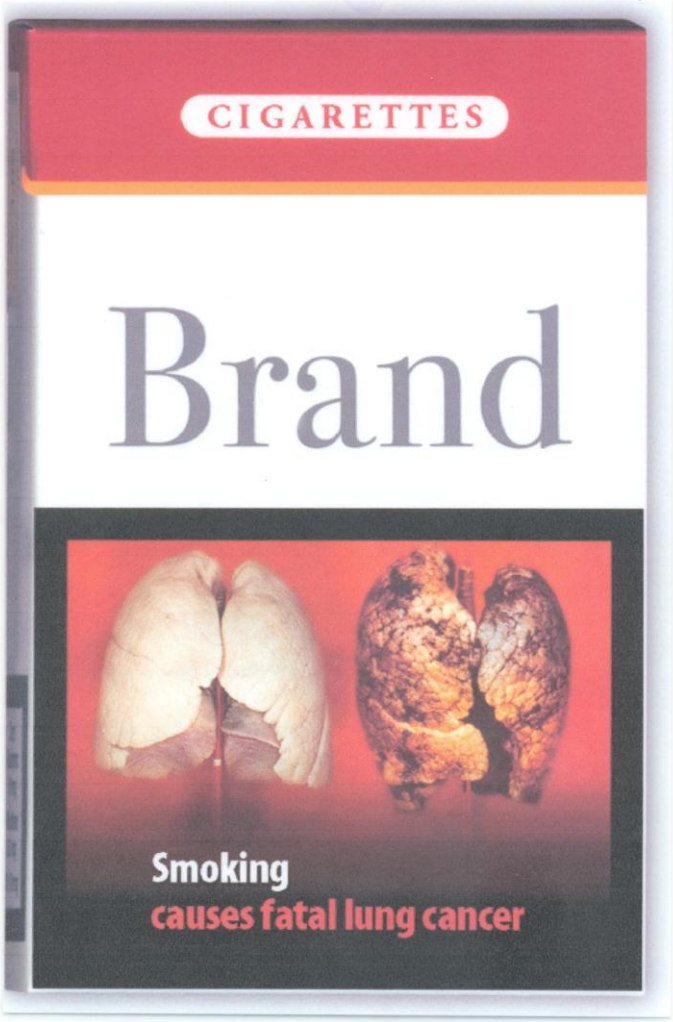
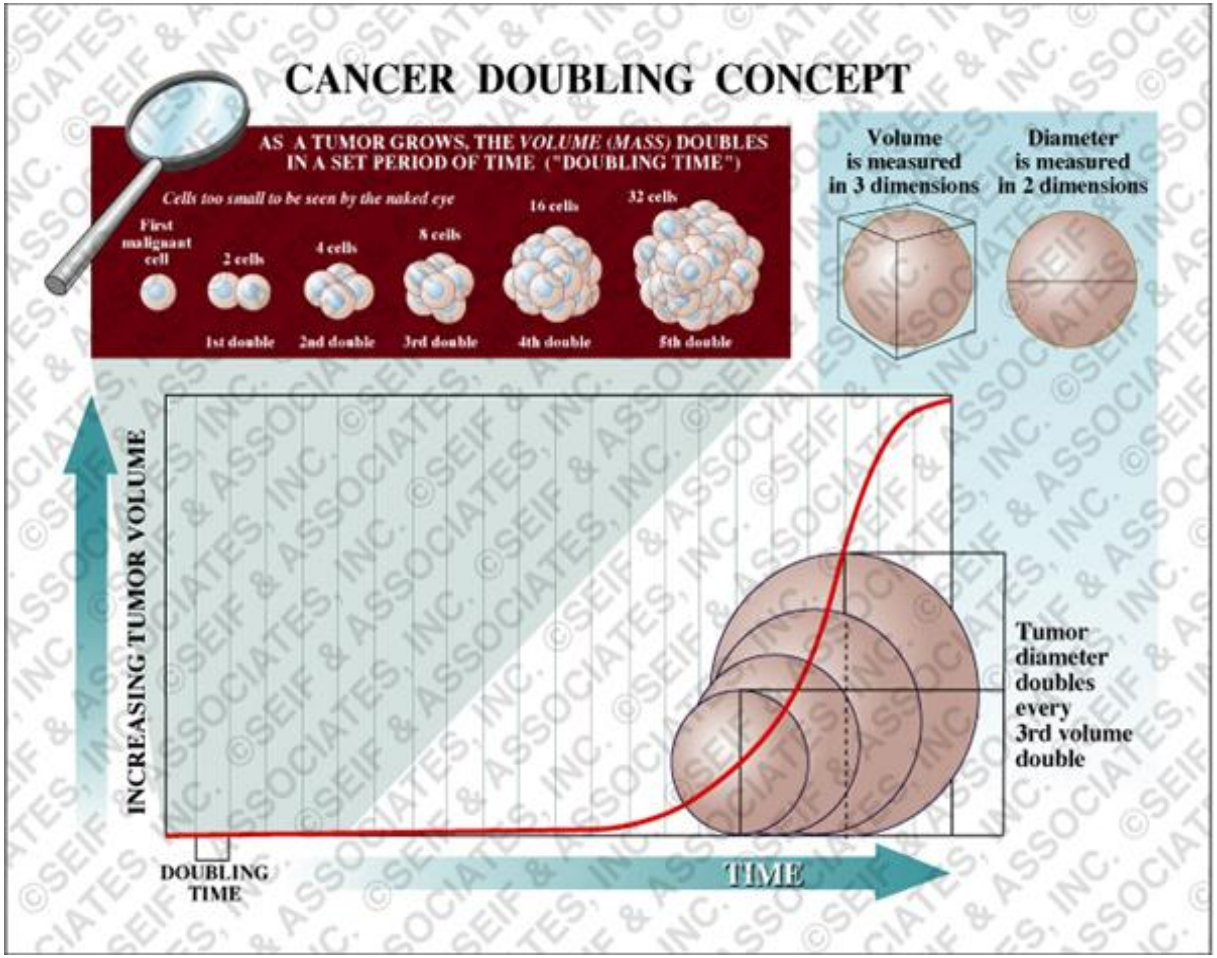
MANAGING LUNG CANCER
GP CME South 19.8.12

Roland Meyer
Respiratory Physician, Southern DHB

137R.00 137S.00



It takes years to be detectable
27 tumor doublings for 1cm

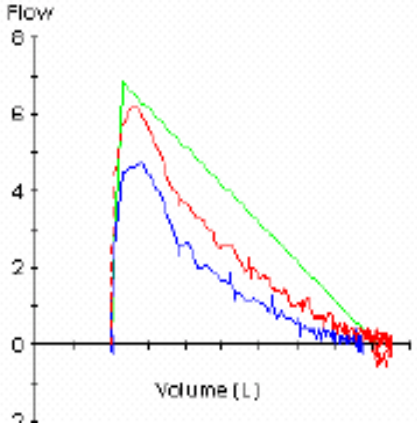


Spirometry to identify those at risk Read Code H3.00

Age: 35 Height(cm): 159 Weight(kg): 86.0 Body Mass Index: 34.02 Gender: Female

Spirometry
(BTPS, Ref: NHANESIII)

		REF	PRE-Rx Meas	PRE-Rx %REF	POST-Rx Meas	POST-Rx %Chg	95%C.I.
FEV1	Liters	2.98	** 2.14	** 72	2.58	20	0.56
FVC	Liters	3.56	3.36	95	3.76	12	0.66
FEV1/FVC	%	83	^^ 63		^^ 68		10
FEV6	Liters	3.53	3.34	95	3.72	11	0.65
FEV1/FEV6	%	85	** 64		** 69		9
FEF25-75%	L/sec	3.22	** 1.23	** 38	** 1.69	38	1.18
StdFEF25-75	L/sec		1.34		1.75	31	
PEF	L/sec	6.80	** 5.08	** 75	6.19	22	1.64
FET100%	Sec		7.68		6.99	-9	
FVL ECode			000000		000000		



PRED___ PRE___ POST___

Medication: COMBIVENT

Lung Cancer MoH

- **Lung cancer** is the biggest cause of cancer death in New Zealand – largely because it is often detected late, when the disease is very advanced and has spread to other parts of the body.

Targeting Shorter Waits For Cancer Treatment

- Everyone needing radiation or chemotherapy treatment will have this within 4 weeks.
- This target previously focused on radiotherapy. DHBs have consistently performed well against the target, and it now includes chemotherapy.

Cough Cough Cough NHS

Midland Cancer Network NZ : "Cough Cough Cough" campaign

"Signs of lung cancer"

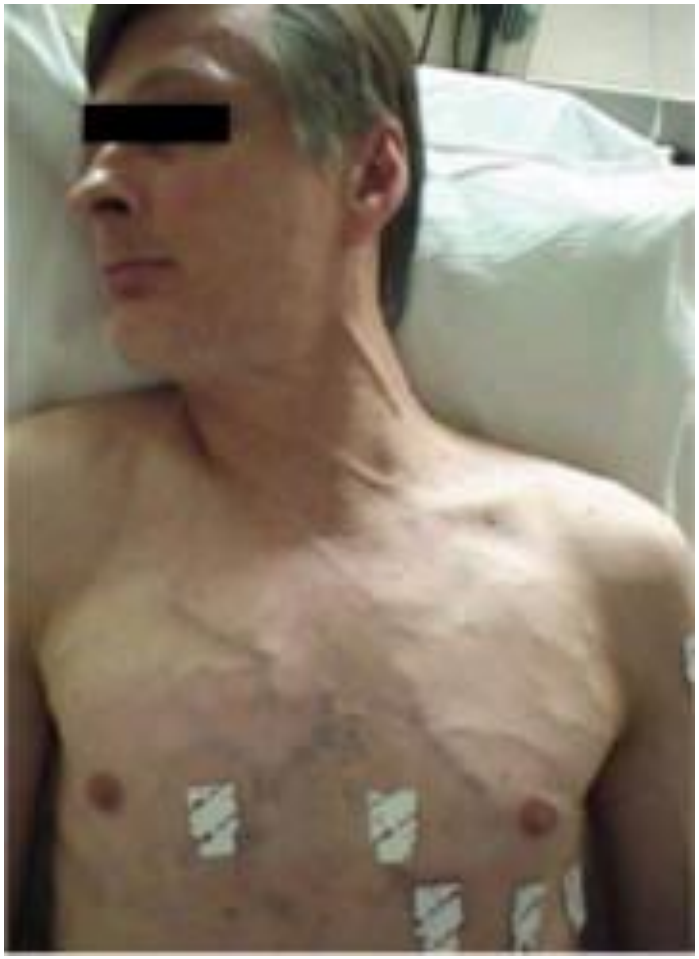
- Recognition of ….. is particularly important if you smoke or have ever smoked as you are more likely to suffer from throat and lung diseases.
- If you have any of these symptoms, see your GP immediately. It doesn't necessarily mean that you've got lung cancer, but it's best to get it checked out. The earlier the condition is diagnosed, the better the chance of treatment being successful.

Haemoptysis <http://healthpathways.org.nz>

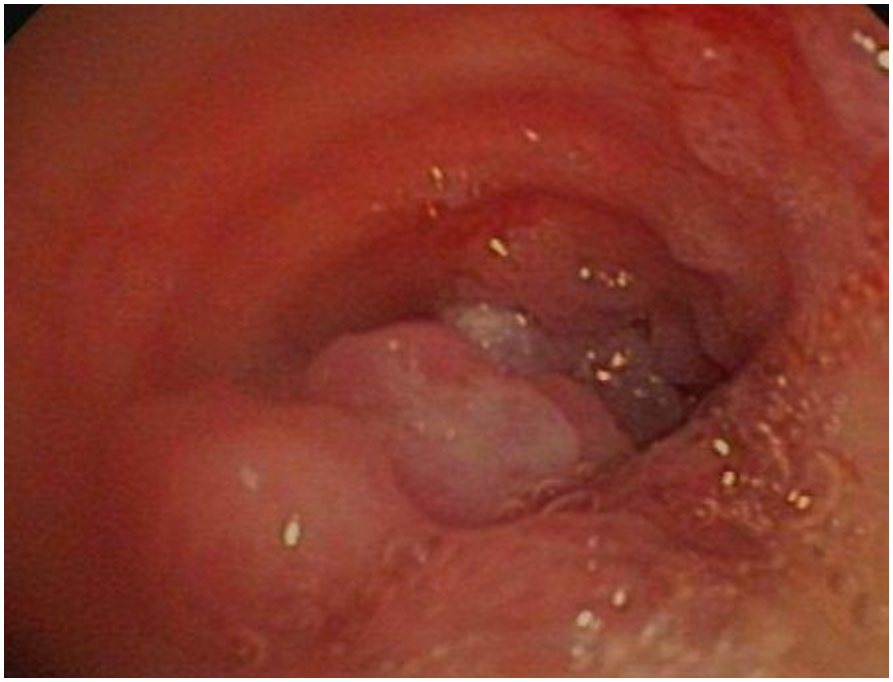
Red Flags

- acutely unwell
- large :e.g., > 30 ml / 24 h
- acute SOB and/or pain
- Refer for acute admission or phone the acute respiratory physician 0800-….
- Note: Arranging a community based chest X-ray will cause unnecessary delay.

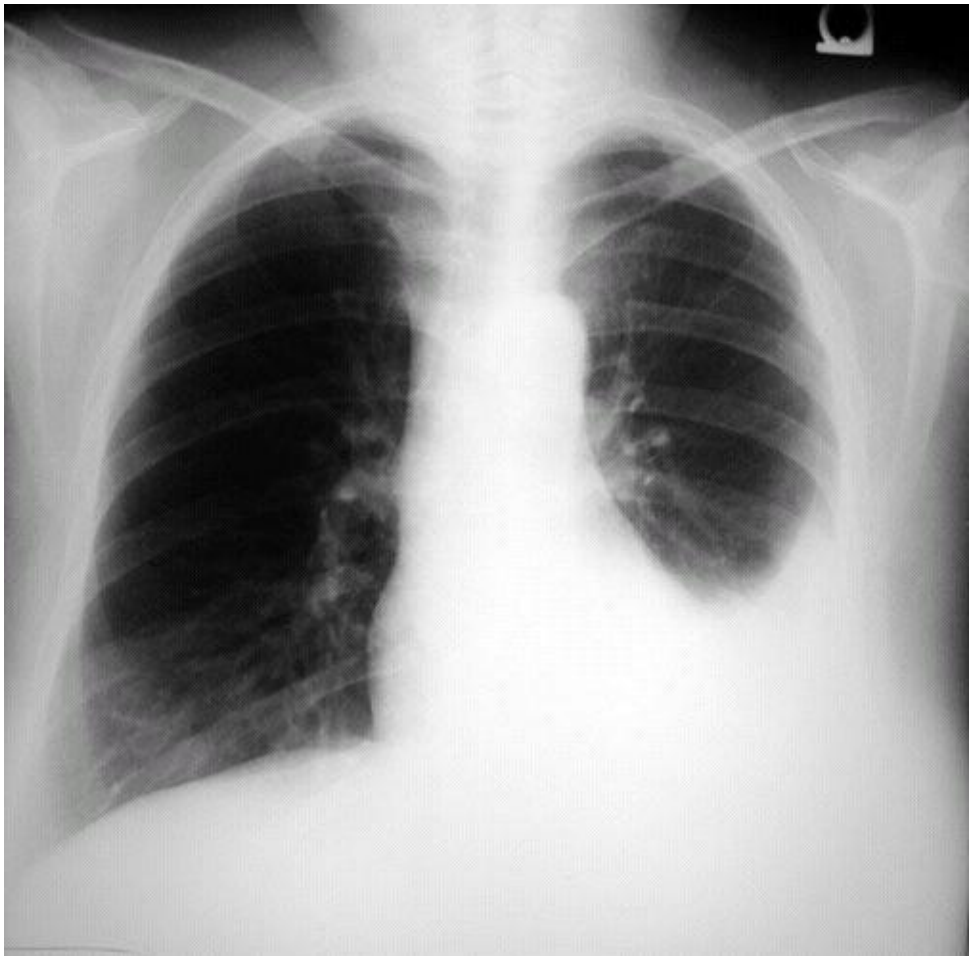
Late Presentation with LC: SVCO



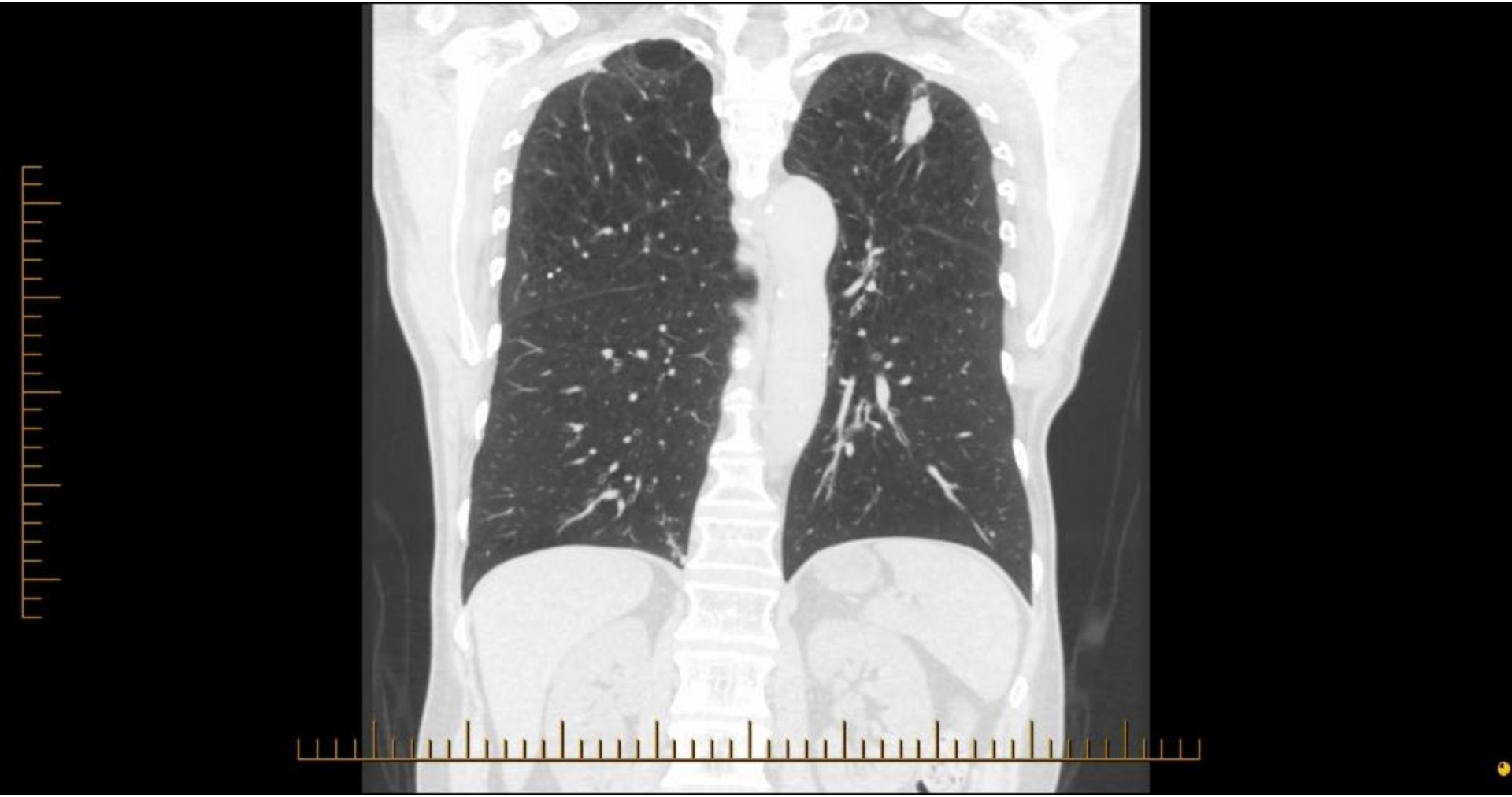
SOB and Stridor, Normal CXR: Large Airway Obstruction



Late Presentation: Pleural Effusion



Early = likely chance of finding



Symptoms only if ….involvement of larger bronchus, pleura, bones….

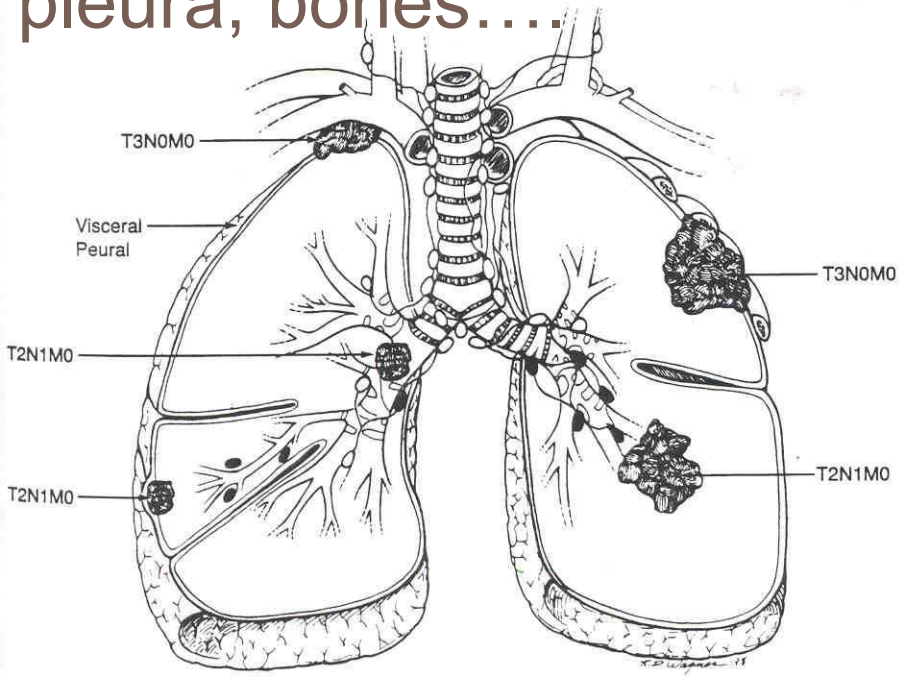
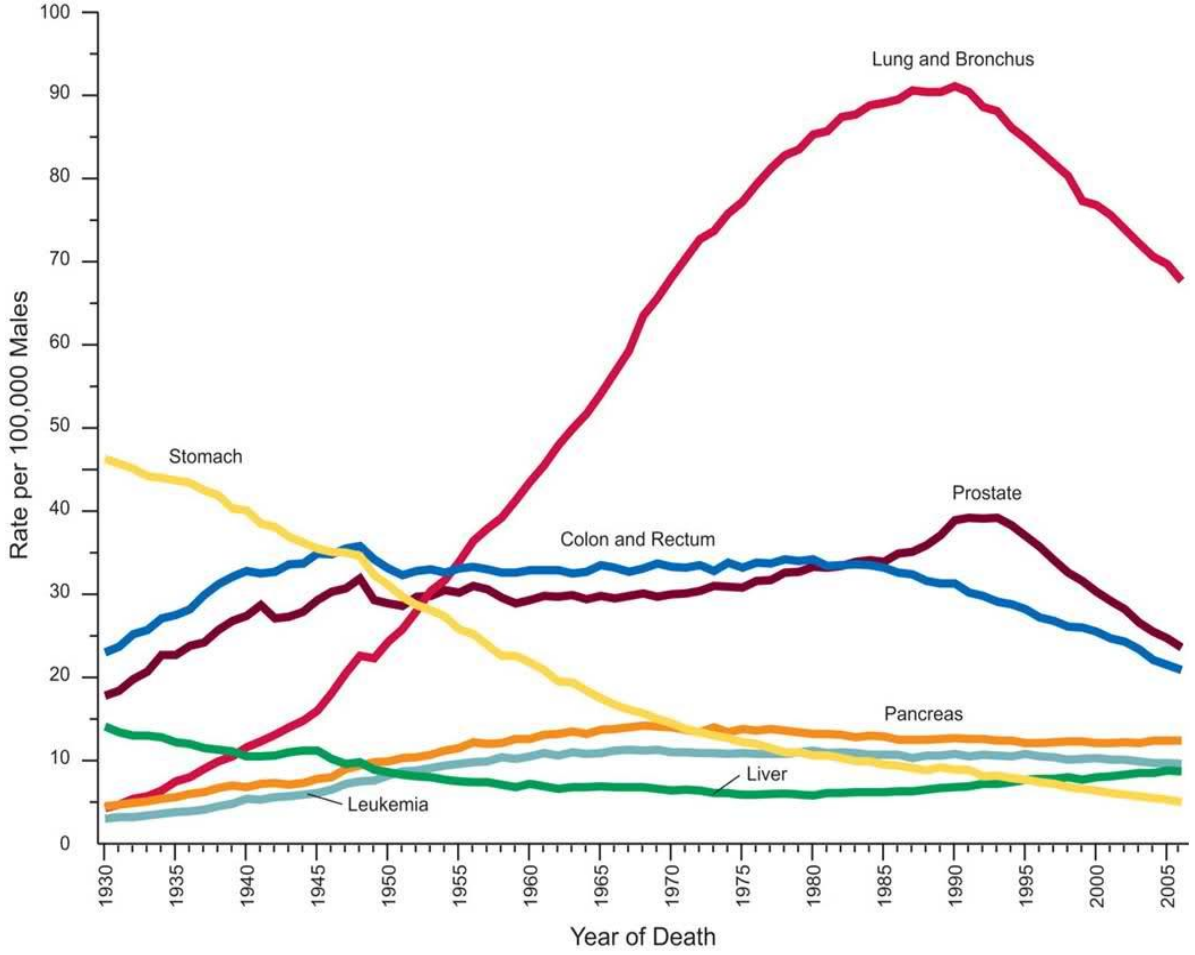


FIGURE 32.4. Stage IIB (*T2N1MO* and *T3NOMO*) lung cancer includes (1) tumors larger than 3 cm., or with other T2 characteristics, that involve peribronchial and/or hilar lymph nodes by direct extension or metastasis. No further lymph node or distant metastasis is present, and (2) tumors with limited, circumscribed, extrapulmonary extension, T3, such as peripheral tumors invading the chest wall or central tumors involving the pericardium, with no evidence of metastasis. (From Mountain CF, Libshitz HI, Hermes KE. Lung cancer—handbook for staging, imaging, and lymph node classification. Houston: Clifton F. Mountain Foundation, 1999, with permission.)

Cancer Mortality

–high but not rising- but F>M



What is new ?

- NZ GL for cancer diagnosis 1° care 2009
- Standards for Lung Cancer services NZ 2011
- Cancer CNS / care coordinators MoH May 2012
- New(er) treatments:“personalised”/ “targeted” (EGFR…)
- New(er) diagnostic modalities : PET scan, EBUS
- More never-smokers (F > M) with LC
- Screening (CT:NEJM July 2011)
- Gene test proposed 2010 . Early CDT

Lung Cancer - 2004 NZ
1700 new cases per year

- 929 male deaths and 626 female deaths per year
- 5yr survival ~ 6% (15% USA, 12% Aust.)
- 1. presentation to referral: Stage I-II 100d, St IV 49d, “N” CXR 222d
- <<20% for Rx with curative intent
- AKL/ N-land 2004 study: 50% did not receive initial cancer therapy
- NZ Maori 2 x as likely to die

Lung Cancer 2008 NZ

- Variations in outcomes between NZ DHBs generally below some comparable countries
- **3.5y survival 3.1%-13.3%**
- Operative procedure in 1.5% - 18.2%
- Chemotherapy 6.7% -26.9%
- Radiotherapy 25%-60.4%

Lung Cancer Audit2008 Southern DHB

- ED presentations with new Dx : 39-46%
- Waiting times:nonED patients:FSA 9-11d
- Referral to Rx 77-93d
- Weekly MDM Lung Cancer started

SCN 2008 “Patient Journey”- issues, recommendations

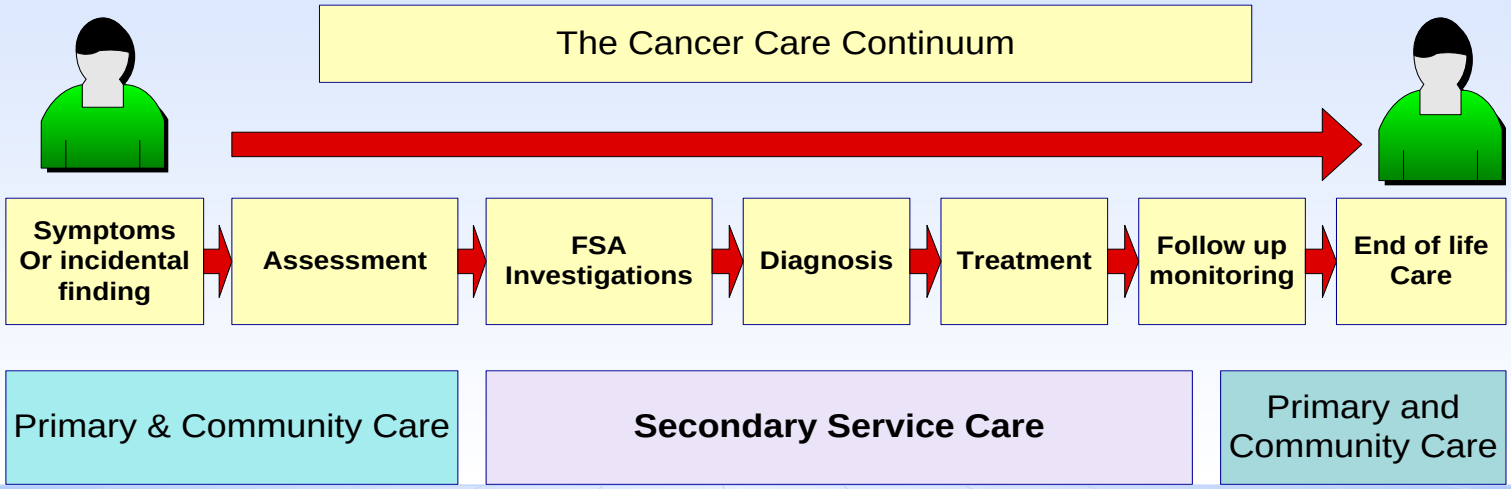
- Variations during initial GP Ax
- Variations in time to complete Dx/staging and referral for Rx
- Need for better Mx for dealing with psycho-social effect of Dx
- Better communication
- Cultural awareness needed

Lung Cancer Audit 2010

- Waiting for very 1. FSA (=“entry”) av. 6 d
- 88% seen within 14d
- 80% discussed at a MDM
- Referral-to-Rx: 60-65% within 62d

The Cancer Patient Journey

1° 2° and 3° care



HDC Case 10HDC00610

- Between June 2008 and February 2010, Ms A presented to Dr B on multiple occasions with complaints of persistent coughing, chest and throat pain, fever and sweating, haemoptysis,and SOB
- At the very least, Dr B should have physically examined Ms A and referred her for an urgent chest X-ray in May 2009. By failing to do so, Dr B breached Ms A‘s rights under Right 4(1)6 and Right 4(4)7 of the Code of Health and Disability Services Consumers‘ Rights (the Code).

ACC "Misadventure" = (now) **Treatment injury**: CXR report not followed, not just 1° care

- 50y smoker hospital admission with pneumonia 5/06
- FU CXR requested by hospital 7/06, "*to be FU by GP*" - abnormal, not acted upon
- 7/08 : disseminated NSCLC
- Died Jan 09

Suspected Cancer in 1° Care NZ Guidelines NZGG /MoH 2009

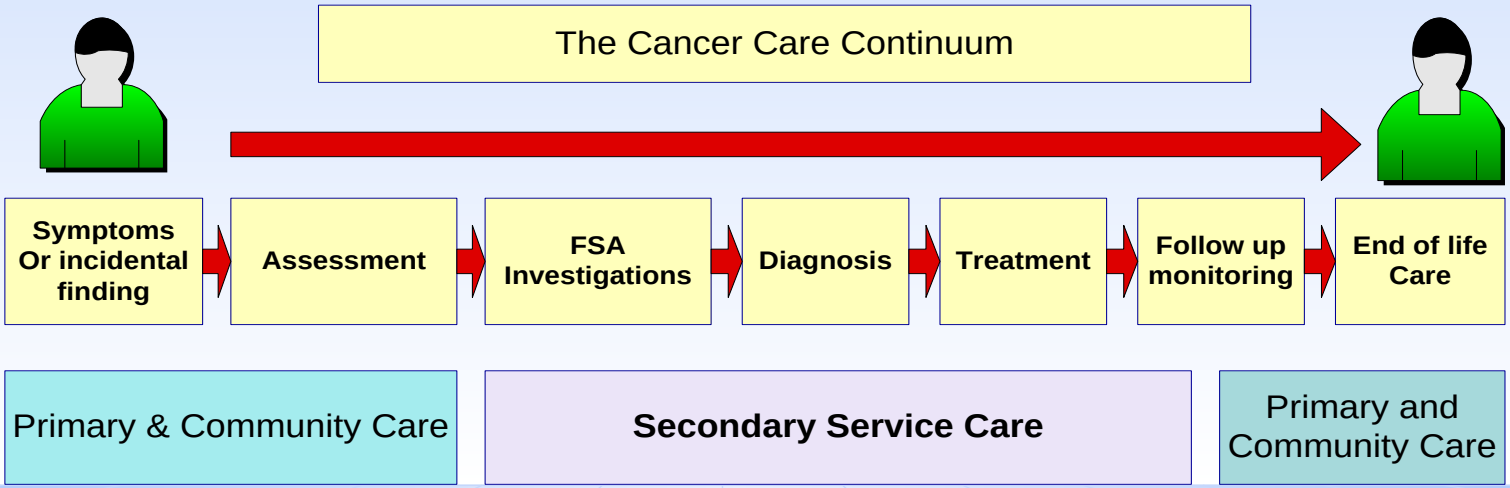
- A person presenting with Sx /signs suggestive of LC requires urgent Ix which may include referral to a specialist team “
- A person should be referred urgently to a specialist if they have: persistent haemoptysis and are (ex)smokers >40y; or if a CXR is suggestive of LC (Grade C)
- A person should be referred urgently for a CXR if they have unexplained haemoptysis or unexplained /persisting resp signs /Sx (chest/shoulder pain, SOB, weight loss, focal chest signs, hoarseness, clubbing, ,cervical Lnd, cough, features of metastasis- Risk in (ex)smokers, previous asbestos exposure, Hx of cancer – head /neck)

Suspected Cancer in 1° Care NZ Guidelines 2009-(2) "good practice"

- Smoking status should be recorded and regularly updated
- After urgent referral for CXR , it should be completed and reported <=1/52
- A person with risk factors for LC who has consolidation on an initial CXR should have a repeat CXR within 6 weeks to confirm resolution
- Sputum cytology is not recommended for the Ix of LC

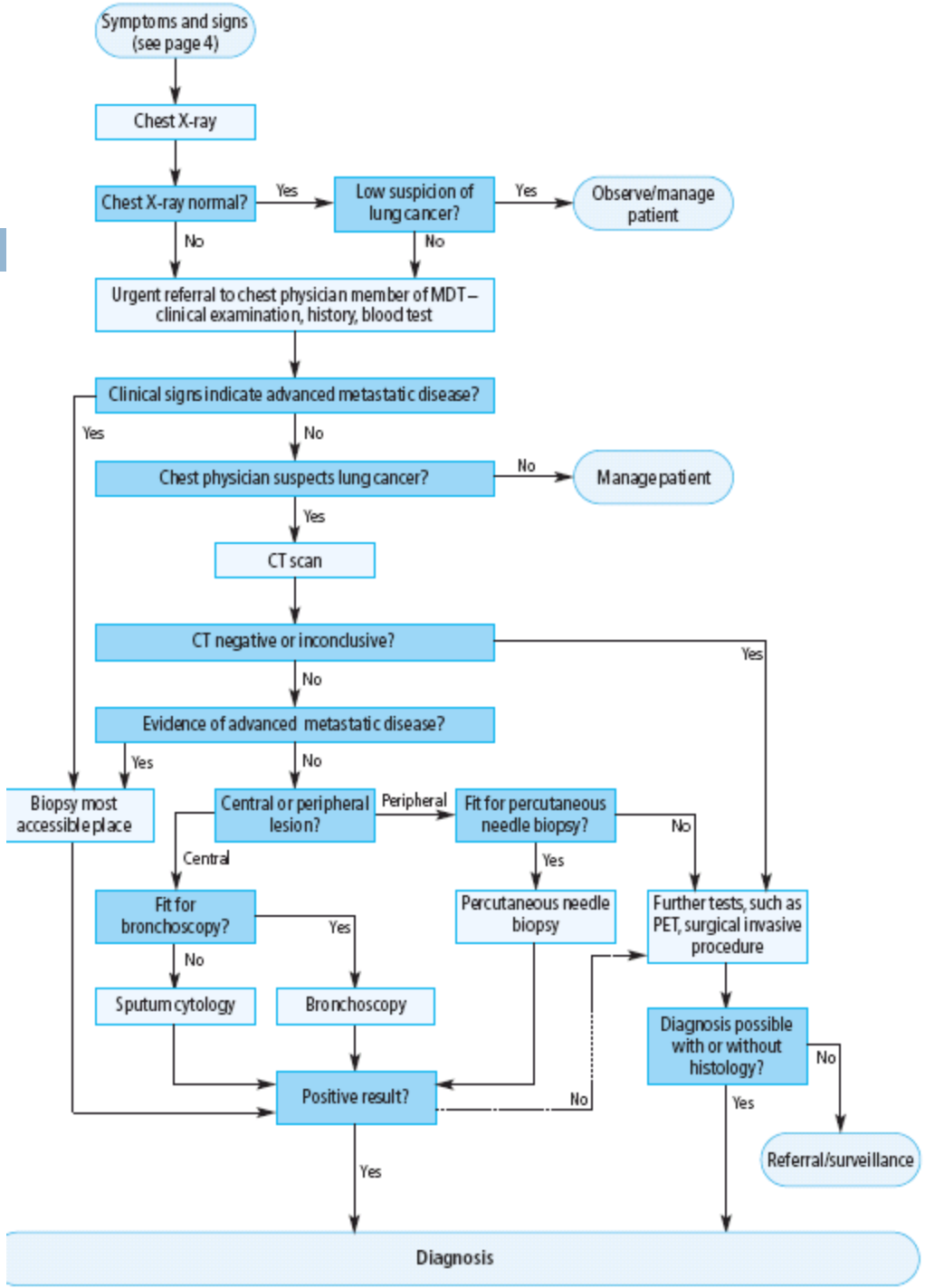
The Cancer Patient Journey

? Less waiting possible

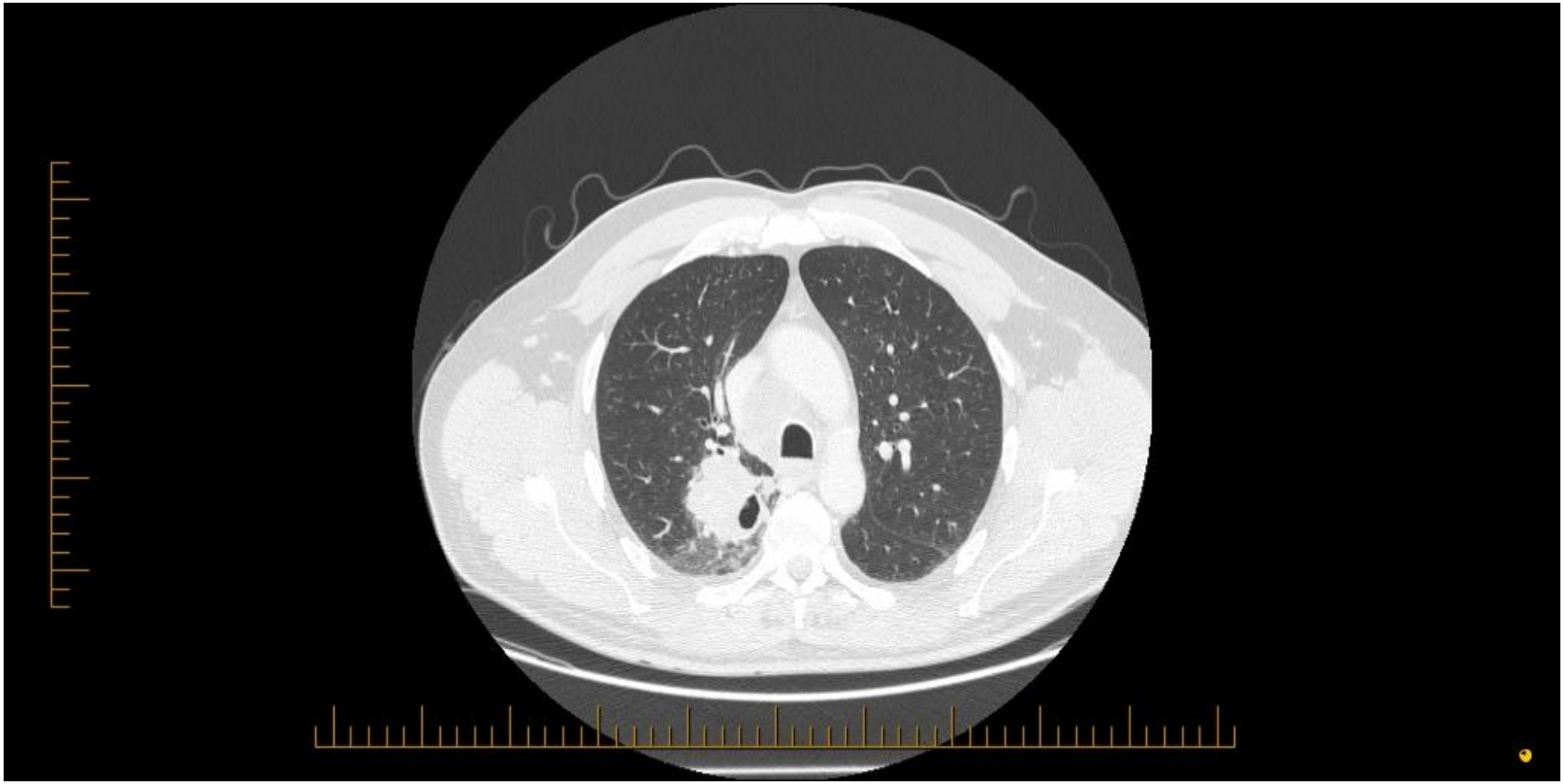


The Lung Cancer Work up

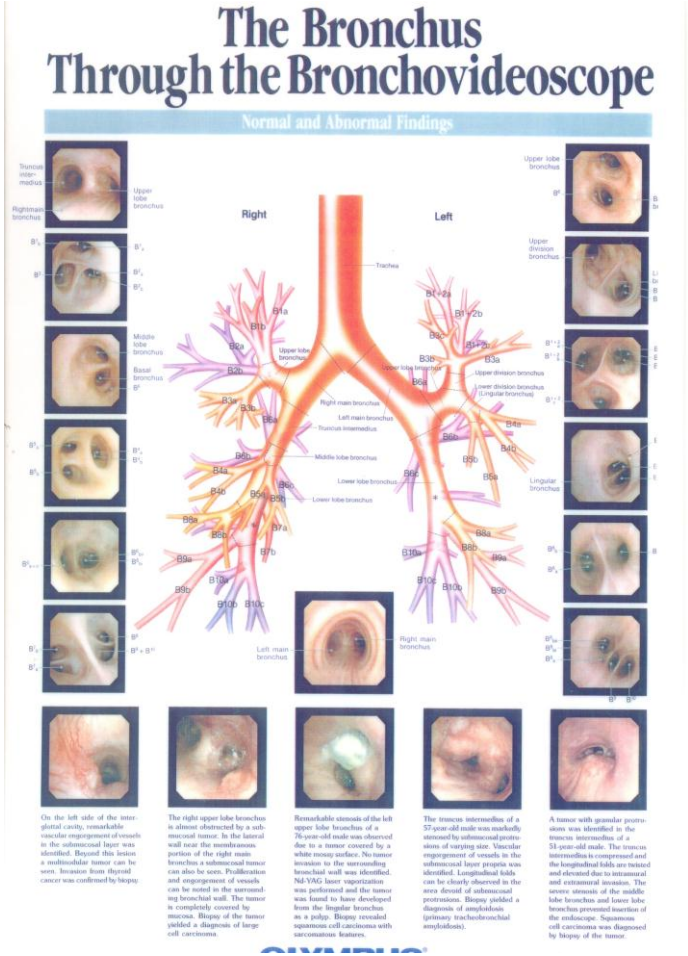
- Confirm diagnosis
- Establish cell type (+/- genetic profile ..)
- Staging
- Assess for co-morbidity = other medical conditions and ability to undergo potentially aggressive Rx, e.g. thoracotomy, chemo-radiation….
- Psycho-social, cultural issues / context


Symptoms and signs (see page 4)
Chest X-ray
Chest X-ray normal?
Yes
Low suspicion of lung cancer?
Yes
Observe/manage patient
No
No
Urgent referral to chest physician member of MDT – clinical examination, history, blood test
Clinical signs indicate advanced metastatic disease?
Yes
No
Chest physician suspects lung cancer?
No
Manage patient
Yes
CT scan
CT negative or inconclusive?
Yes
No
Evidence of advanced metastatic disease?
Yes
No
Biopsy most accessible place
Central or peripheral lesion?
Peripheral
Fit for percutaneous needle biopsy?
No
Central
Yes
Fit for bronchoscopy?
Percutaneous needle biopsy
Further tests, such as PET, surgical invasive procedure
Yes
No
Sputum cytology
Bronchoscopy
Diagnosis possible with or without histology?
No
Positive result?
No
Yes
Referral/surveillance
Yes
Diagnosis

Lung Cancer CT



Bronchoscopy



TBNA, EBUS

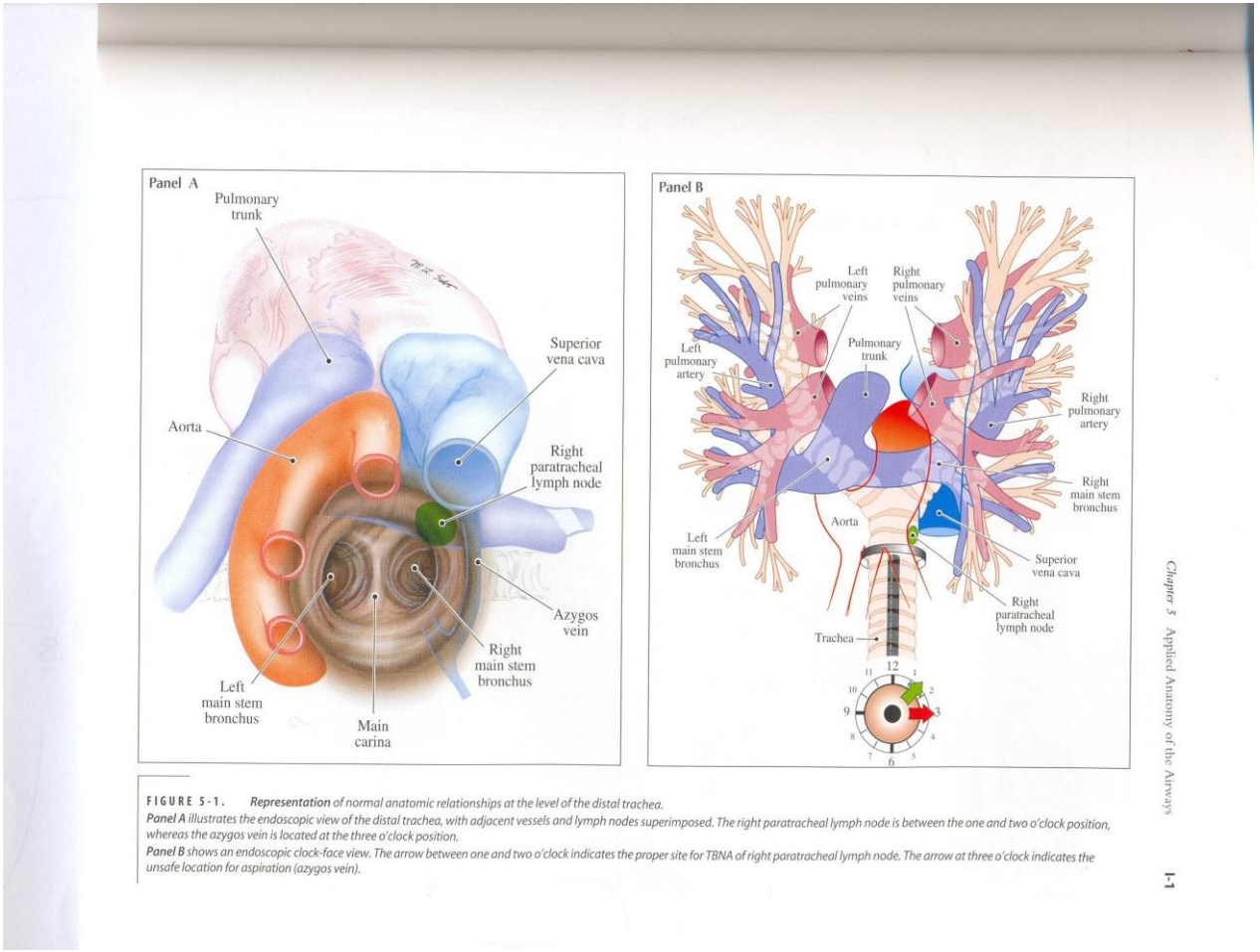
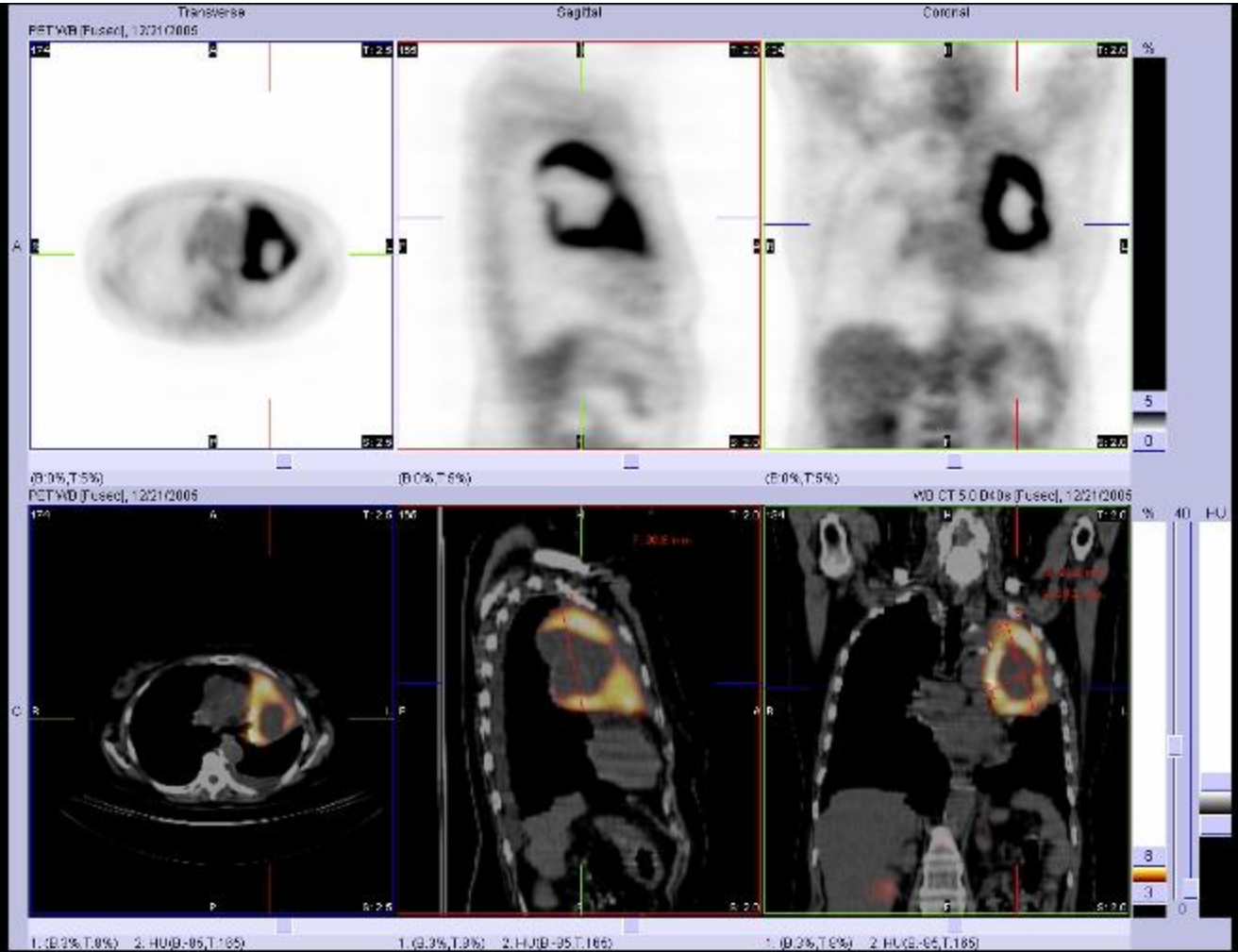
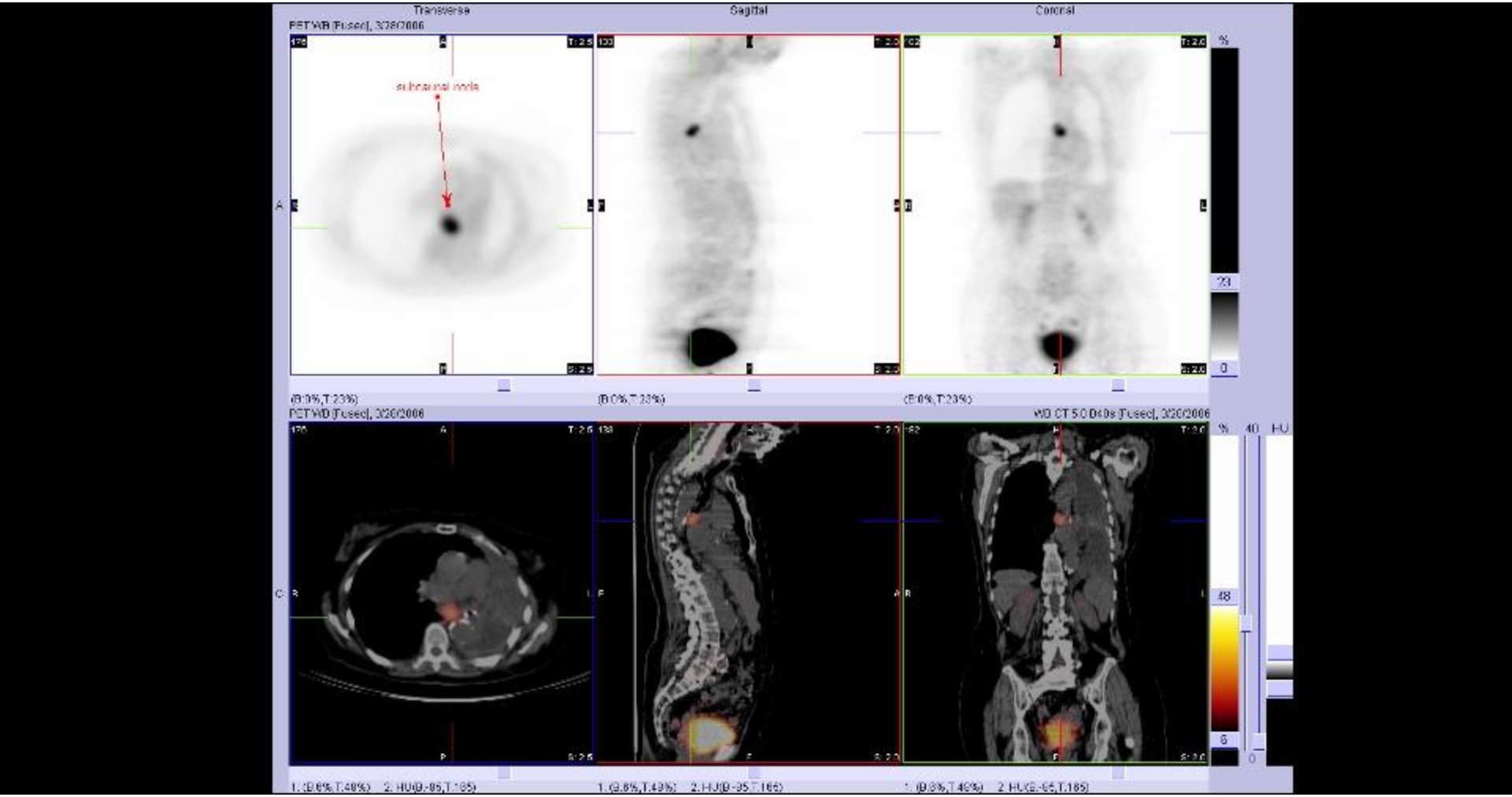


FIGURE 5-1. ***Representation*** *of normal anatomic relationships at the level of the distal trachea.*
Panel A *illustrates the endoscopic view of the distal trachea, with adjacent vessels and lymph nodes superimposed. The right paratracheal lymph node is between the one and two o'clock position, whereas the azygos vein is located at the three o'clock position.*
Panel B *shows an endoscopic clock-face view. The arrow between one and two o'clock indicates the proper site for TBNA of right paratracheal lymph node. The arrow at three o'clock indicates the unsafe location for aspiration (azygos vein).*

PET –better imaging



PET –better imaging ? 2



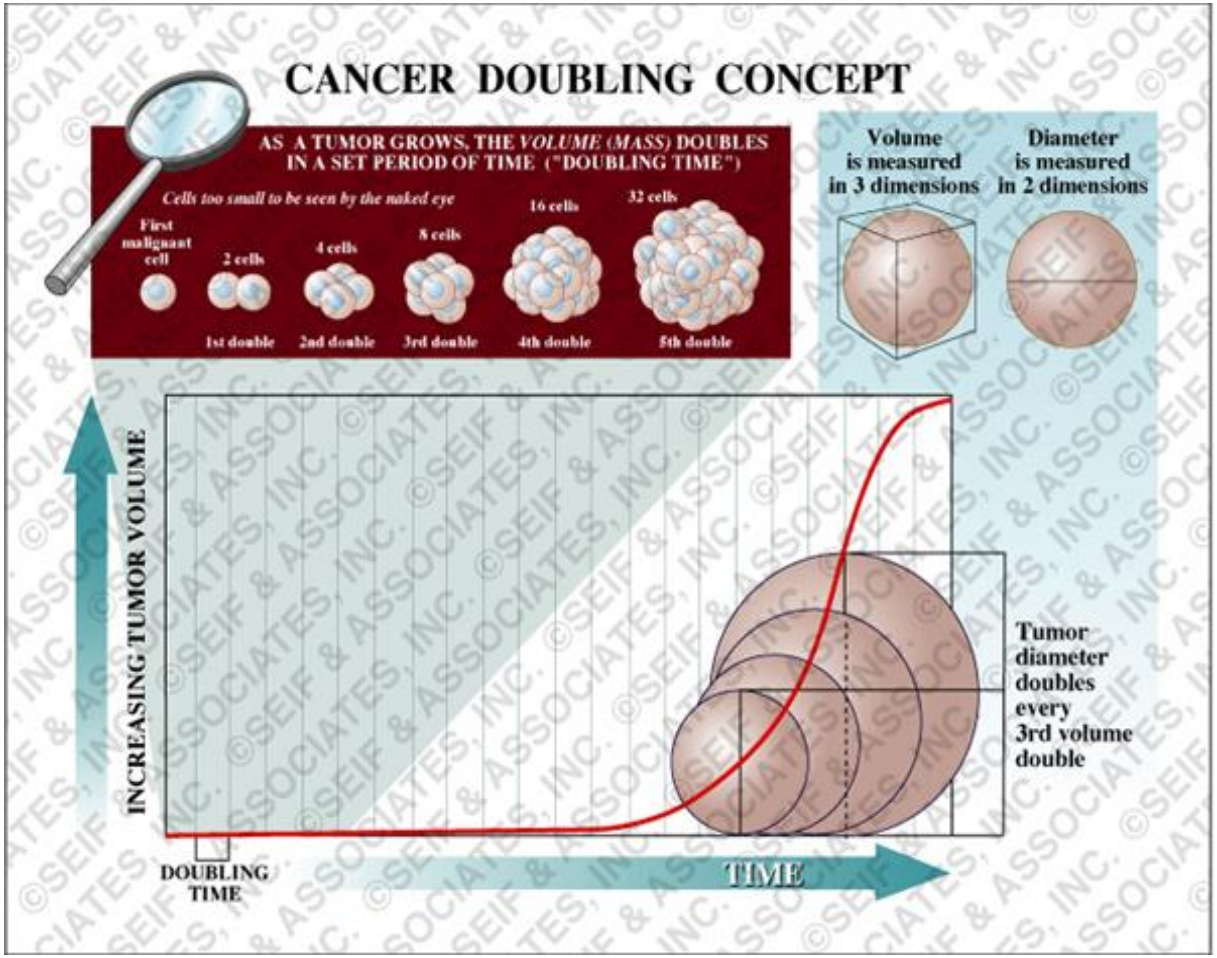
Genetic Profiling

- SNaPshot Multiplex test (>100 mutations)
- KRAS
- EGFR
- BRAF
- PI3K, HER2, AKT, NRAS…..
- FISH test
- ALK (EML4-ALK + other)

Genetic Profiling- Why Does It Matter

- Mutations > in adeno (non-squamous) Ca, light smoking Hx, female , Asian
- EGFR in NZ: from 1 Aug 2012 funded test and then eligible for Gefitinib (Iressa)
- Previous Erlotinib (Tarceva) funded for 2. line Rx (=after Pt based chemo) of advanced unresectable NSCLC
- ALK (EML4-ALK + other) may respond to Crizotinib but as yet trial (eg PROFILE…)

It takes years to be detectable
27 tumor doublings for 1cm



1cm : already 27 tumor doublings

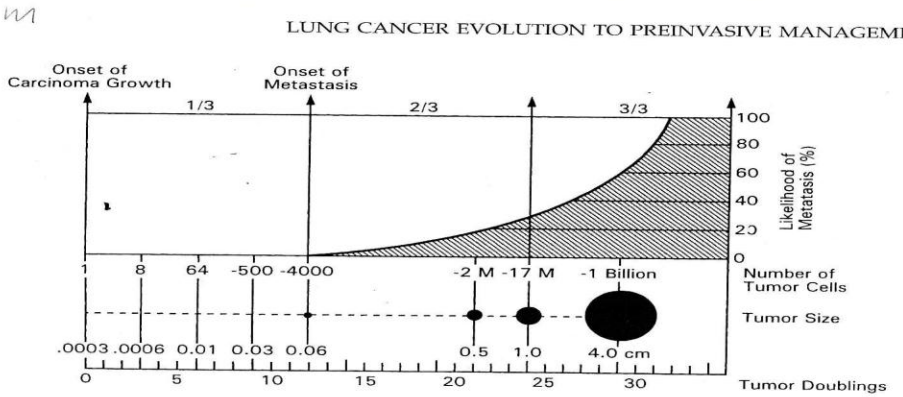


Figure 1. Progressive theory of carcinogenesis suggesting that frequency of metastatic dissemination is related to tumor size. (*Modified from* Krokowski: Basic Concepts, 1964 *In* Kaiser, WA (ed): MR-Mammography, Berlin, Springer-Verlag, pp 3–22, 1993; with permission.)

“Informed consent for CT screening” *(Earnest F Radiology2003;226:633-)*

- Small LC may be detected, surgical removal could be life-saving
- CT is more sensitive than CXR, there may be a benefit not apparent in previous studies using CXR
- There is no established benefit of mortality reduction from LC screening with any method
- >50% will have 1 or more nodule(s) on CT, most of those will require at least 3 further CT and possibly biopsy and resection (with risks)
- 98% of found nodules will be benign
- 10% will have another abnormality that requires further tests- most of these however are of no consequence to health
- Each CT has radiation dose of 10 2-view CXR & 1 mammography, if then further diagnostic CT is required the dose is even 10x higher (LDCT 0.2-0.4 cGy [=rad], CT chest 2-5 cGy / 0.54 cSv [=rem]; CT guided FNA 20-60 cGy /min

Screening should be effective, viable , appropriate…. UK National Screening committee

- Disease with serious consequences
- High prevalence
- “Pseudo-disease” not a major problem
- High accuracy for detecting detectable pre-clinical disease & before critical point
- Little morbidity caused by screening test
- Affordable and available
- Rx for the disease exists
- Rx more effective if applied before Sx onset
- Rx not too risky or toxic

PLCO Cancer Screening Trial

J Nat Cancer Inst 21.12.2005

- N=154,942 enrolled 1993-2001
- 67,038 baseline CXR
- 5,991 abnormal (8.9%)
- 126 (=2.1% of abn) had Dx of LC within 1y, 44% stage I
- 6.3/1000 in current smokers
- 4.9 in ex-smokers , 0.4 in never

CT Screening MAYO clinic

(SJ Svensson et al)

- N=1,520 , >=1 non-calcified “indeterminate” nodule in N=782 (51%) = 1,646 nodules
- After 5 y CTs 3,356 NCN in N=1,118 (73.5%)
- Y0-2 : 696 other abnormal findings
- <3mm 0.2% malignant; 4-7mm :0.9%; 8-20mm: 21%, 21-30mm 33%; >30mm :all
- 48 LC : 26 (Y0) + 10 (Y1& 2), + 12 (Y3-5)
- 5 missed
- N=55 had 60 op’ s, 10/55 benign , 1 died
- T-Vol x 2 <100d =33% , 100-400 =40% , >400=27%

Of 48 cancers

NLST National Lung Screening Trial USA
N Engl J Med 4 Aug 2011

- 2002-2004 3 q1y screen with LDCT versus CXR (N=53454, 55-74y, >30pyHx)
- 90% adherence, +ve in 24.2% vs 6.9%
- 1060 vs 941 LC (50 vs 31% St I, 21 vs 36% St IV)
- 247 vs 309/100000py LC deaths
- **LC mortality: -20%**
- Any cause mortality -6.7%

NLST

N Engl J Med 4 Aug 2011

- 2002-2004 3 q1y screen with LDCT versus CXR (N=53454, 55-74y, >30pyHx)
- If +'ve screen : 2033 vs 636 invasive Procedures
- 457 vs 115 invasive Proc but not LC
- 1471 vs 397 PET scans

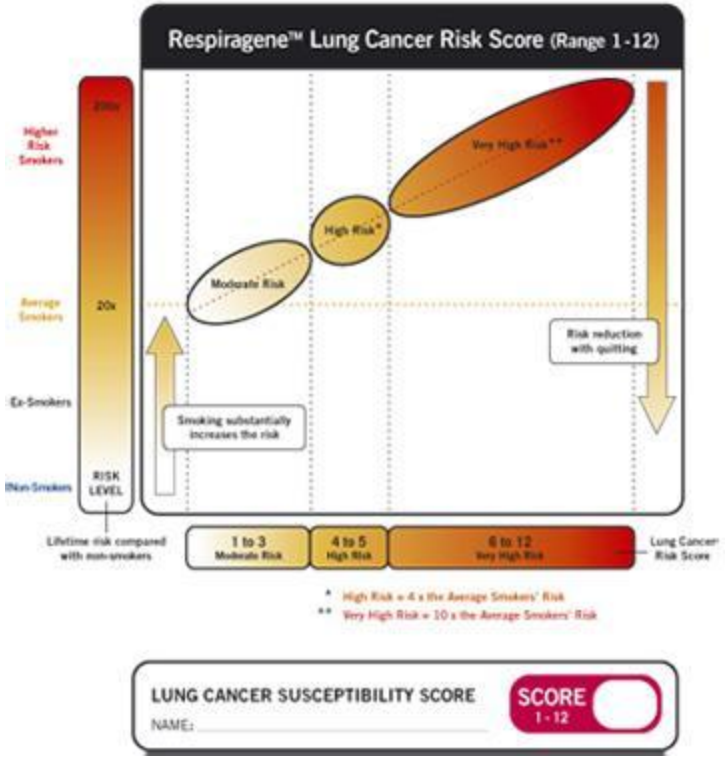
Early CDT Lung

Ann Oncol doi:10.1093/annonc/mdq361

- Trial NHS Scotland 2012
- Aim increase early detection by 25%
- Serum: 6 auto-Ab: p53, NY-ESO-1, CAGE, GBU4-5, Annexin 1, SOX2
- ? +'ve >3y earlier than CT Dx
- Sensitivity ~40%, Specificity ~90% (~Mammography for high risk young women)
- In high risk group (20/1000) PPV=7.5%, NPV=98%
- CT: PPV=2.5%, NPV=98%,

Gene Test For Lung Cancer R Young Et Al

COPD and LC are linked at a molecular genetic level through overlapping pathogenetic pathways which are activated by smoking in susceptible smokers



Gene testing- questionnaire + SNP single nucleotide polymorphism test

- “Breakthrough “ : NZ$275, £300 in UK
- RP Young et al AKL
- GP CME Rotorua 2009- wide media coverage PRESS, Dominion Post, 3 News , also UK Sun, Daily Telegraph, France Figaro…
- Known that : 25—30% of smokers develop COPD, 65-75% of LC patients have COPD
- Additive model of susceptibility: age (RR2.8), FH, COPD (FEV1 RR 6.4) – analogous to eg Gail score for breast Ca, and SNP test

Gene Testing

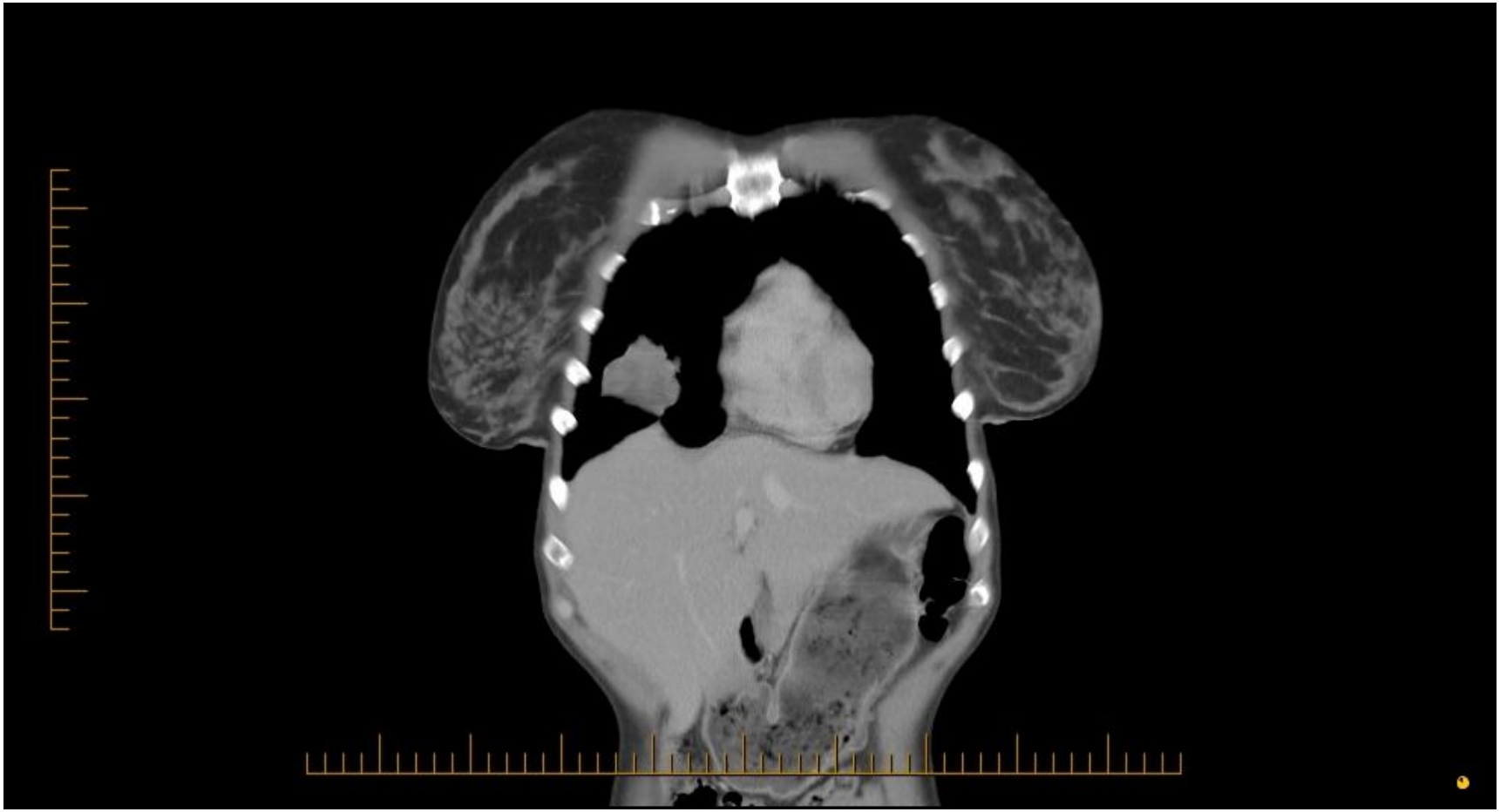
- Risk score 1-12
- 1-3 =“moderate” RR 20-30 to non-smoker, 1 in 10 will develop LC
- 4-5=“high” RR 4 to “average” smoker
- 6-12= “very high” RR 10 to “average” smoker
- Sensitivity 90%, specificity 45% at cut-off 4

Gene Testing

- Initial Case control study N=930 :446 smokers with LC , 484 “resistant” smokers
- 160 candidate SNP, from 157 genes *(matrix remodeling, inflammation /innate immunity , anti-oxidant response, apoptosis, DNA repair)*
- Prospective study N=728

Never smoker , low gene test score

50y female



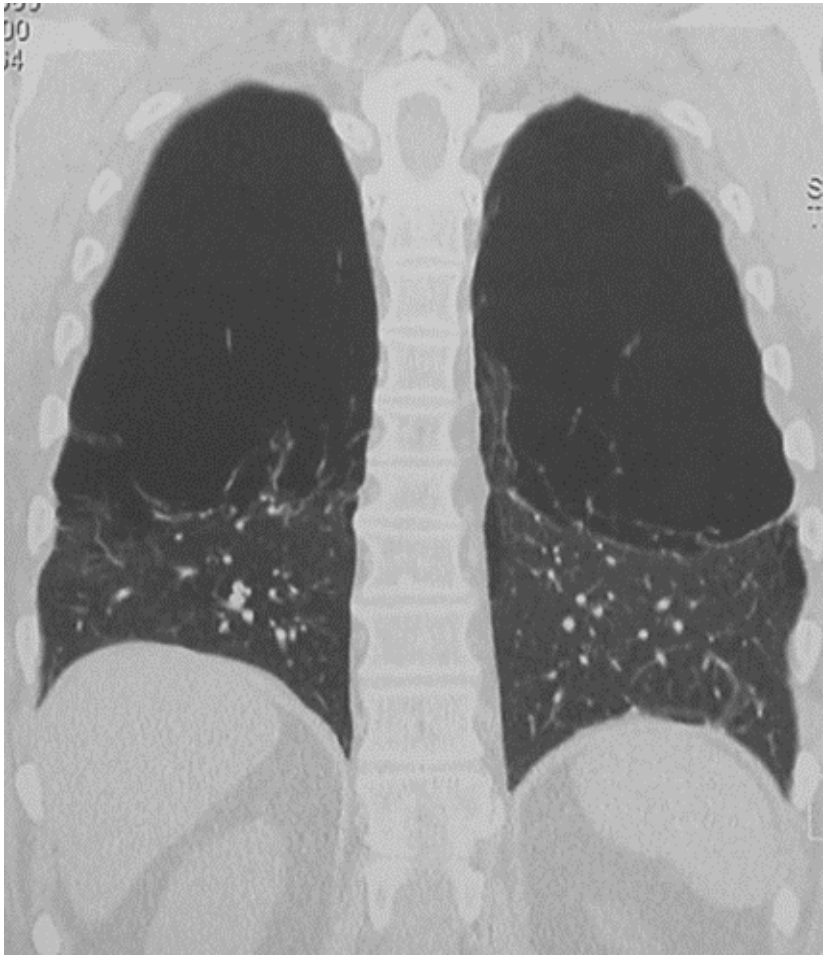
Known risk –what next ?

- Average smoker 1 in 10 chance
- Previous head and neck cancer: 1 in 5 chance
- Gene test score >6 ? Almost 1/1 chance
  +’ve early CDT

Prevention

- Prophylaxis
- Screening
- Earlier treatment ?

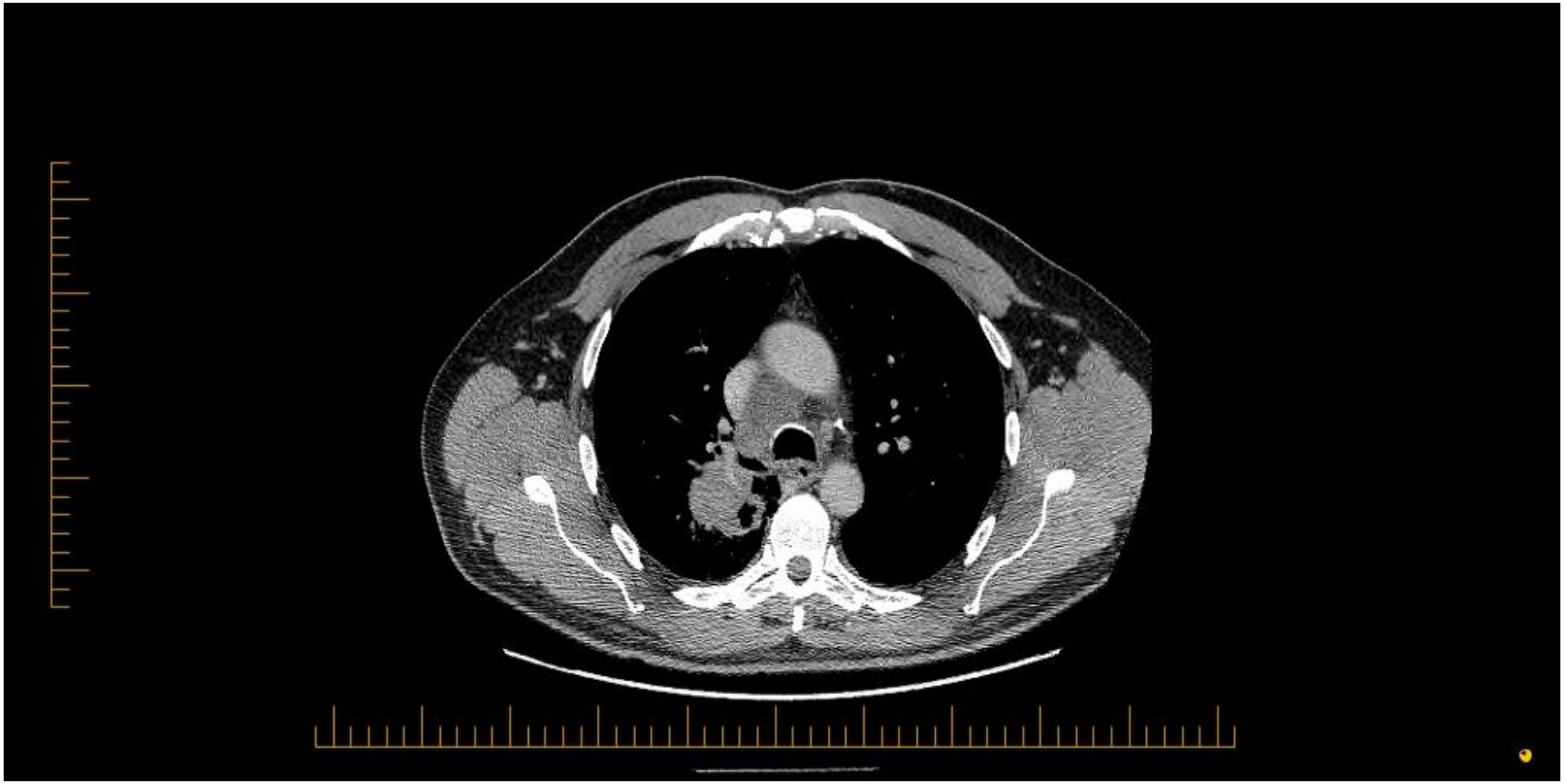
COPD Emphysema: LC risk



Lung cancer NSCLC Management

- Surgery
  - “Operable Stages” I a-II b
  - Wedge resection- Lobectomy - Pneumonectomy Sleeve resection, chest wall resection
- Chemotherapy
  - Palliative- vinorelbine
  - Adjuvant :Cisplatin based, ~5% @ 5y
  - Combined modality/ concurrent /neo-adjuvant – T4 , N2 disease
- Radiotherapy
  - Curative intent in non surgical cases (eg 20# , 52Gy)
  - Combined modality / chemo radiation
  - Local disease-palliative to 1° or to 2°
- Treat /support patient / carer/ family/ whanau

Lung Cancer CT T2N2



TNM STAGING OF LUNG CANCER

Supraclavicular	Scalene(ipsi-/contralateral)	Mediastinal (contralateral)	Mediastinal (ipsilateral)	Subcarinal	Hilar (contralateral)	Hilar (ipsilateral)	Peribronchial (ipsilateral)	LYMPH NODE (N)
+ /	+ /	+		/	+			N3
–	–	–	+ &/ +		–			N2
–	–	–	–	–	–	+ &/ + *		N1
–	–	–	–	–	–	–	–	N0

Stage IV
M1 (any T, any N)

Stage III B

Stage III A

Stage II A **Stage II B**

Stage I A **Stage I B** **Stage II B**

M0

Stage 0
(Tis, N0, M0)

T1	T2	T3	T4	PRIMARY TUMOR (T)
a&b&c	anyof a,b,c,d	(a&c)/b/d	(a&c)/d	Criteria
≤ 3 cm	> 3 cm	any	any	a. Size
No invasion proximal to the lobar bronchus	Main bronchus (≥ 2 cm distal to the carina)	Main bronchus (< 2 cm distal to the carina)	–	b. Endo-bronchial location
surrounded by lung or visceral pleura	Visceral pleura	Chest wall **/ diaphragm/ mediastinal pleura/ parietal pericardium	Mediastinum/ trachea/heart/ great vessels/ esophagus/ vertebral body/ carina	c. Local Invasion
–	Atelectasis/ obstructive pneumonitis that extends to the hilar region but doesn't involve the entire lung	Atelectasis/ obstructive pneumonitis of the entire lung	Malignant pleural/peri-cardial effusion or satellite tumor nodule(s) within the ipsilateral primary-tumor lobe of the lung	d. Other

METASTASES (M)

M0 : Abscent

M1 : Present

Separate metastatic tumor nodule(s) in the ipsilateral nonprimary-tumor lobe(s) of the lung also are classified M1

Tis : Carcinoma *in situ*

Staging is not relevant for Occult Carcinoma (Tx, N0, M0)

* Including direct extension to intrapulmonary nodes

** Including superior sulcus tumor

(& : and) (/ : or) (&/ : and /or)

Lung Cancer Prognosis

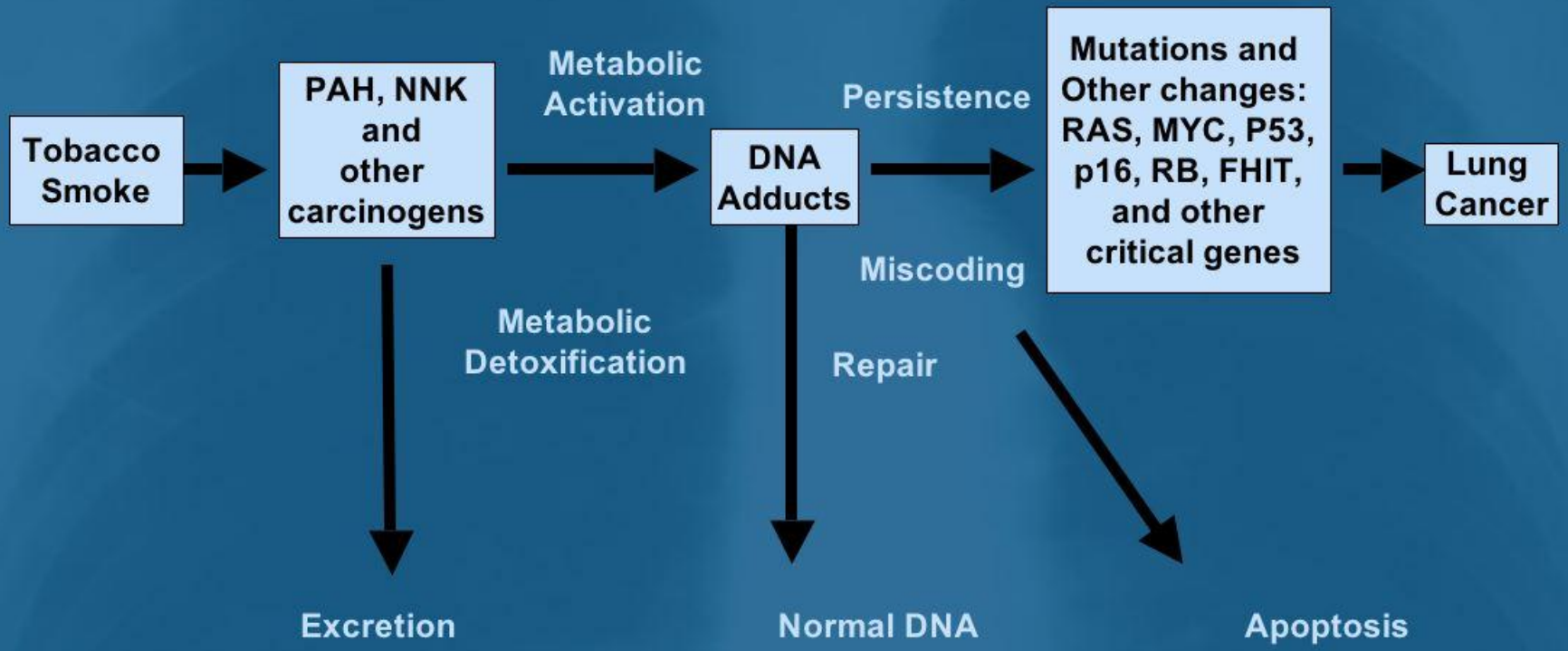
Prognosis of Non-small Cell Lung Cancer By Stage†

Clinical Stage	N	Five-year Survival (Percent)
IA	687	61
IB	1189	38
IIA	29	34
IIB	357	24
IIIA	511	13
IIIB	1030	5
IV	1427	1

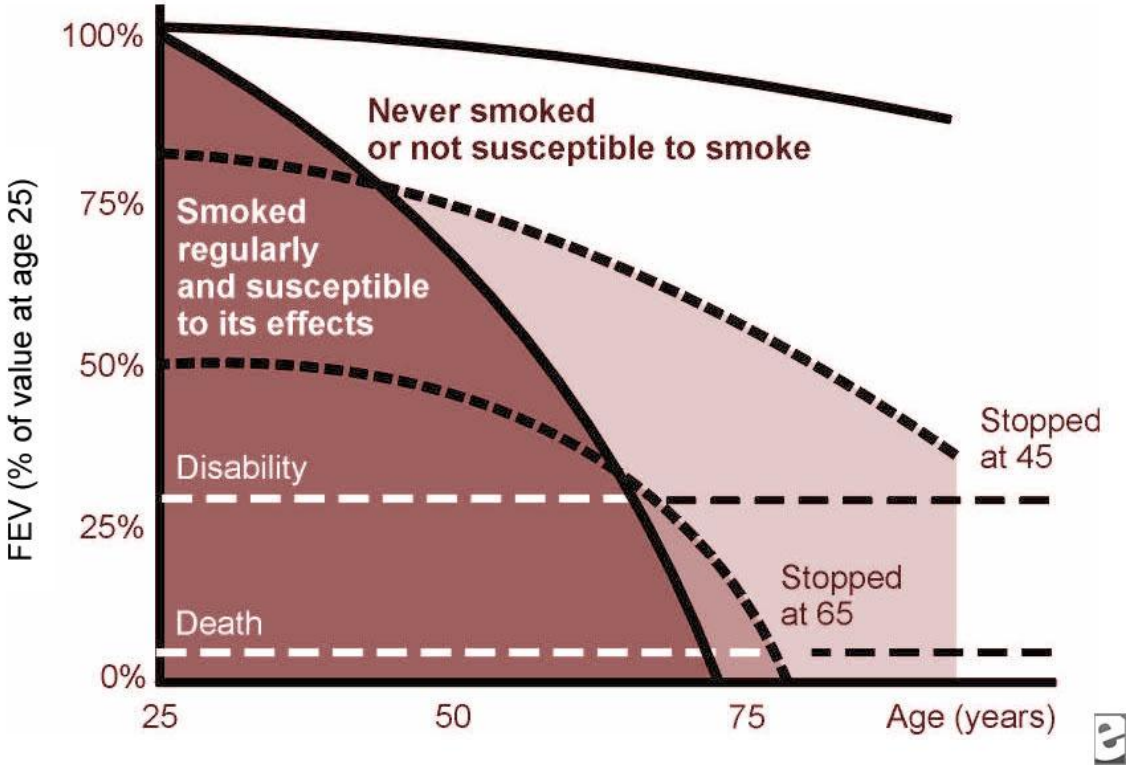
†Adapted from Mountain, CF, Chest 1997; 11 :1710. Data are from 4351 patients treated at the University of Texas MD Anderson Cancer Center and 968 patients treated by the National Cancer Institute cooperative Lung Cancer Study Group between 1975 and 1988.

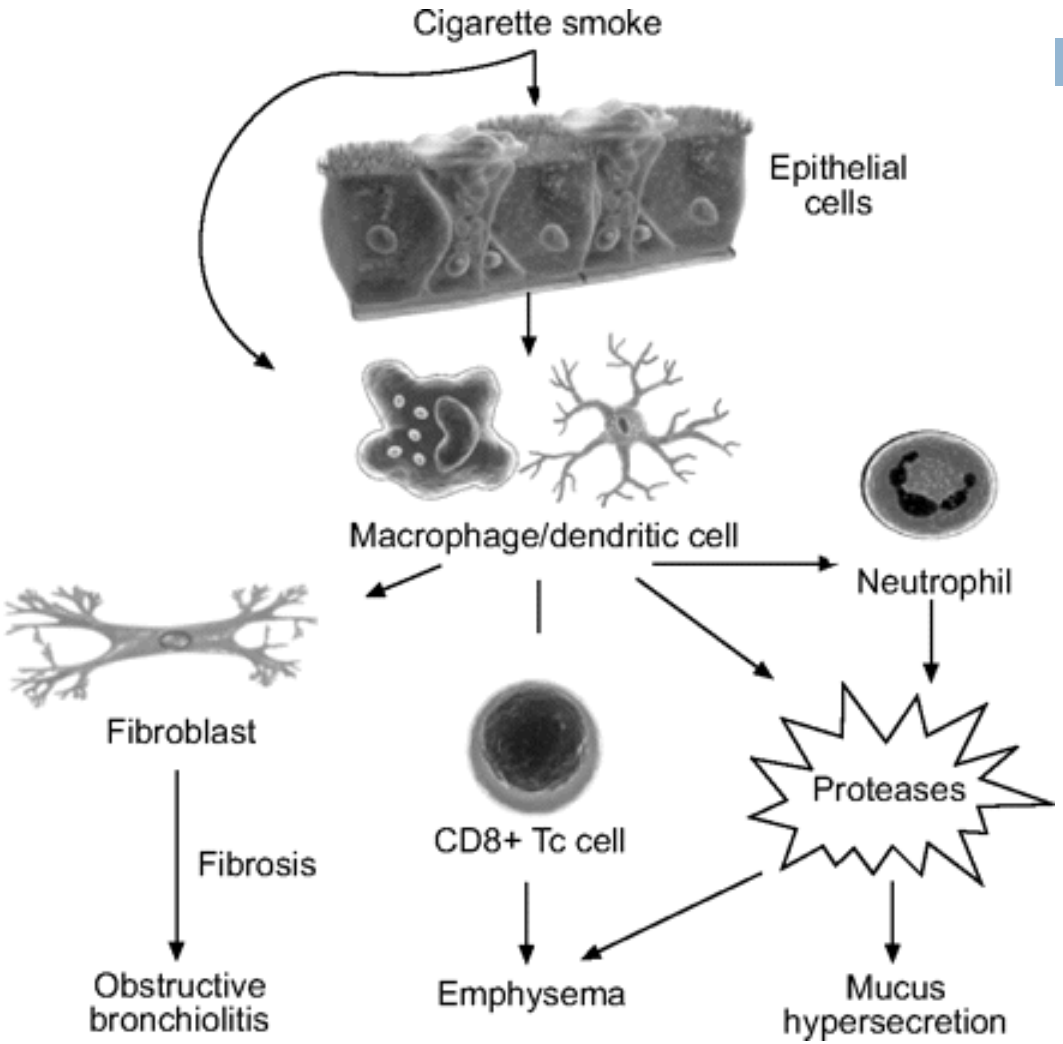
Tobacco Smoke And Lung Cancer

Causal Pathway



Susceptible lungs- Fletcher/Peto Diagram COPD … but also LC




Cigarette smoke
Epithelial cells
Macrophage/dendritic cell
Neutrophil
Fibroblast
Fibrosis
CD8+ Tc cell
Proteases
Obstructive bronchiolitis
Emphysema
Mucus hypersecretion