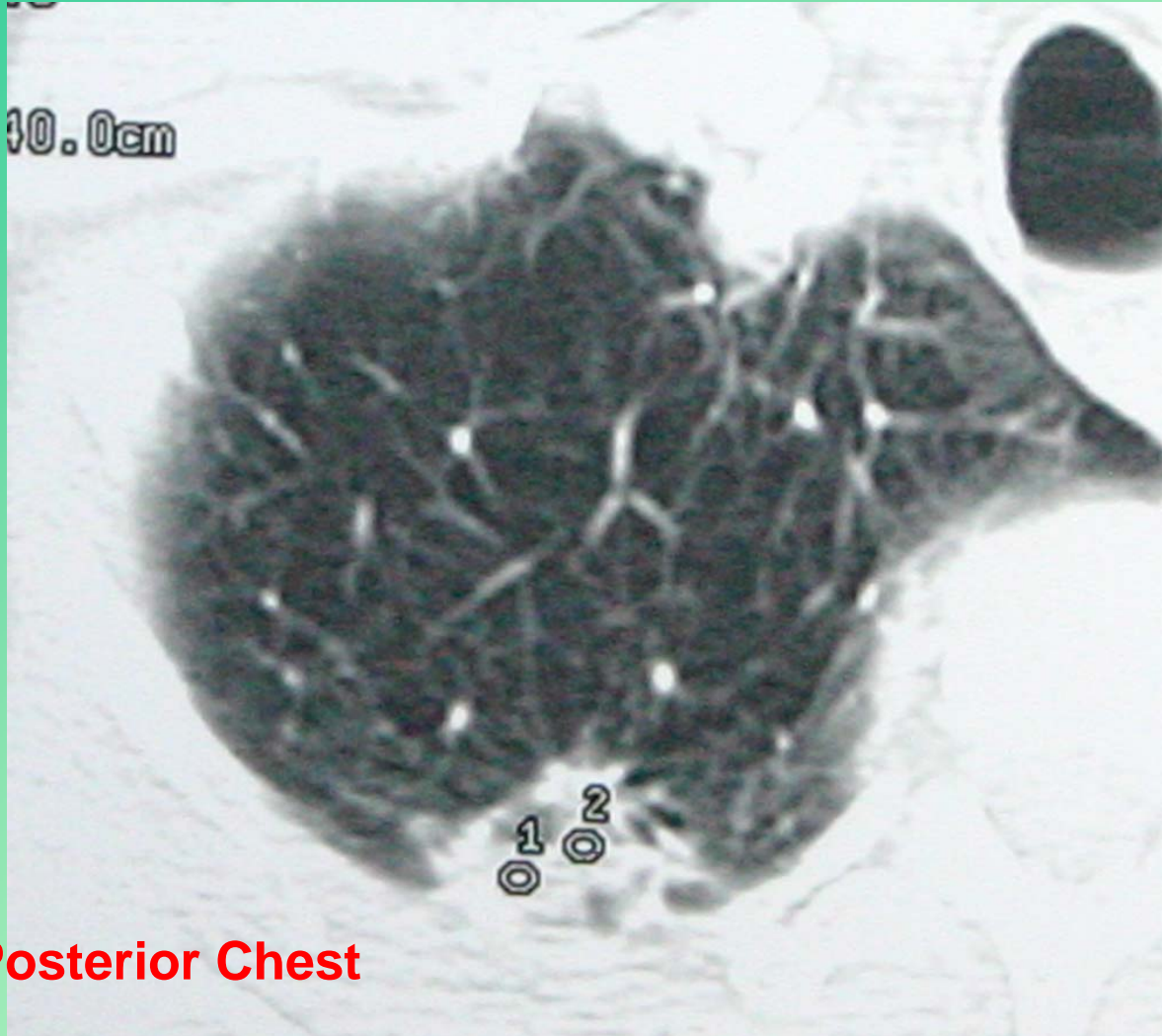


Case Presentation

- 71 yo woman presented in November, 2005, with abnormal chest X-ray, changed from that of a year earlier ...
- CT Scan obtained...



CT Scan magnified view



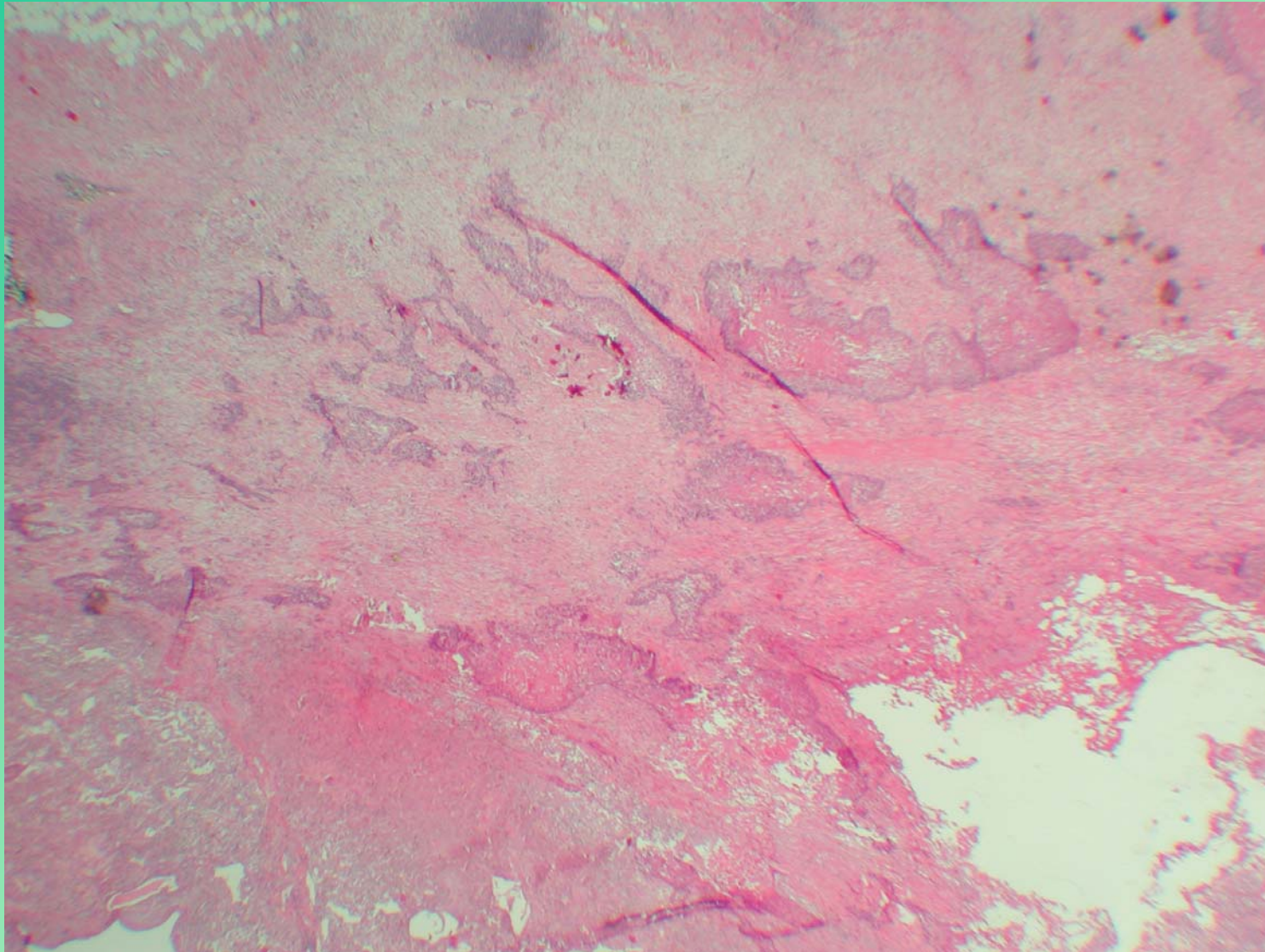
Right Posterior Chest

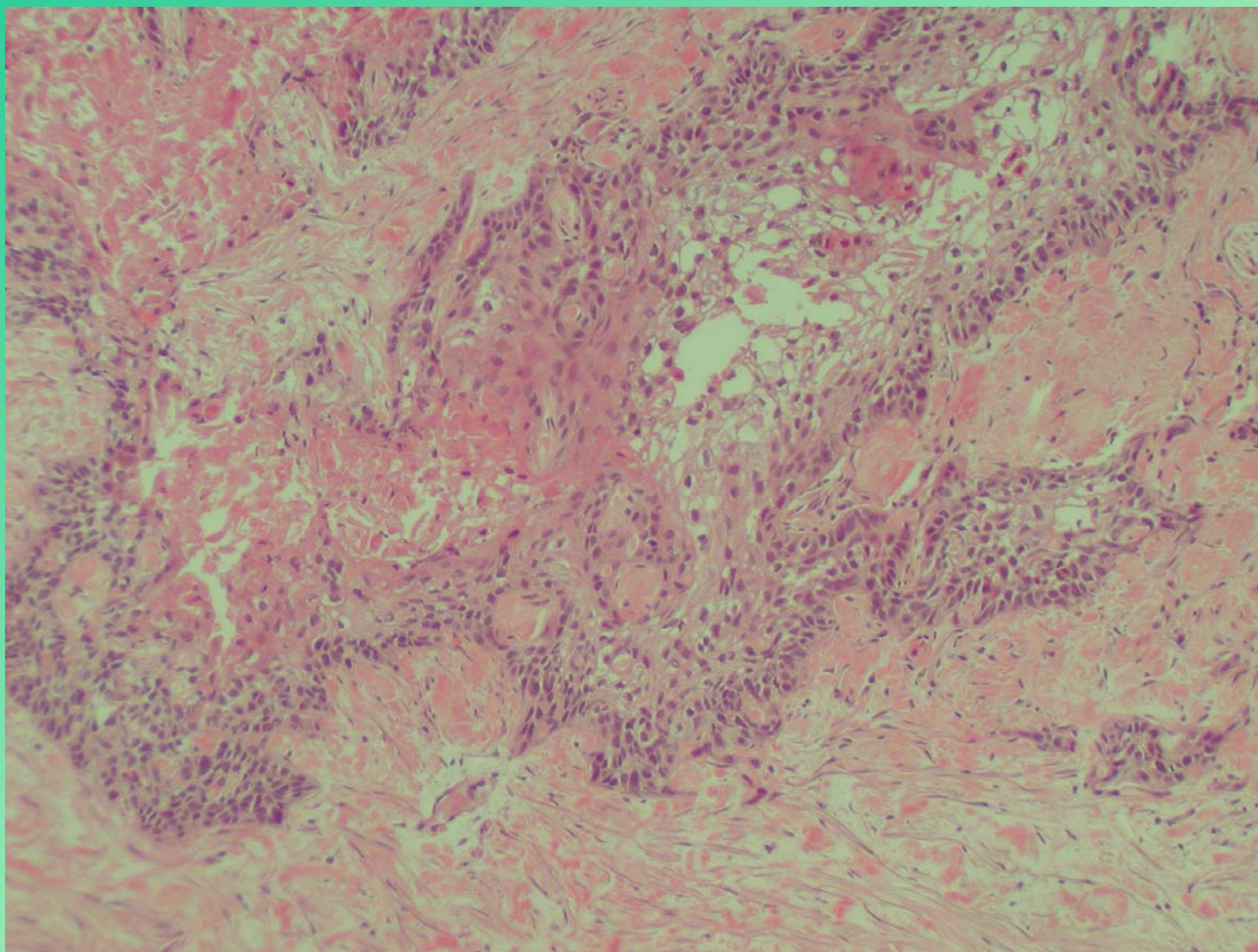


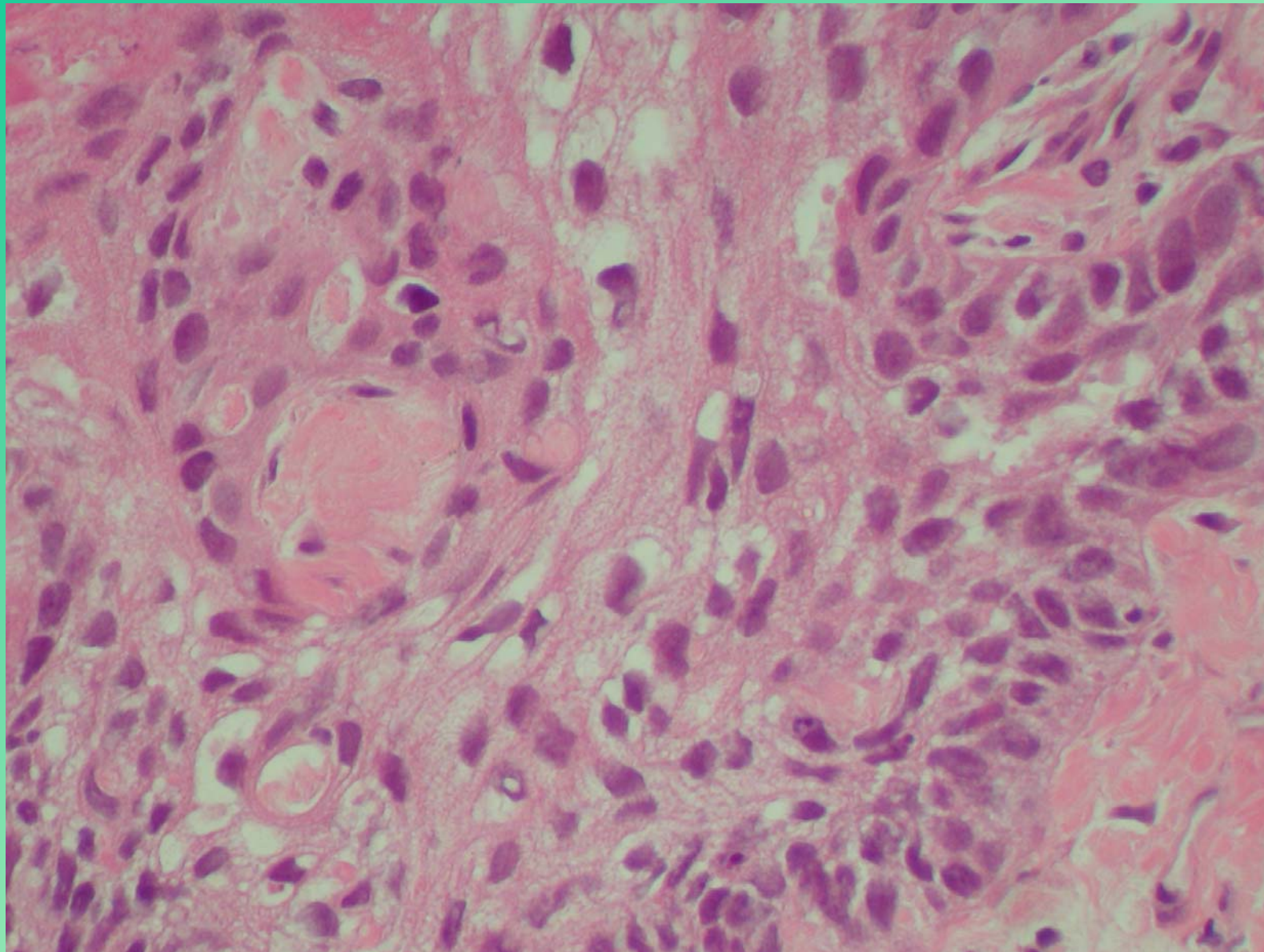
Case Presentation

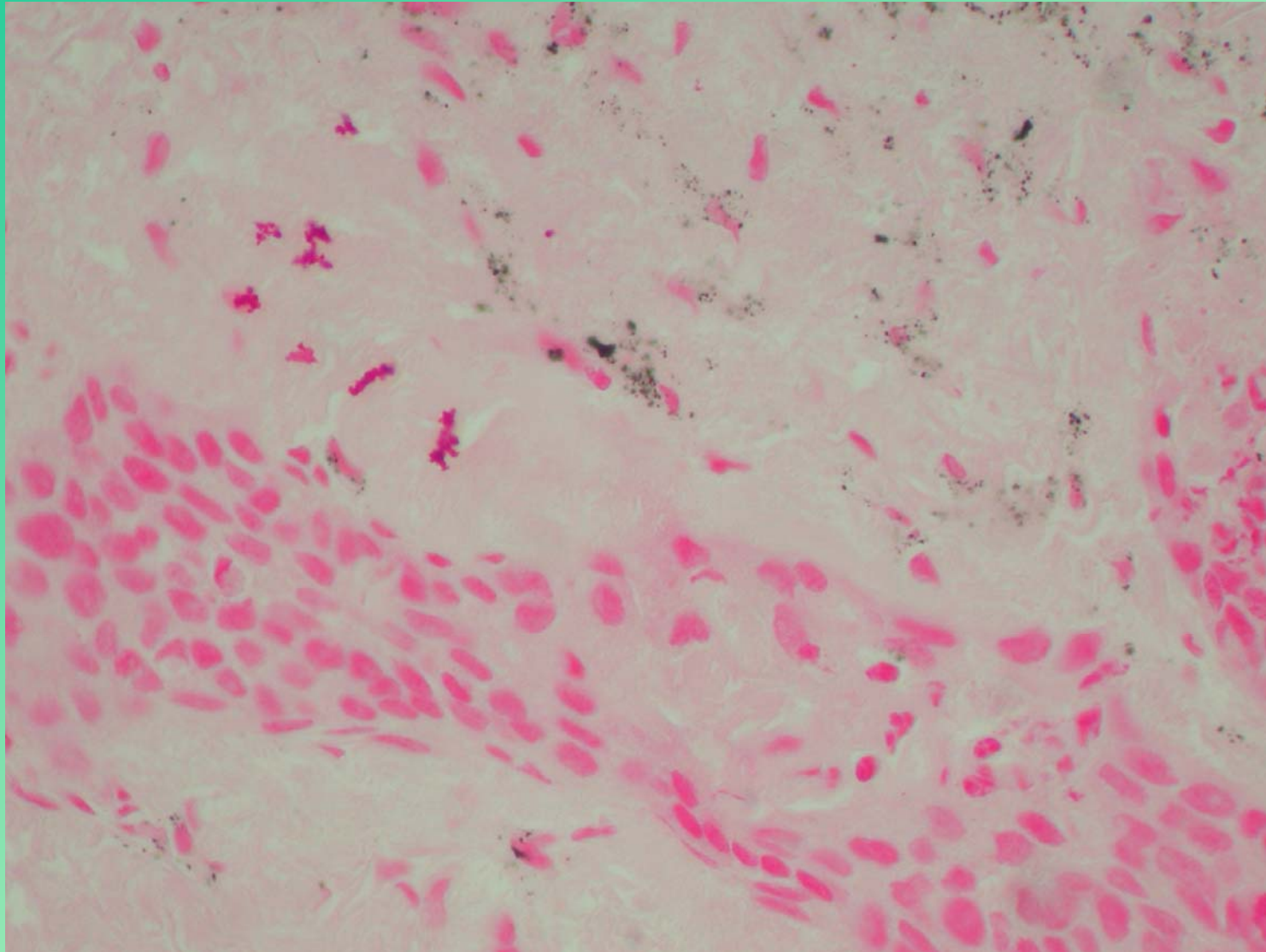
- 71 yo woman presented in November, 2005, with abnormal chest X-ray, changed from that of a year earlier ...
- CT Scan obtained...
- Referred to Dr. Dalesandro: poor surgical candidate but after period of intensive pulmonary rehab underwent surgery
- 3 cm squamous cell carcinoma with invasion into chest wall
- En bloc pulmonary and chest wall resection
- Pathology....





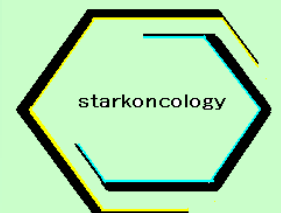




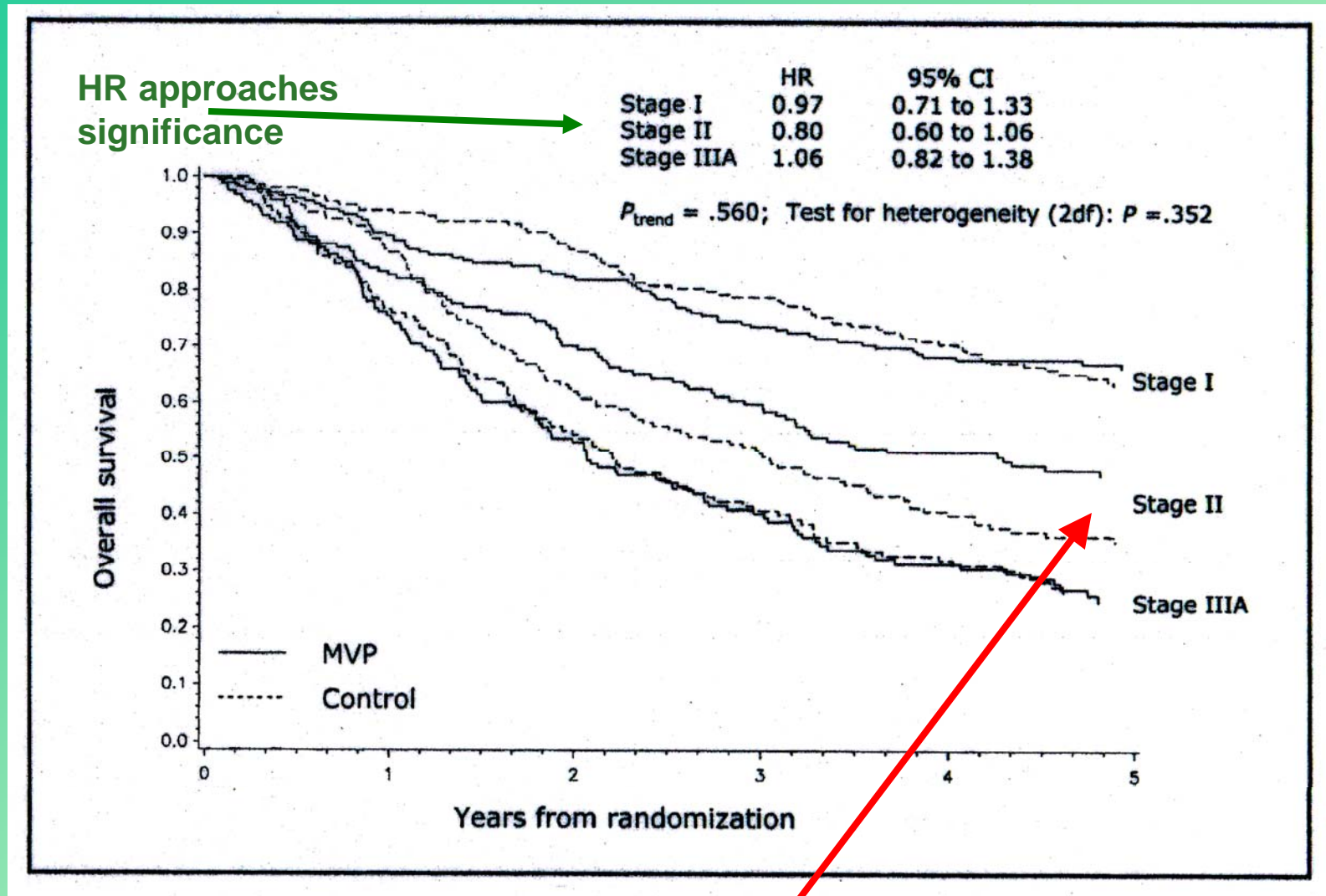


Case Presentation, continued

- Recovered from surgery
- Referred for adjuvant chemotherapy for T3N0 (Stage IIB) lung cancer
- Received four cycles of taxol and carboplatin – moderately well tolerated



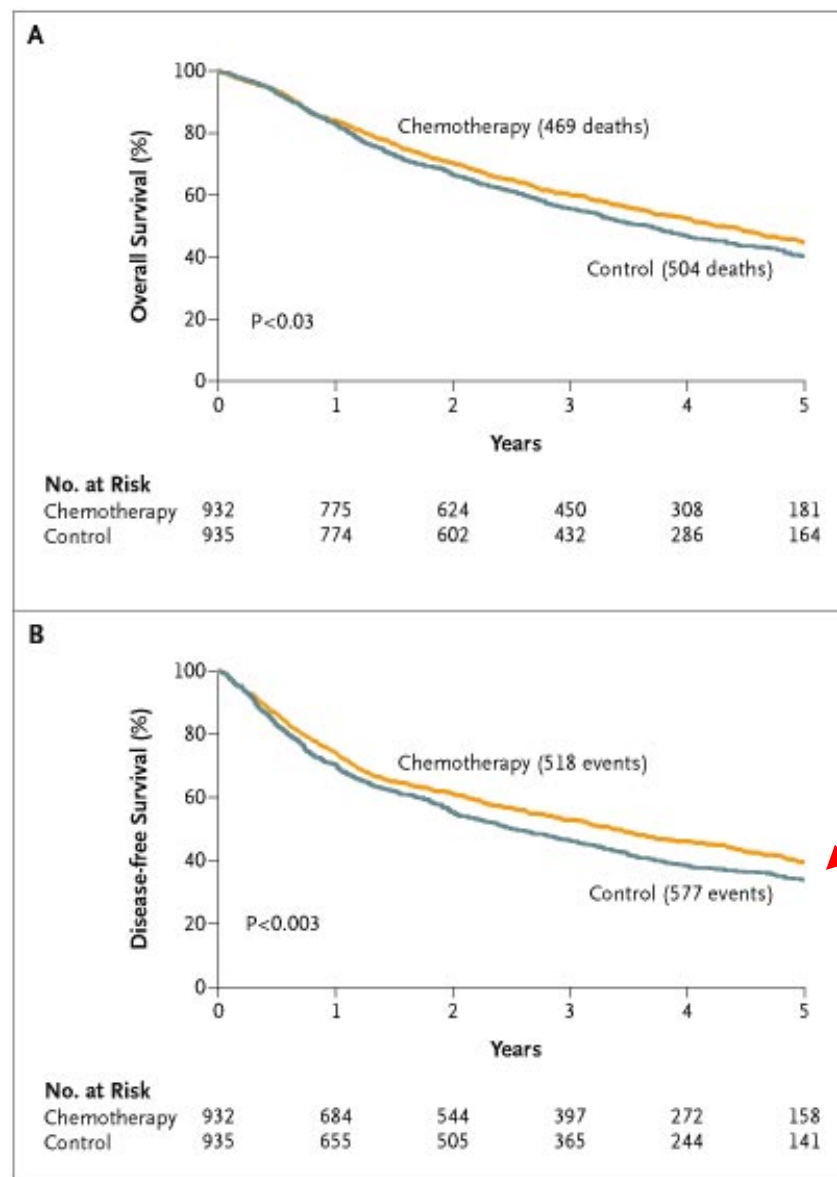
The ALPI trial – overall survival by stage



Difference for Stage II substantial



Overall Survival (Panel A) and Disease-free Survival (Panel B)



Highly significant difference for sample size

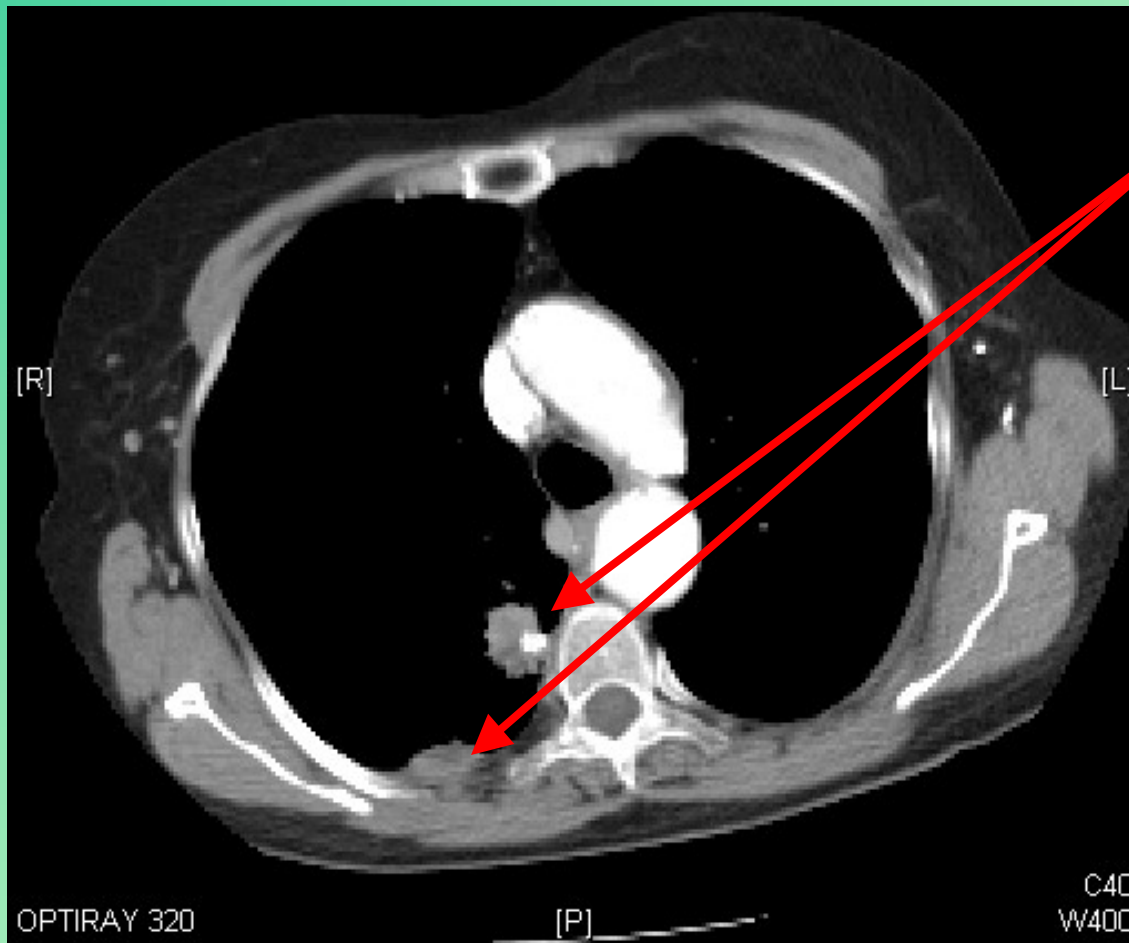


Back to Our Case...

- April, 2007: surveillance CT scan showed 2 new RUL nodes suspicious for local recurrence...



CT Chest done 3/28/07



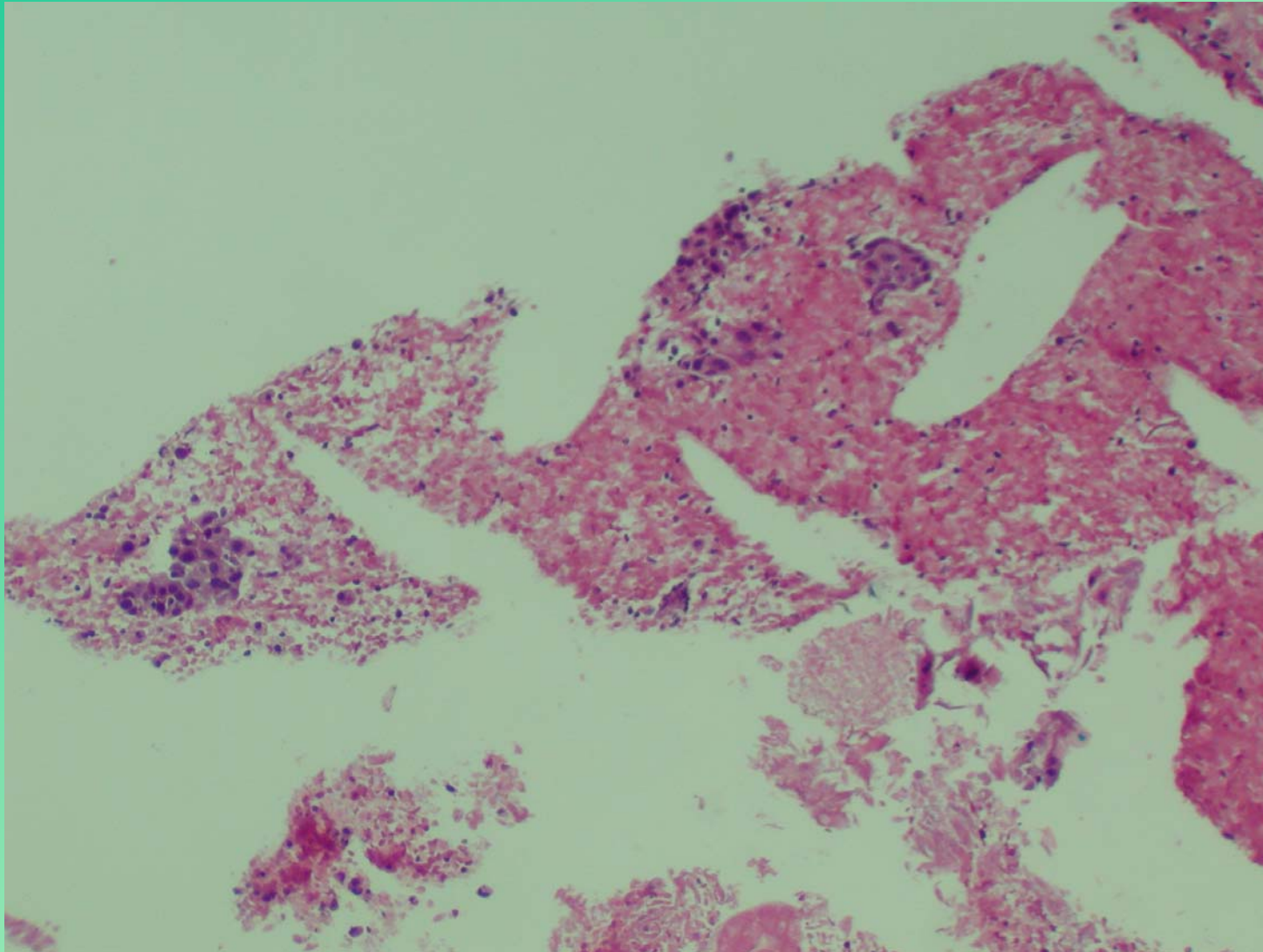
Two pleural-based masses

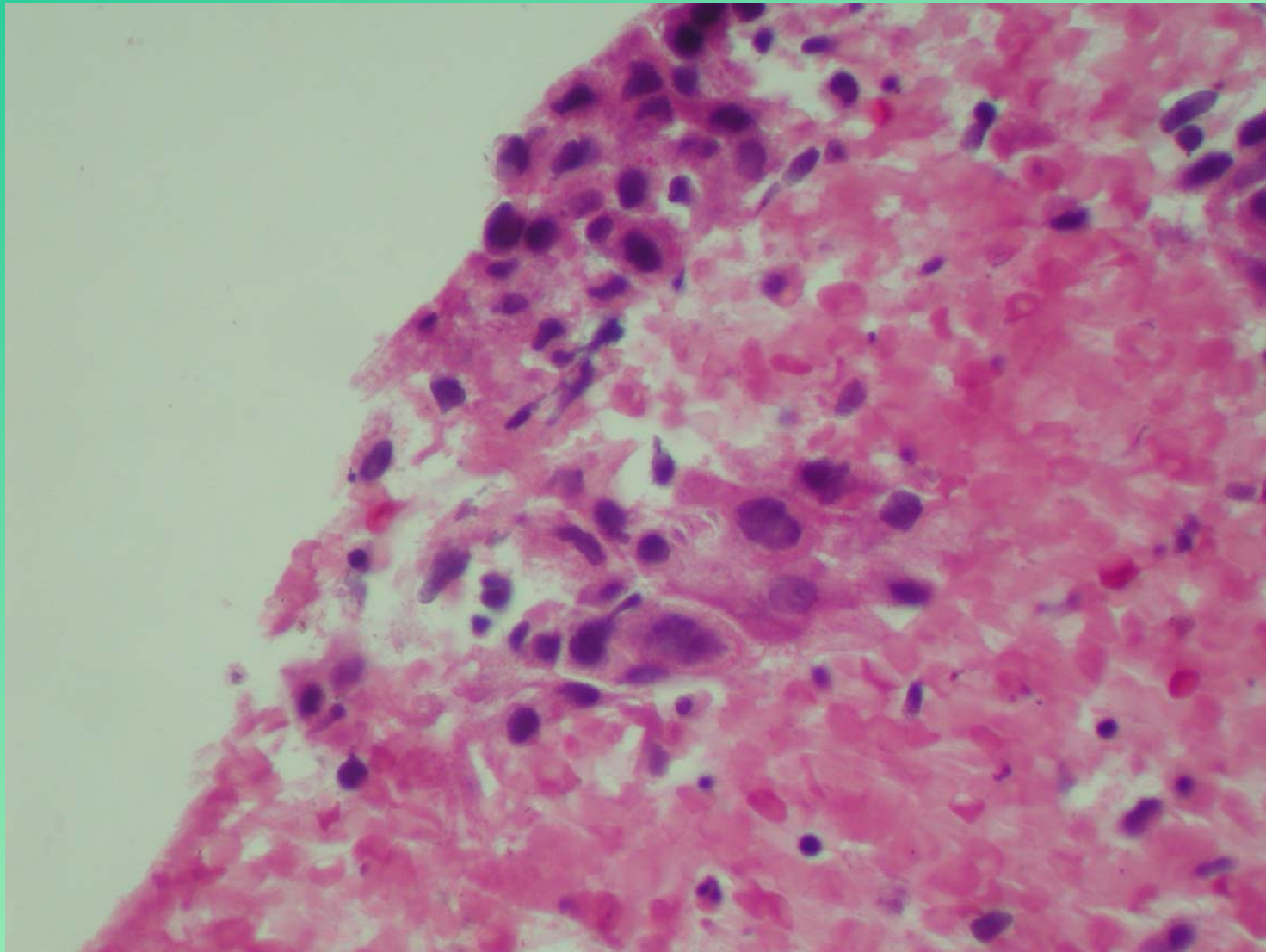


Back to Our Case...

- April, 2007: surveillance CT scan showed 2 new RUL nodes suspicious for local recurrence...
- PET confirmatory with SUV 14
- CT-guided biopsy...







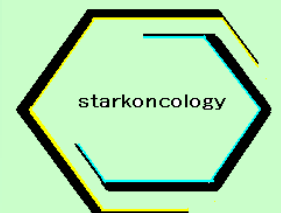
Back to Our Case...

- April, 2007: surveillance CT scan showed 2 new RUL nodes suspicious for local recurrence...
- PET confirmatory with SUV 14
- CT-guided biopsy... + for recurrence
- Referred for radiation therapy; just being completed

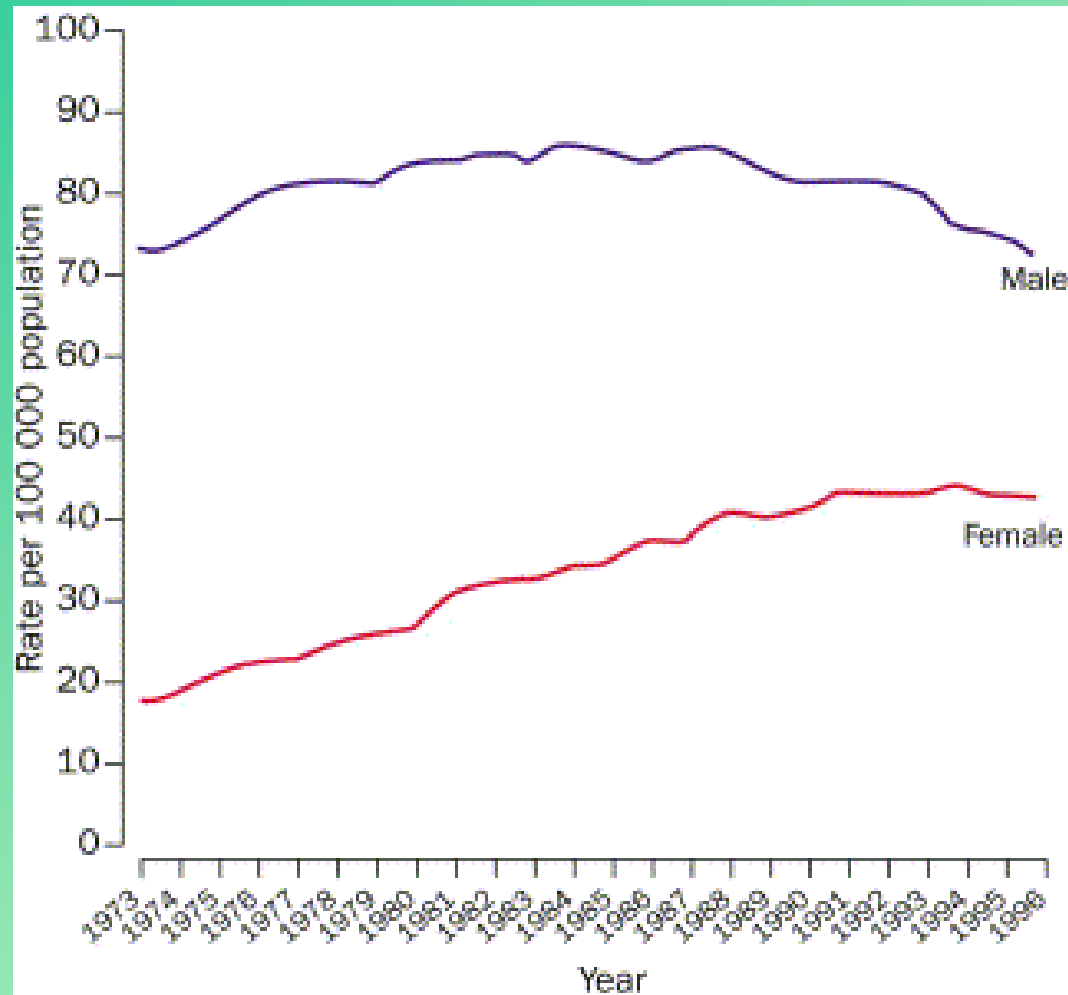


Case Presentation, concluding

- In light of local recurrence outlook is guarded
- Awaiting future developments before initiating additional treatments



Lung Cancer Incidence: The Changing Face of a Common Disease



**From Siegfried,
*Lancet
Oncology*,
August, 2001**



Data Viewed from Perspective of all Cancers

**Reported US deaths from the most common cancers in males and females:
all ages, 1997**

Males

| | |
|----------------------|---------|
| Lung and bronchus | 91 278 |
| Prostate | 32 891 |
| Colon and rectum | 28 075 |
| Pancreas | 13 470 |
| Non-Hodgkin lymphoma | 12 286 |
| Other sites | 103 110 |
| All sites | 281 110 |

Females

| | |
|-------------------|---------|
| Lung and bronchus | 61 922 |
| Breast | 41 943 |
| Colon and rectum | 28 621 |
| Pancreas | 14 205 |
| Ovary | 13 507 |
| Other sites | 98 629 |
| All sites | 258 467 |



Is Lung Cancer in Women Different?

- Hormone Replacement Therapy may provide a key to the answer....



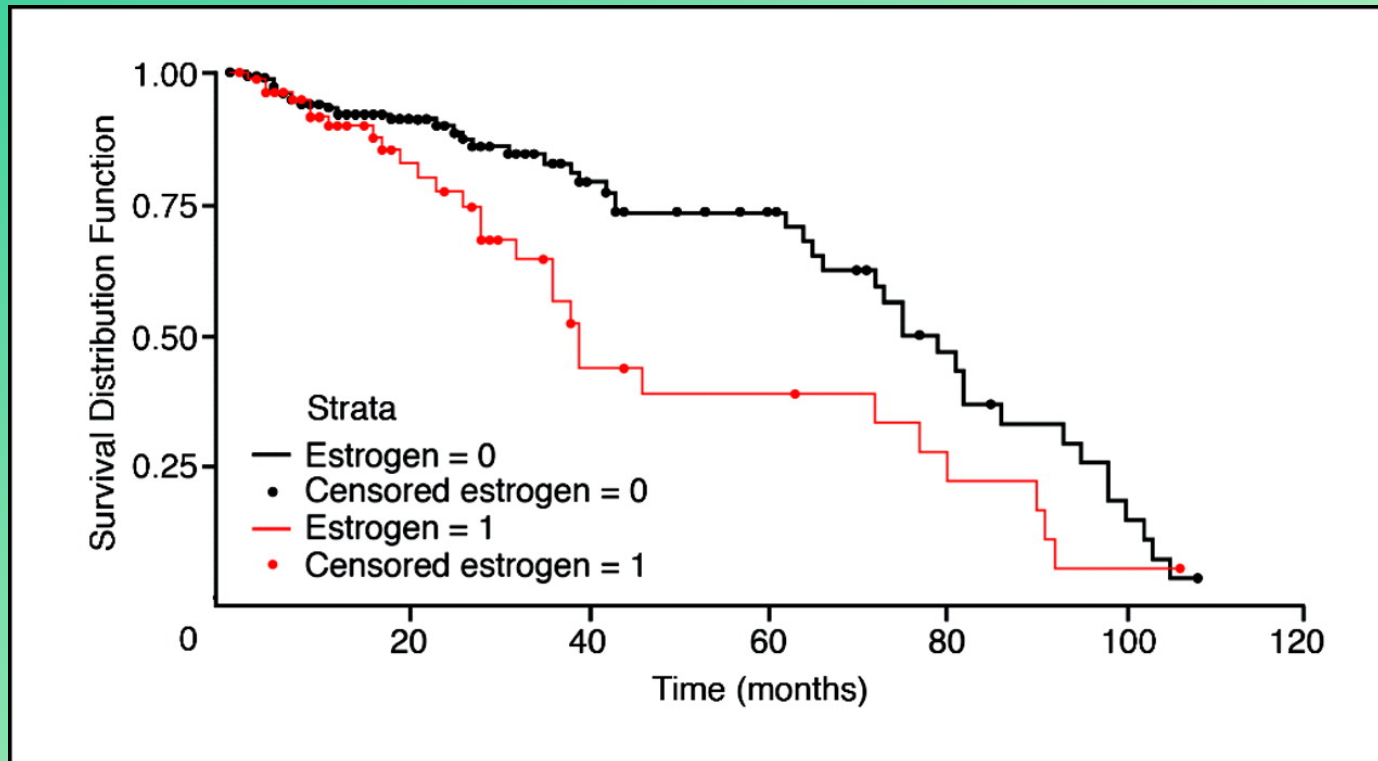
Ganti study*

- Data on 500 female lung cancer patients
- In women on HRT for at least 6 weeks prior to diagnosis:
 - Lower median age at diagnosis: 63 v. 68 yr
 - Much shorter survival: 39 vs. 79 months
- Hazard ratio for HRT and dying of lung cancer: 1.97....



***Ganti et al *J.Clin.Oncol.* 2006**

Survival curves for women with lung cancer based on use of hormone replacement therapy



Ganti, A. K. et al. J Clin Oncol; 24:59-63 2006



Ganti study, continued

- Data on 500 female lung cancer patients
- In women on HRT for at least 6 weeks prior to diagnosis:
 - Lower median age at diagnosis: 63 v. 68 yr
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- Hazard ratio for HRT and dying of lung cancer: 1.97....
- Differences seen only in women who smoked (86% of population)
- What is the basis for this striking finding??



The Estrogen Receptor Effect

- Lung tumors have estrogen receptors
- Estrogens promote growth of lung tumors in the laboratory
- Estrogen can activate the Epidermal Growth Factor Receptor in lung cancers
- Progesterone may have protective effect
 - Can induce apoptosis (programmed cell death) in lung tumors



Further Analysis: The K-ras effect in Stage I Lung Cancer

- When mutated, encodes for a protein that is carcinogenic
- Mutation at “Codon 12” specific for adenocarcinomas, especially of lung
- Novel protein produced by point mutation activates tyrosine kinase – critical for cell growth – and other pathways as well
- Cigarette smoking probably induces the mutation



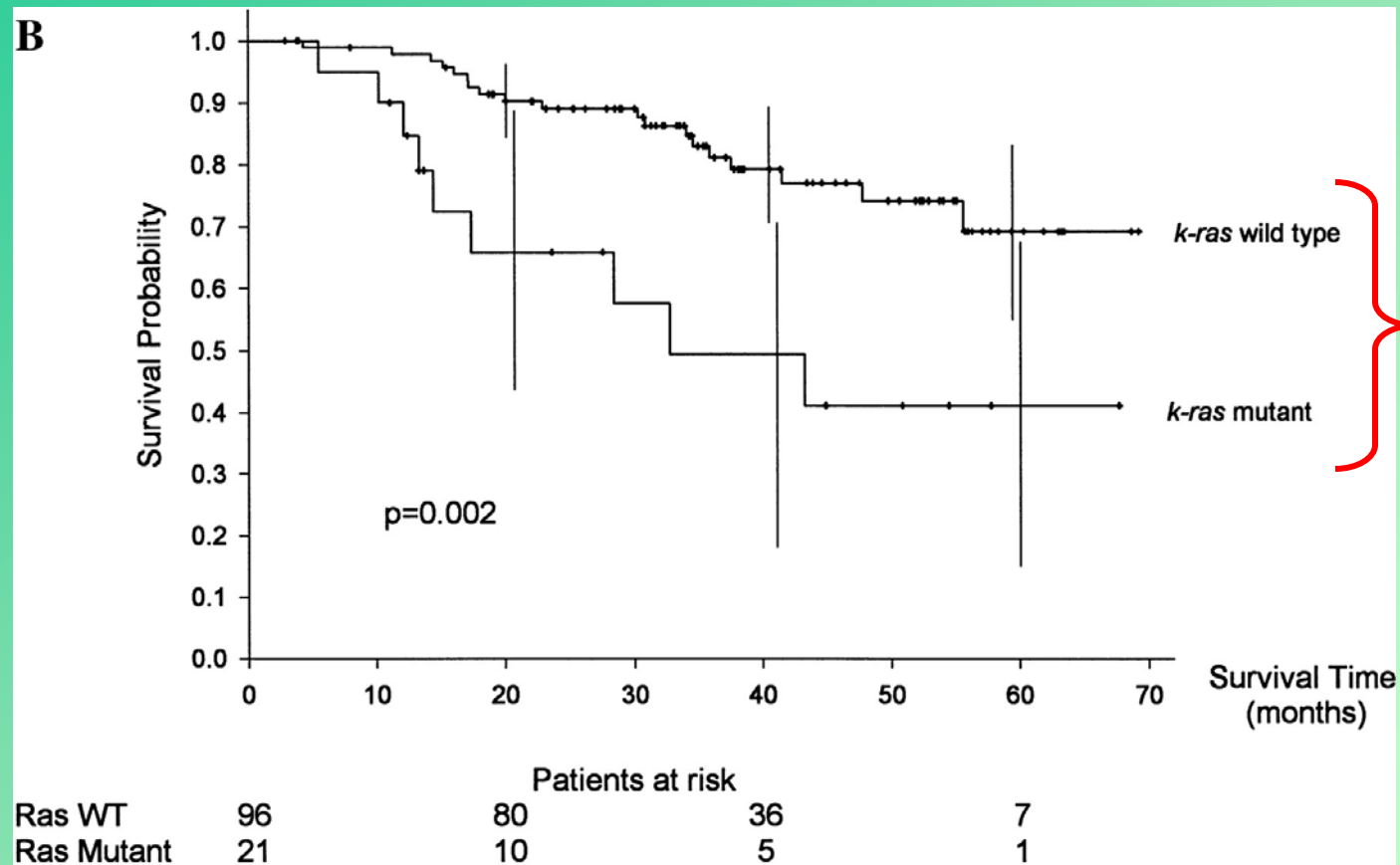
K-ras mutations in women with lung cancer

- Studied as part of larger study of K-ras conducted at Mass General*
- Confirmed deleterious effect of K-ras on prognosis
- **Startling result: female gender conferred odds ratio of 3.3 of having K-ras mutation in patients with adenocarcinoma of the lung**
- Effect of gene mutation...

* Nelson et al. J. Natl. Cancer Inst. 91:2032, 1999



Effect of Mutation in K-ras on outcome in patients with Stage I lung cancer who underwent curative resection



Huge
difference
in outcome
based on
mutation

Nelson, H. H. et al. J. Natl. Cancer Inst. 1999 91:2032-2038;

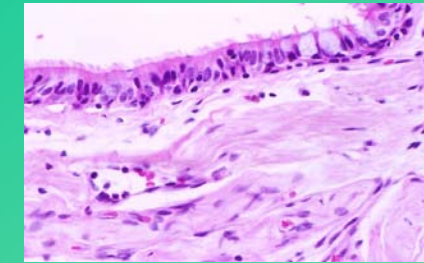


K-ras in women, continued

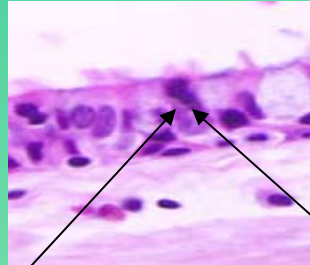
- Estrogen can have effect:
 - Adenocarcinoma cells with the K-ras mutation contain estrogen receptors and may be influenced by an estrogen-rich milieu
 - As in the earlier data on women on HRT who get lung cancer



Schematic of Process

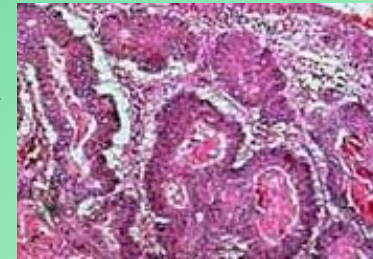


Normal lung
epithelium

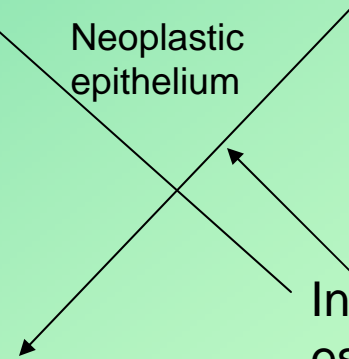


SMOKING

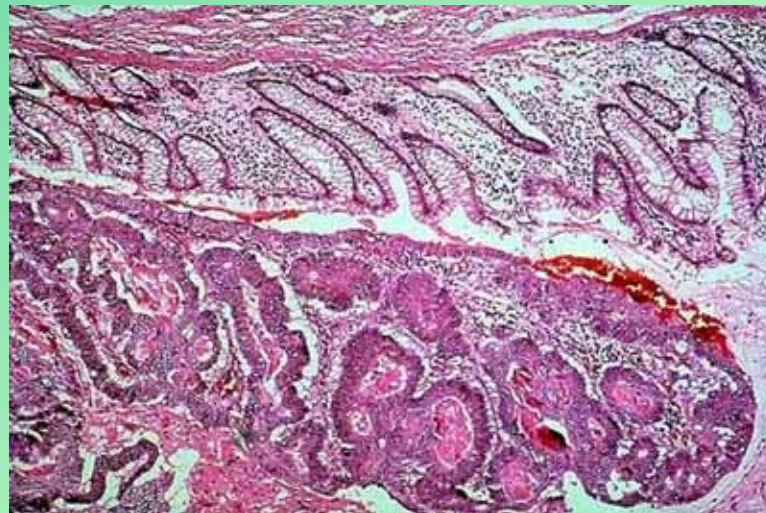
Mutation at
Codon-12 in single
cell (K-ras)



Neoplastic
epithelium



Influence of
estrogen



Another side to the story: overall survival

- Some data suggest that overall women have better survival stage for stage than men
- ECOG study 1594 tried to identify a superior chemotherapy regimen for Stage IIIB (malignant effusion) and IV (blood-borne metastases) non-small-cell lung cancer
- Four regimens tried; none proved superior
- Subset analysis undertaken to see if women overall did better than men



Overall Survival

TABLE 2. Patient Outcomes for ECOG 1594

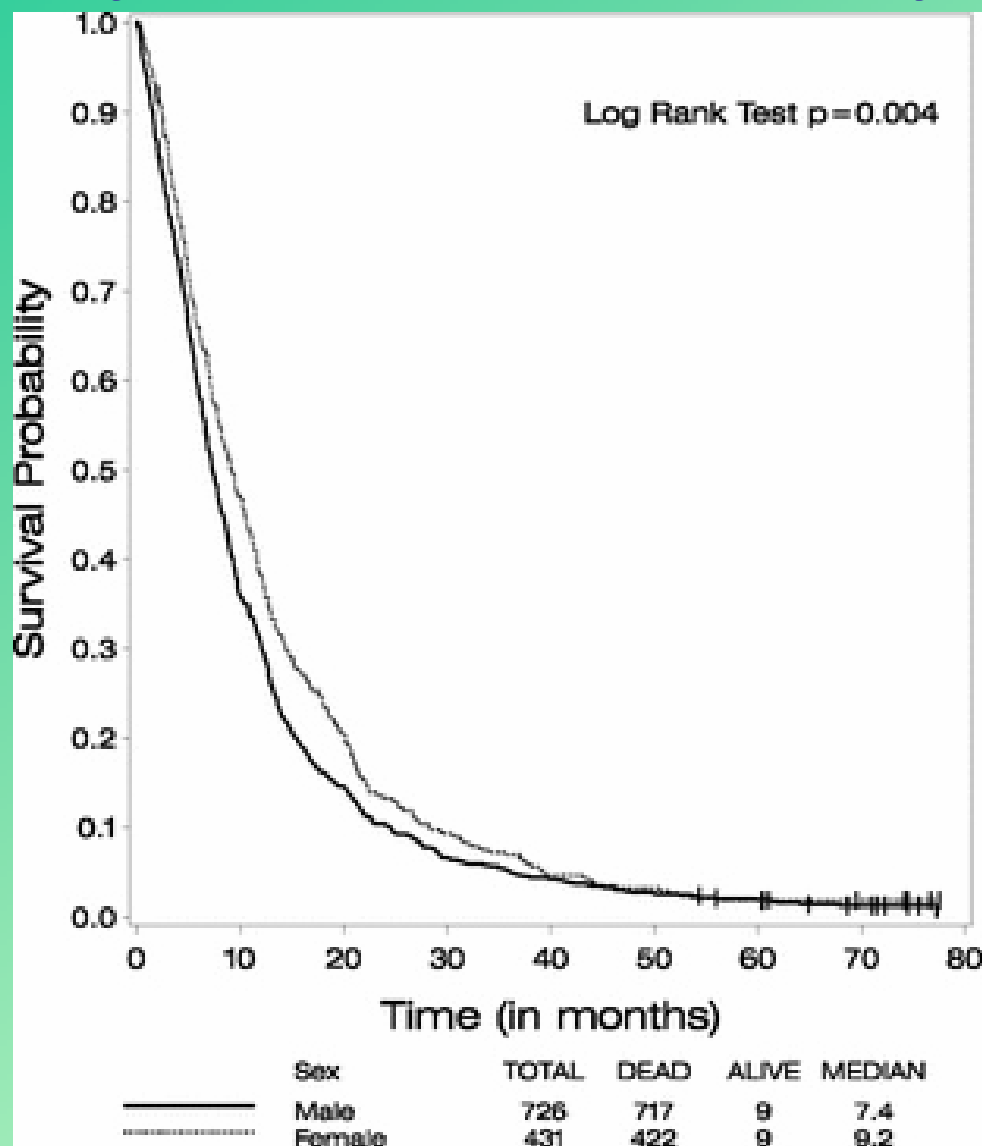
| | Women | Men | <i>P</i> value |
|---------------------------------------|--------------------------|-------------------------|----------------|
| <i>N</i> = 1157 (eligible) | 431 (37%) | 726 (63%) | |
| Censored | 9 (2.1%) | 9 (1.2%) | 0.26 |
| Response rate (%) | 19 | 19 | 0.99 |
| Median progression-free survival (mo) | 3.8 (3.6–4.3) 95% CI | 3.5 (3.0–3.8) 95% CI | 0.022 |
| Median survival time (mo) | 9.2 (8.1–10.4) 95% CI | 7.3 (6.8–8.0) 95% CI | 0.004 |
| Alive at 1 yr (%) | 38 | 31 | |
| Alive at 2/3 yr (%) | 14/7 | 11/5 | |

ECOG, Eastern Cooperative Oncology Group.



*Wakelee et al. *J. Thoracic Oncol.* 1 (5): 441-6, 2006

Analysis of E1594 by Gender*



*Wakelee et al. *J. Thoracic Oncol.* 1 (5): 441-6, 2006

Survival by Chemo Regimen, Analyzed by Gender

| | MST (mo)Women | Men | <i>P</i> value |
|---------------------------|----------------------|---------------|-----------------------|
| A: cisplatin/paclitaxel | 9.2 (7.0–11.4) | 7.6 (6.5–8.7) | 0.089 |
| B: cisplatin/gemcitabine | 9.4 (7.8–12.2) | 7.4 (6.3–8.8) | 0.22 |
| C: cisplatin/docetaxel | 9.2 (7.0–11.3) | 6.7 (6.0–8.5) | 0.12 |
| D: carboplatin/paclitaxel | 9.0 (7.0–11.6) | 7.7 (6.2–9.4) | 0.19 |
| <i>P</i> value | 0.81 | 0.49 | |

Values are median (95% confidence interval). ECOG, Eastern Cooperative Oncology Group; MST, median survival time.

**Authors at recent ASCO meeting
tried to make a big deal out of these
differences.**



Is there a conflict?

- Abundance of data of impact of gender and hormones on survival in early stage lung cancer
- Salutary effect of female gender on survival of late-stage disease modest
- ??Different mechanisms of action applicable to the two circumstances: early vs. late stage disease
- Stay tuned....



Conclusions

- Lung cancer in women is different biologically
 - Higher expression of K-ras oncogene
 - Effect of endogenous and exogenous estrogens upon K-ras pathway and hormone receptors on tumor cells
 - Women with advanced cancer may do slightly better for unclear reasons



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