LUNG CANCER

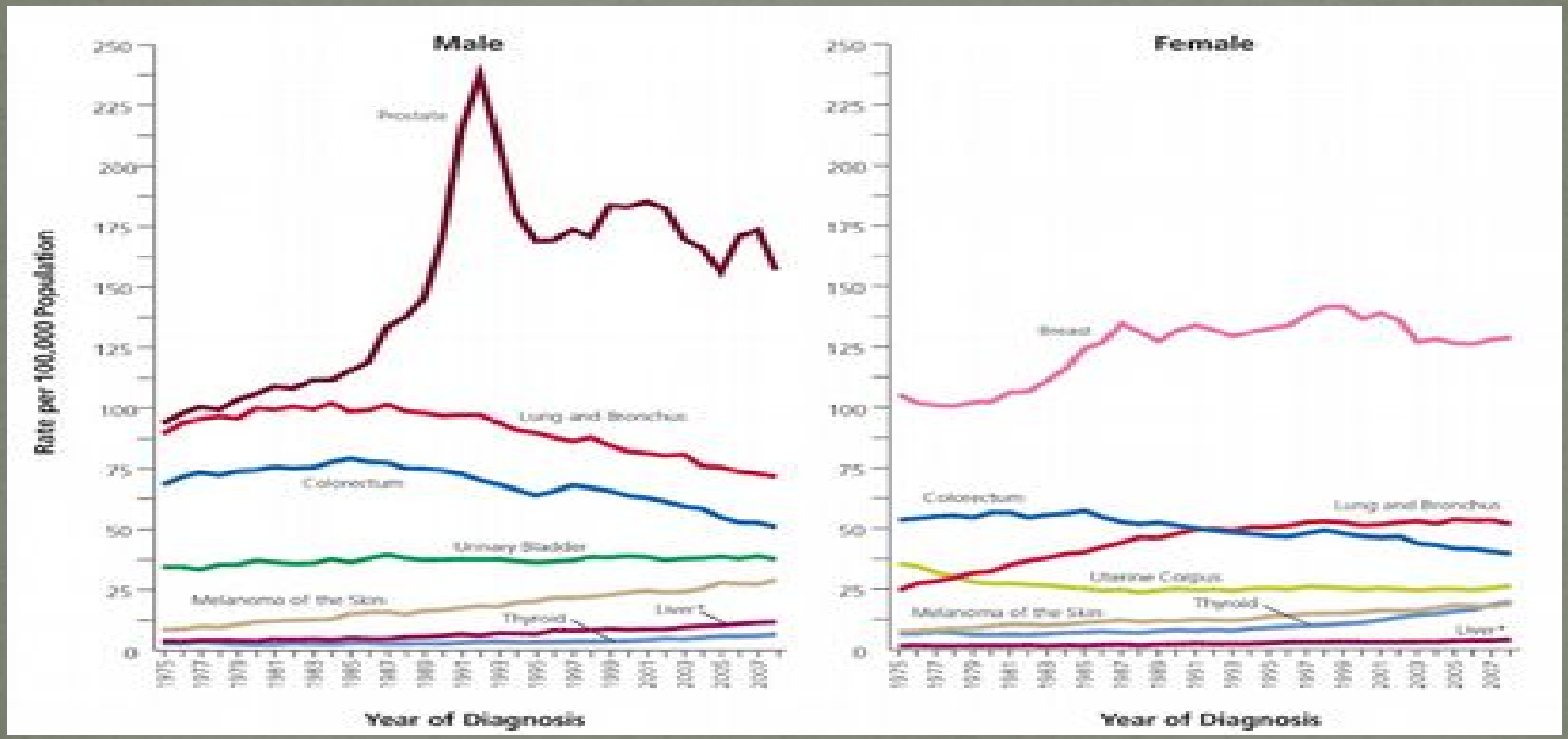
Agnieszka Słowik, MD

Department of Oncology, University Hospital in Cracow

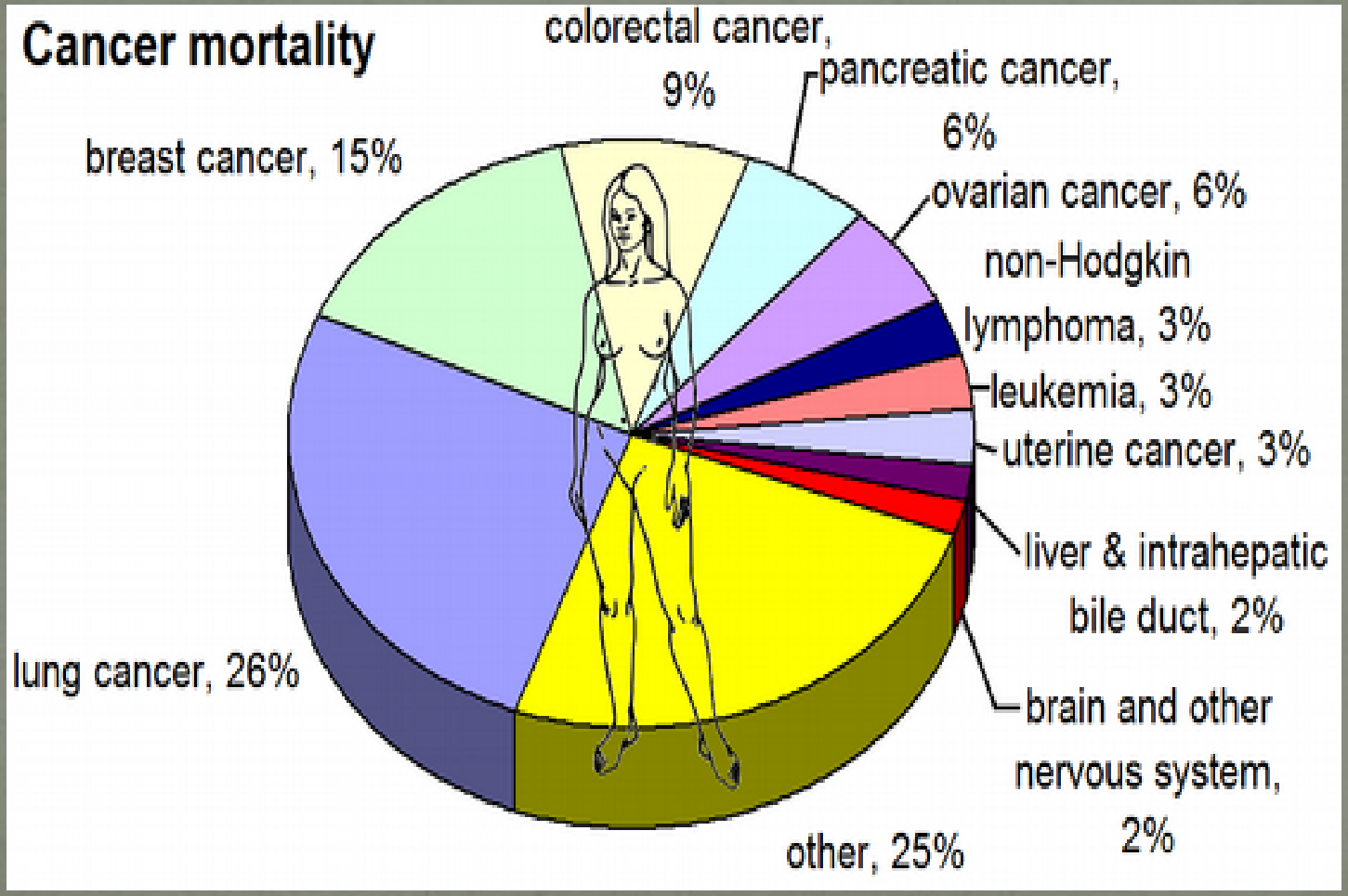
Jagiellonian University

Epidemiology

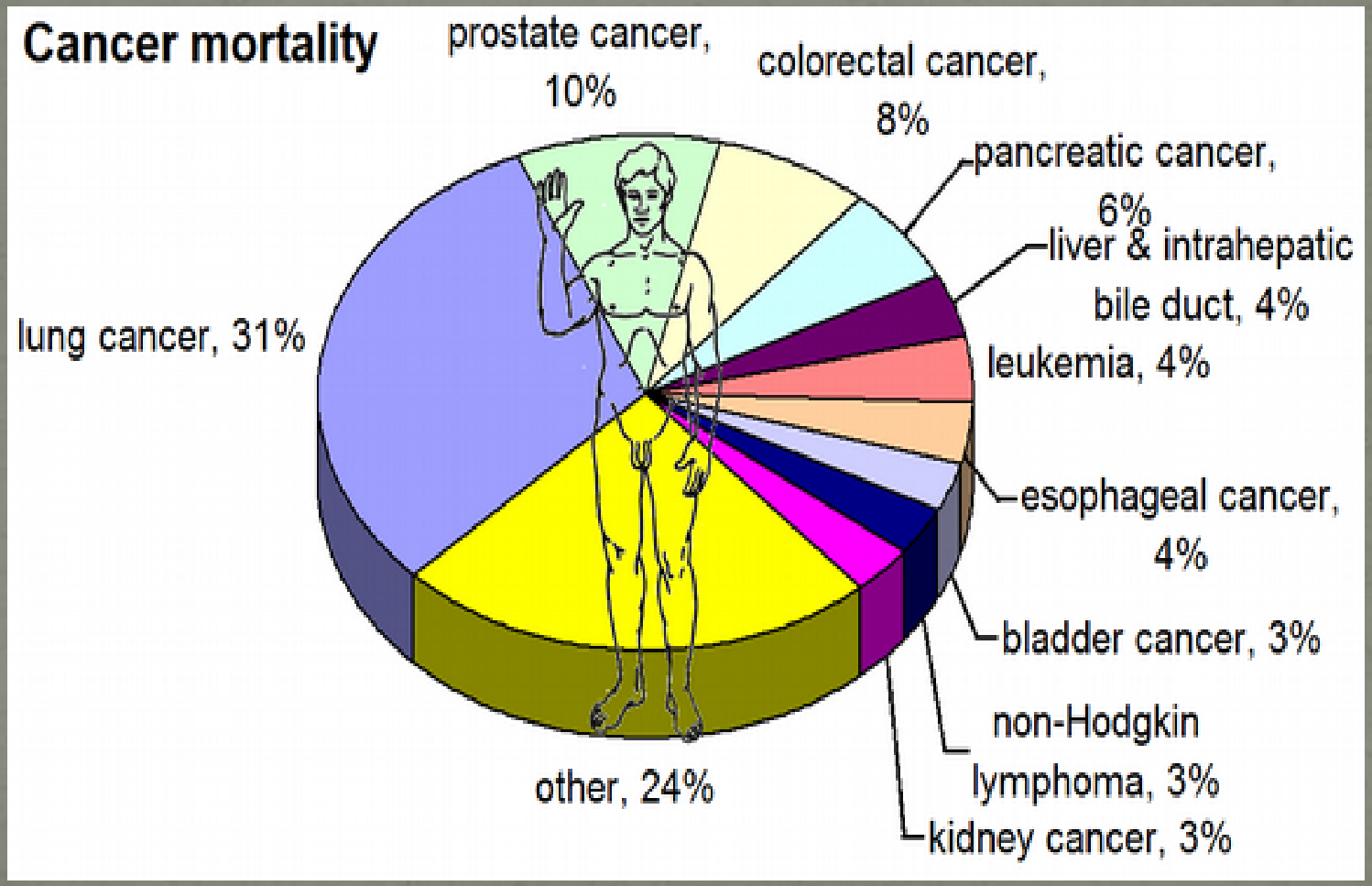
- Most common malignancy worldwide



Place of lung cancer among other malignancies - females

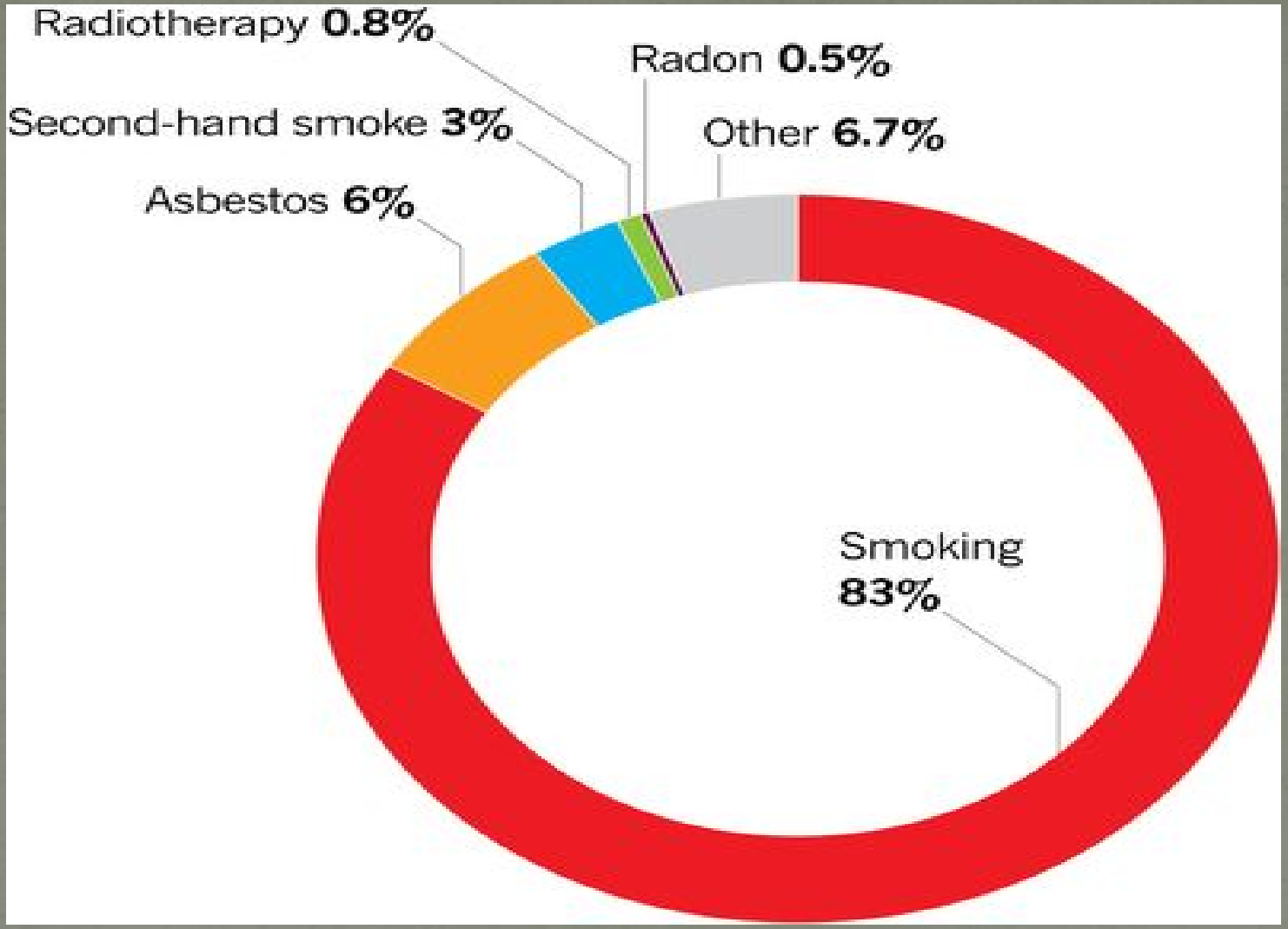


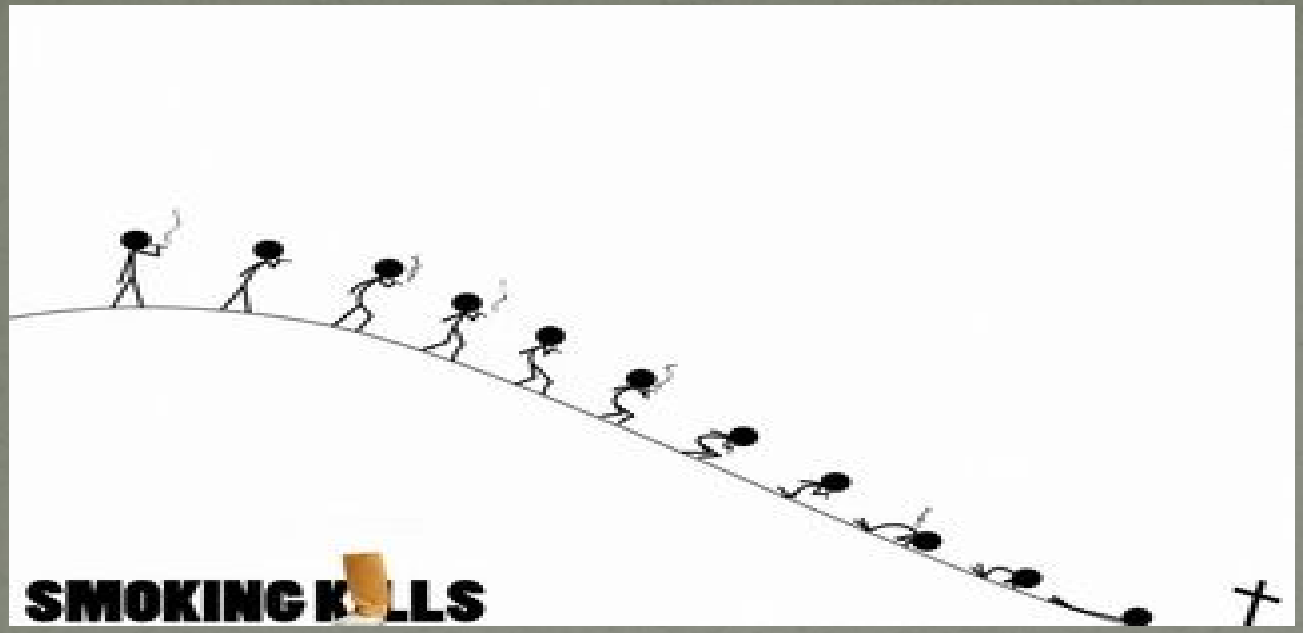
Place of lung cancer among other malignancies - males

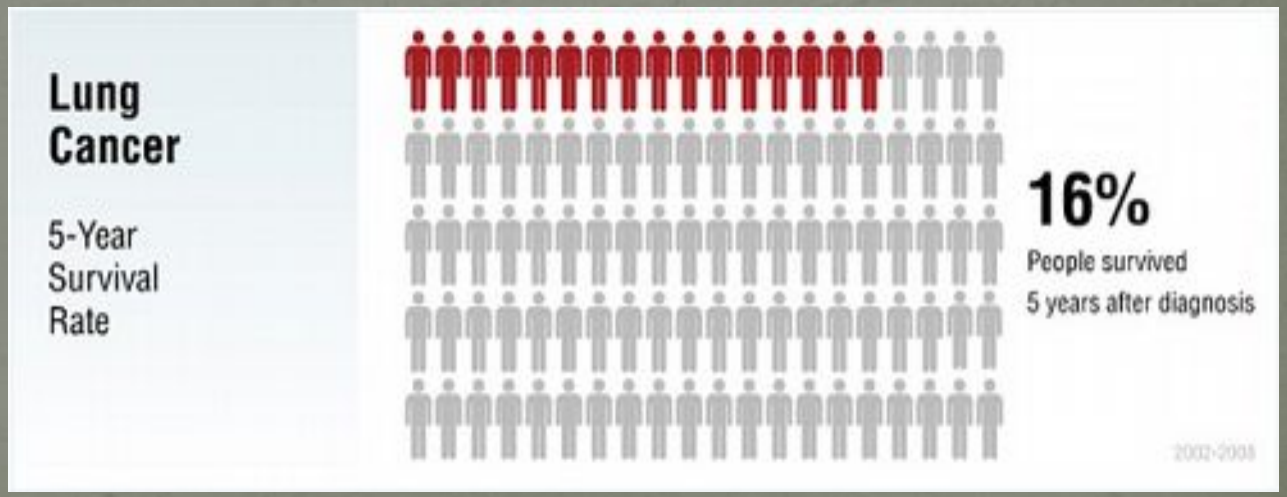


Etiology

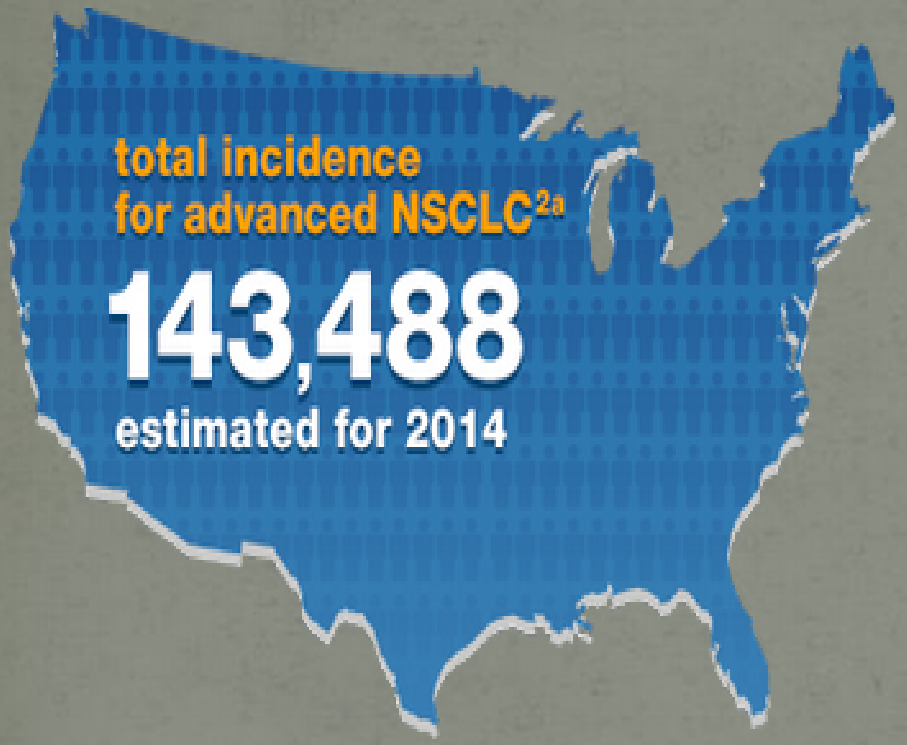
- **Smoking** – responsible for more than 80% of lung cancer, smoking 20 cigarettes per day increases one's risk of cancer 20-fold;
- **Second-hand smoke** - 30% increased risk
- **Asbestos** – especially when combined with smoking (90-fold increased risk)
- Other


Radiotherapy 0.8%
Radon 0.5%
Second-hand smoke 3%
Other 6.7%
Asbestos 6%
Smoking
83%


SMOKING KILLS


Lung Cancer
5-Year Survival Rate
16%
People survived 5 years after diagnosis

Poor prognosis



stage at diagnosis[1]

60%

5-year survival[3]

only
4%

more than
100,000 deaths from lung cancer each year[1]

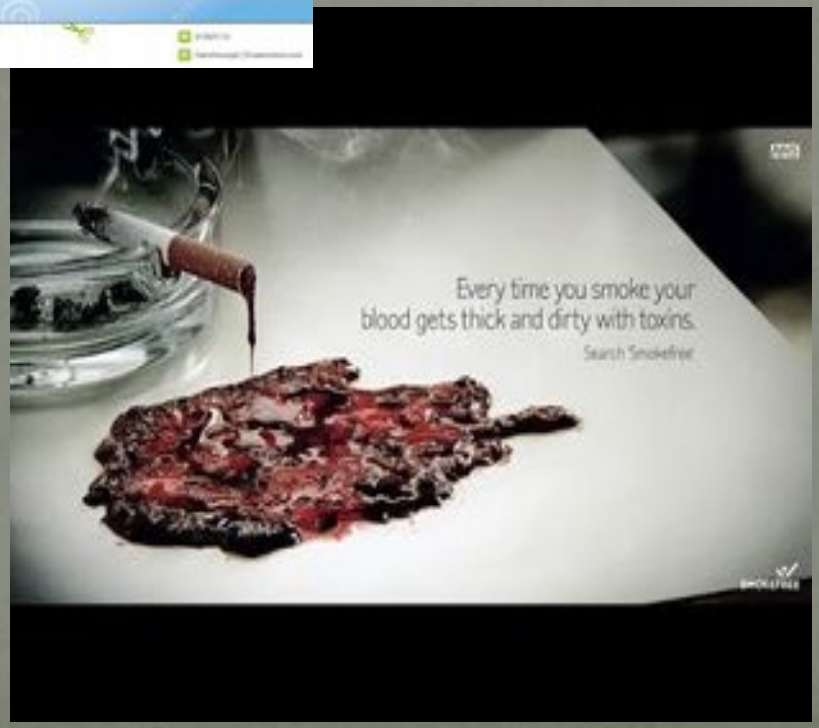
What
can we do to change this?

Primary prevention
Better

treatment

Secondary

prevention



Prevention

Media/Other:

a. Information
b. Consequeces
c. Awareness
d. Fear
e. Policies
f. Motivation

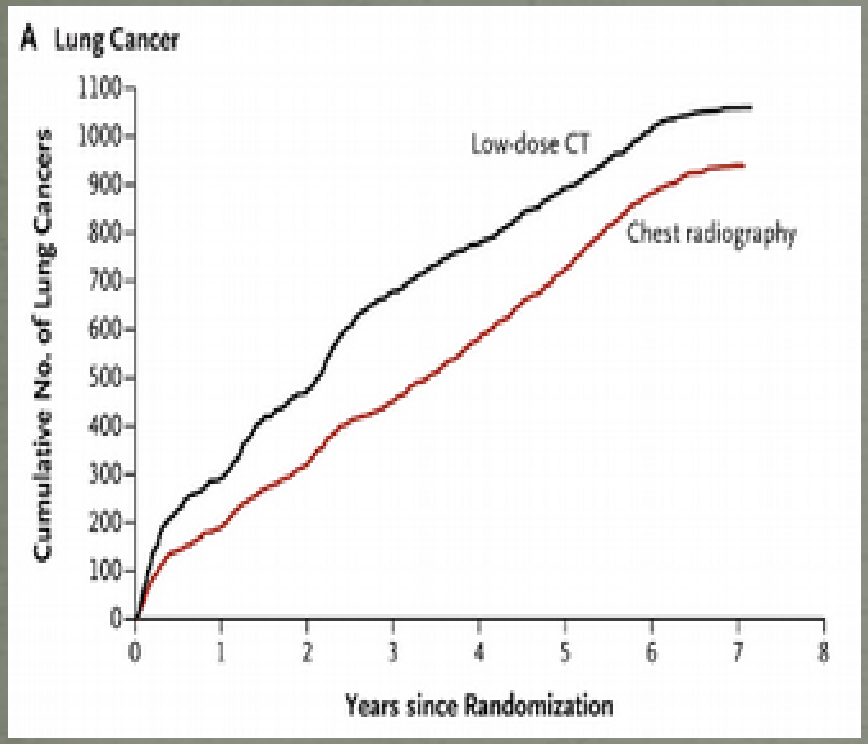
↓

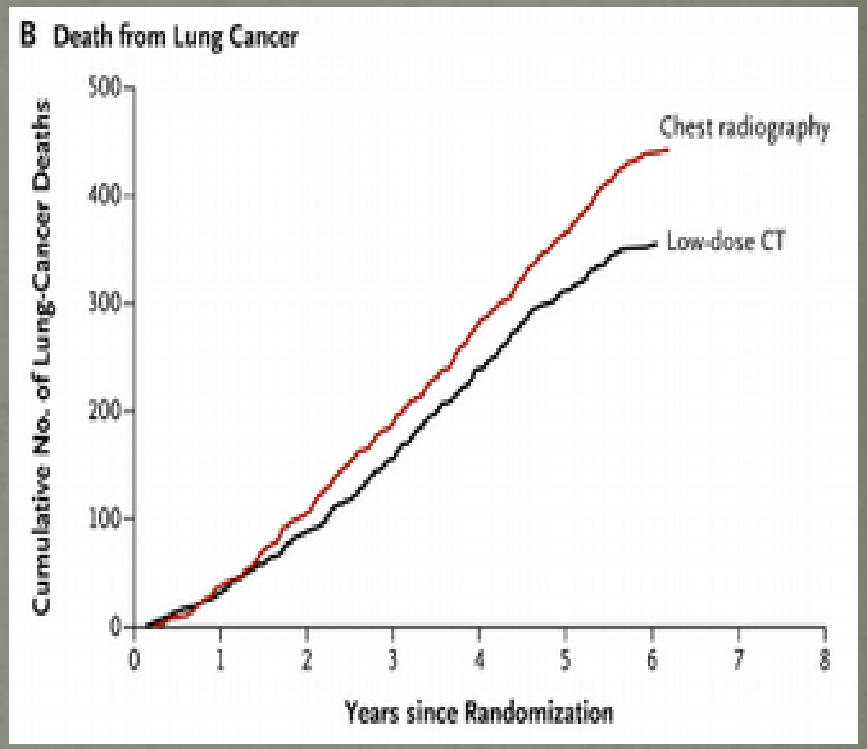
Changing behaviour/ habits!

Screening

Is there any screening method that proved to be effective in diagnosis of unsymptomatic lung cancer?

The National Lung Screening Trial (NLST)





National Lung Screening Trial Research Team. N Engl J Med 2011; 365: 395-409.

- A total of 1060 lung cancers (645 per 100,000 person-years) were diagnosed in the low-dose CT group, as compared with 941 (572 per 100,000 person-years) in the radiography group (rate ratio, 1.13; 95% confidence interval [CI], 1.03 to 1.23).

- 20.0% decrease in mortality from lung cancer was observed in the low-dose CT group as compared with the radiography group.

SYMPTOMS

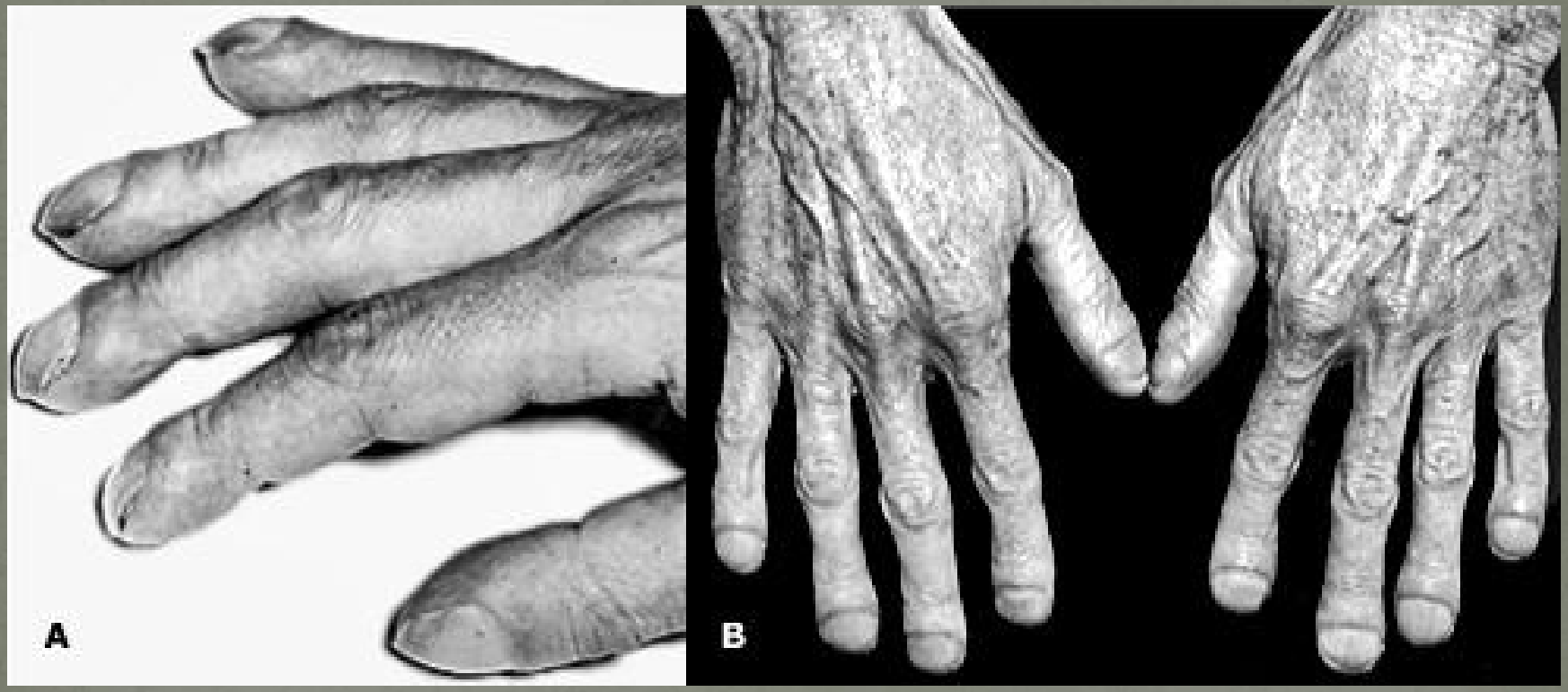
- Cough – 80% of symptomatic pts,
- Dyspnea, stridor, haemopytsis
- Reccuring pnaeumonia – bronchi obstruction
- Pleural effusion (exudate)
- Chest pain
- Shoulder and arm pain
- Horner’s syndrome
- Unilateral diaphargm paresis

SYMPTOMS

Do know what kind of symptoms is it?

Do you know it may be a first symptom of undergoing malignant process?

Clubbing



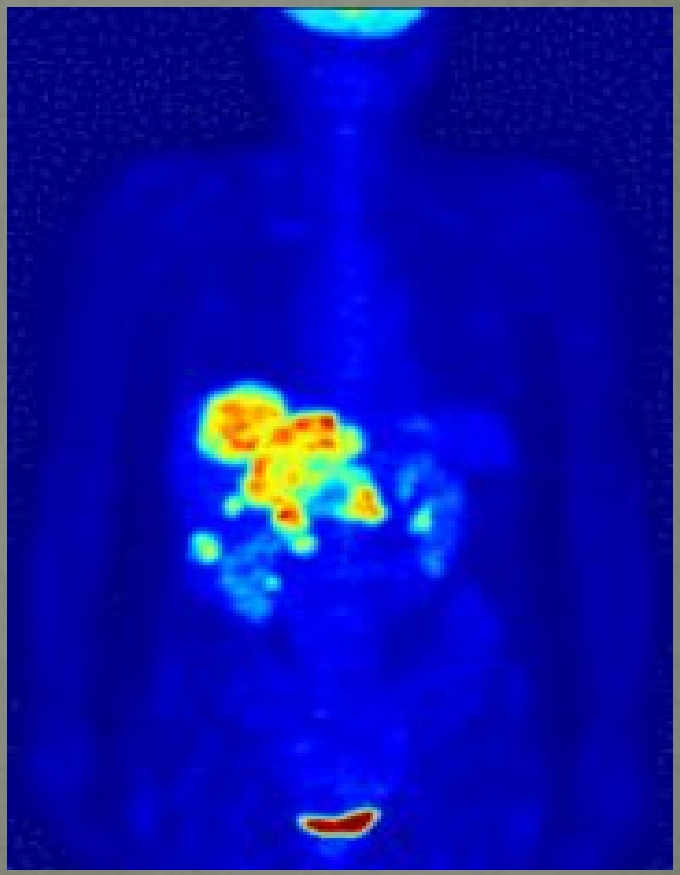
Lung cancer – Dx& staging

- History and physical examination
- Chest X-ray
- CT scan – chest and upper abdomen (liver and adrenal glands), mediastinal lymph nodes
- PET – distant metastases, mediastinal lymph nodes (+/-)
- Histology/cytology:
  - Central tumors: bronchoscopy,
  - Peripherial tumors – transthoracic needle biopsy, thoracotomy

Staging

- PET scan

  Treatment strategy change in up to 40% of patients.



Staging

- Mediastinoscopy – medistinal lymph nodes biopsy (neoadjuvant treatment beneficial in N2 positive cases)
- EBUS/EUS
- Thoracoscopy and thoracentesis

Staging NSCLC

The most common sites of metastases

BLAB

Bone – **L**iver – **A**drenals – **B**rain

Lung cancer often diagnosed already when there are metastases present!

8th edition of TNM for LC

8th Edition of the TNM Classification for Lung Cancer

	N0	N1	N2	N3	M1 a	M1 b	M1c
T1a	IA1	IIB	IIIA	IIIB	IVA	IVA	IVB
T1b	IA2	IIB	IIIA	IIIB	IVA	IVA	IVB
T1c	IA3	IIB	IIIA	IIIB	IVA	IVA	IVB
T2a	IB	IIB	IIIA	IIIB	IVA	IVA	IVB
T2b	IIA	IIB	IIIA	IIIB	IVA	IVA	IVB
T3	IIB	IIIA	IIIB	IIIC	IVA	IVA	IVB
T4	IIIA	IIIA	IIIB	IIIC	IVA	IVA	IVB

International Association for the Study of Lung Cancer, 2015

What changed?

T-descriptor

Every cm counts…

Proposed (TNM 8th)	*Previous (TNM 7th)*
Up to 1 cm: T1a	T1a
>1-2 cm: T1b	T1a
>2-3 cm: T1c	T1b
>3-4 cm: T2a	T2a
>4-5 cm: T2b	T2a
>5-7 cm: T3	T2b
>7 cm: T4	T3

Rami-Porta R, J Thoracic Oncol, 2015
International Association for the Study of Lung Cancer, 2015

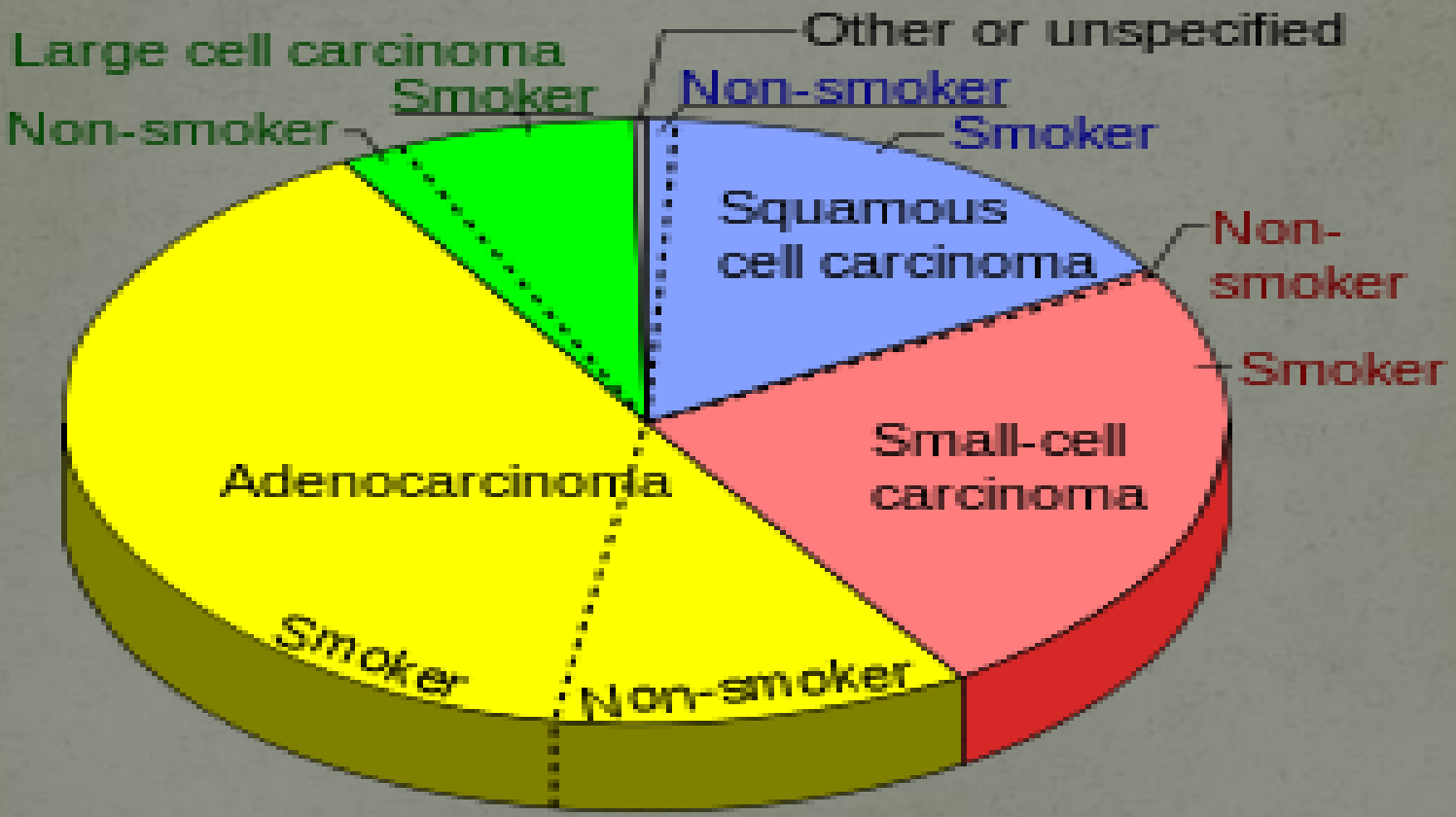
LUNG CANCER

Non-small cell LC (NSCLC) **87%**

- **Adenocarcinoma**
- **Squamous cell carcinoma**
- **Large cell carcinoma**
- **NOS carcinoma**

Small cell LC (SCLC)
13%

Histopathology&Smoking



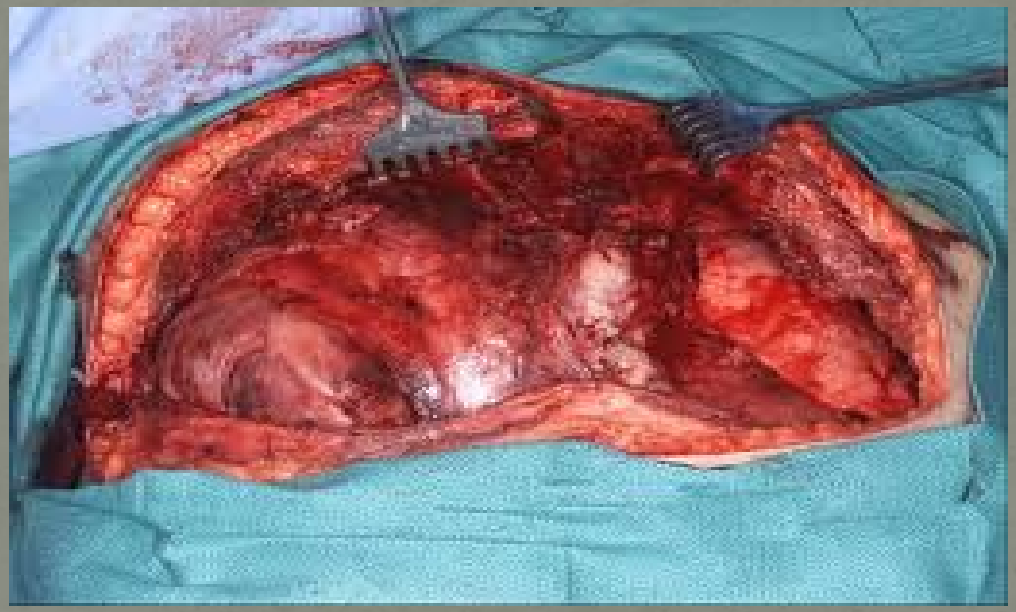
LUNG CANCER TREATMENT

MULTIDISCIPLINARY TEAM:

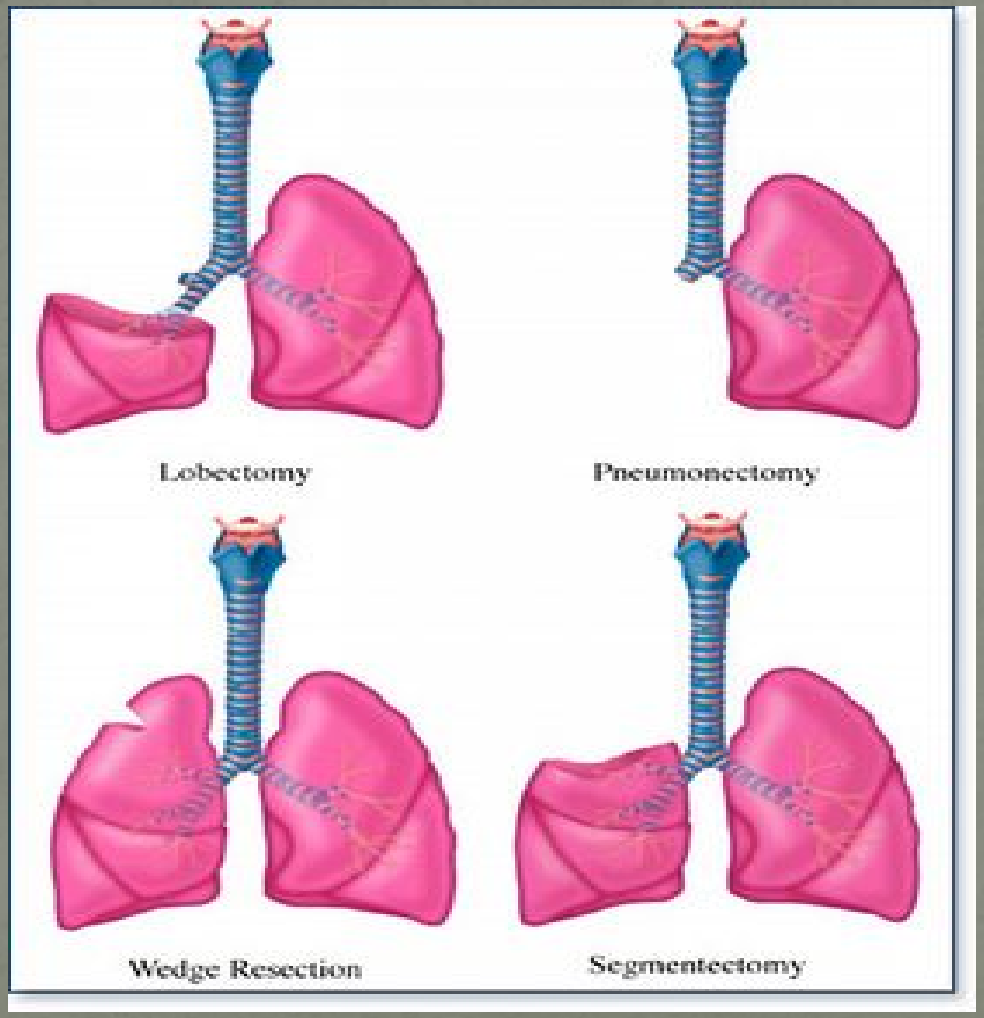
- SURGEON
- ONCOLOGIST
- RADIOLOGIST
- RADIOTHERAPIST
- PALLIATIVE CARE
- REHABILITATION

NSCLC - Surgery

Stage IA – IIIA

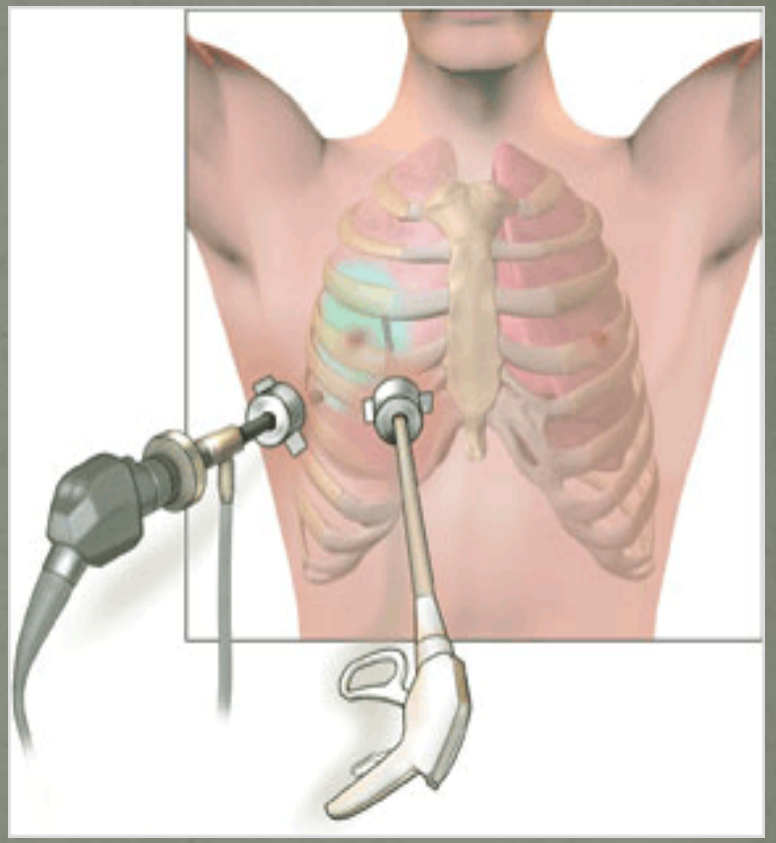


NSCLC - Surgery



VATS

- VATS
- Peripheral tumors up to 6 cm
- Neither hilar nor mediastinal adenopathy



NSCLC - Radiation therapy

- **Adjuvant RTH**
- N2 postivie ?
- R1 resection

(=positive surgical margins

- Narrow margins

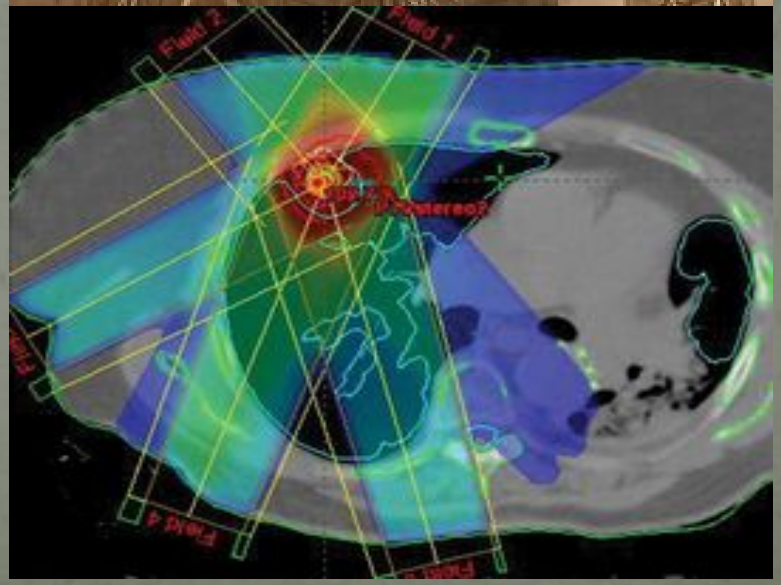
NSCLC - Radiation therapy

- Stereotactic
- RadioSurgery (SBS/SBRT)

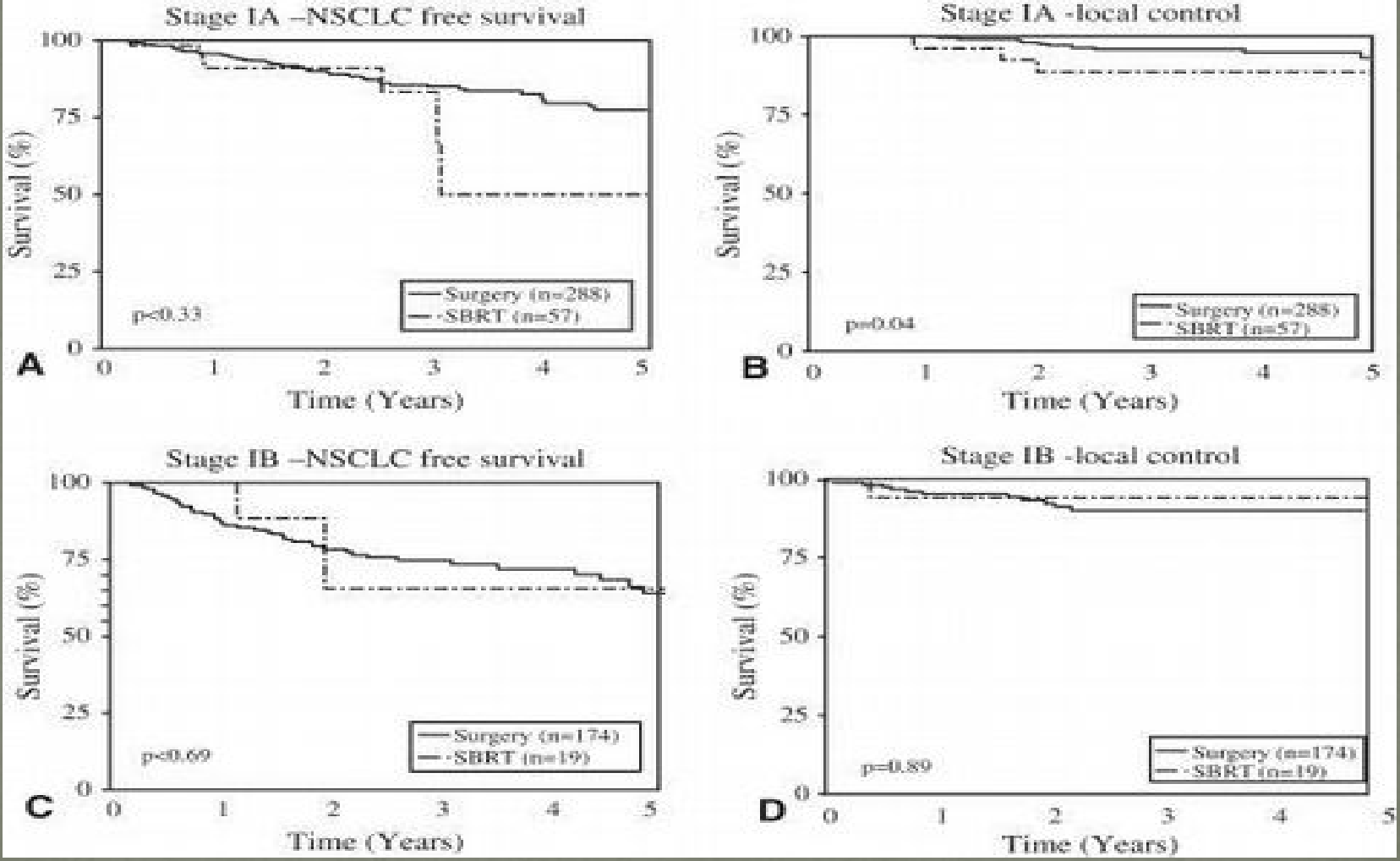
- Precise delivery of high doses of radiation to the limited volume of tissue in hypofractionated schedule.

NSCLC - Radiation therapy

- Non-small cell lung cancer
- T1-T2 N0 M0
- Peripheral tumor
- Medicaly unfit to undergo sugery
- Declined surgery



NSCLC - Radiation therapy (SRS)



NSCLC - Radiation therapy

Palliative RTH:

- Bone metastases
- Brain metastases
- Local control (haemoptysis, dyspnea)

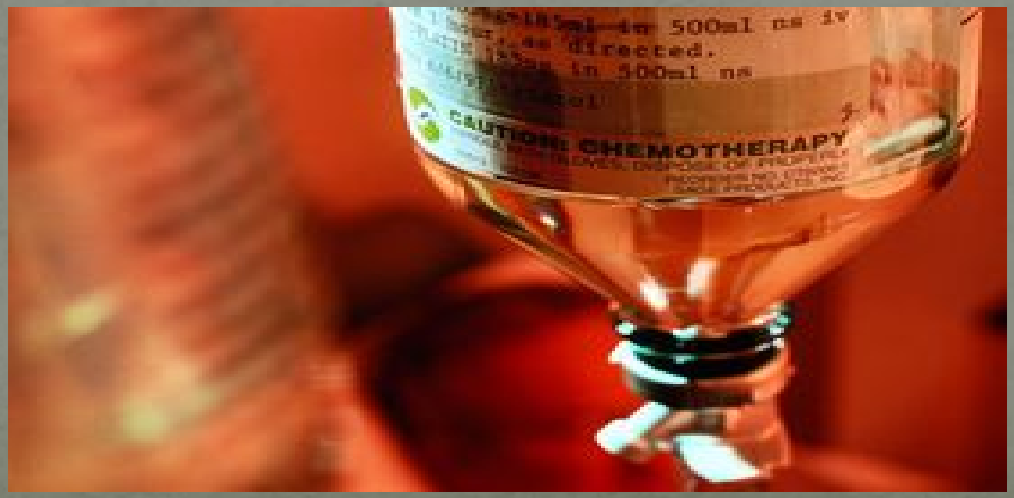
NSCLC – Adjuvant Chemotherapy

IB (tumor diameter > 4 cm), IIA, IIB, IIIA

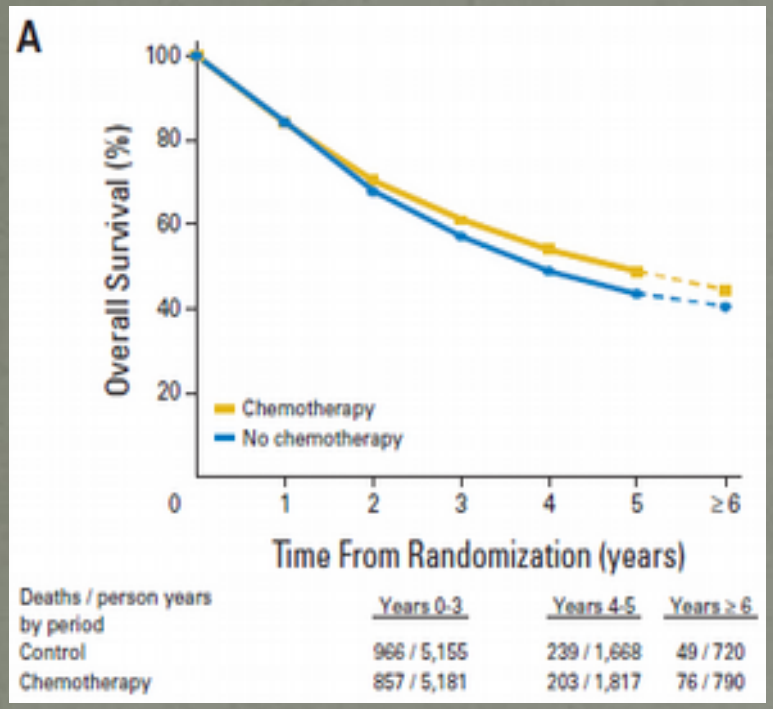
Adjuvant chemotherapy

Two cytostatics

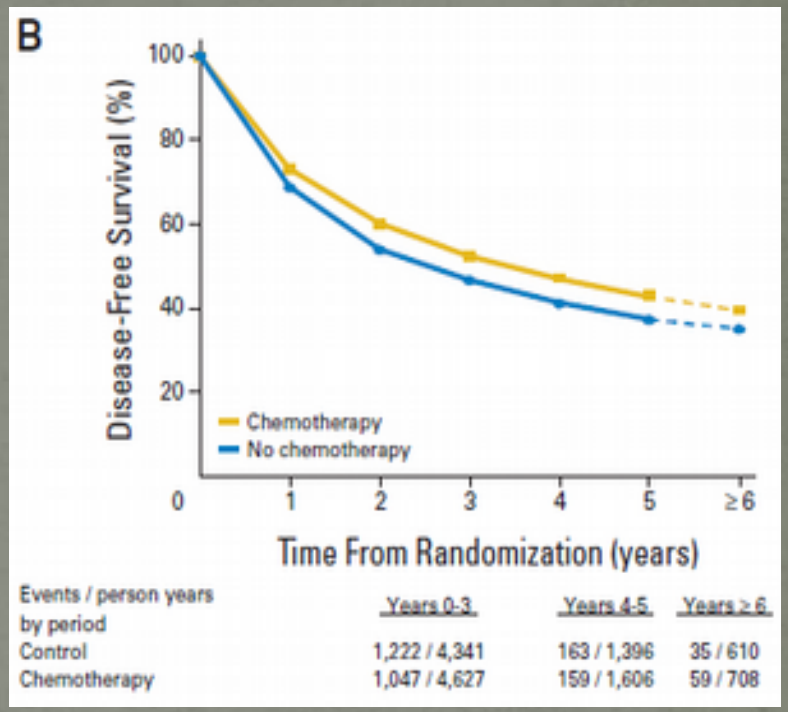
cisplatin + vinorelbine, 4 cycles, q3w



NSCLC - Adjuvant Chemotherapy



Deaths / person years by period	Years 0-3	Years 4-5	Years ≥ 6
Control	966 / 5,155	239 / 1,668	49 / 720
Chemotherapy	857 / 5,181	203 / 1,817	76 / 790

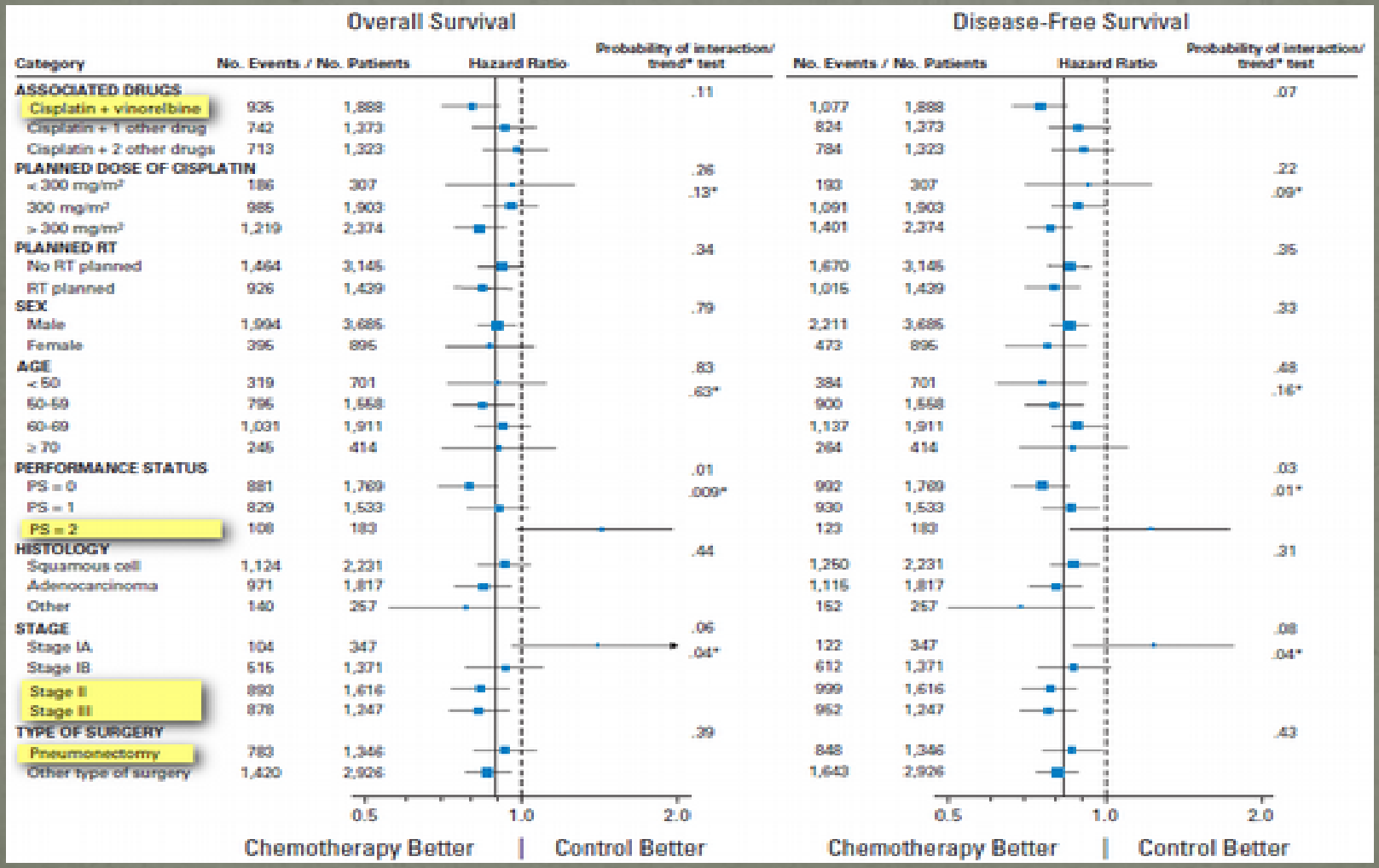


Events / person years by period	Years 0-3	Years 4-5	Years ≥ 6
Control	1,222 / 4,341	163 / 1,396	35 / 610
Chemotherapy	1,047 / 4,627	159 / 1,606	59 / 708

Adjuvant chemotherapy - benefit in OS and DFS

Pignon JP et al. *J Clin Oncol 2008;26:3552-3559*

NSCLC - Adjuvant Chemotherapy



NSCLC – Adjuvant Chemotherapy

Table 5. Chemotherapy Regimens Delivered in Major Trials

Trial	No. of Patients	Agent	Dose (mg/m²/d)
ALPI	1,088	Cisplatin	100 every 3 weeks for 3 cycles
		Mitomycin	8 every 3 weeks for 3 cycles
		Vinblastine	3 every 3 weeks for 3 cycles
IALT	**1,867**	**Cisplatin**	**80-120 every 3 or 4 weeks for 3 or 4 cycles**
		Vinorelbine*	**30 every week to last cisplatin administration**
		Vinblastine†	**4 every week for 5 weeks, then every 2 weeks until last cisplatin administration**
		Etoposide‡	**100 days 1-3 with each cisplatin**
CALGB 9633	344	Carboplatin	AUC 6 every 3 weeks for 4 cycles
		Paclitaxel	200 every 3 weeks for 4 cycles
NCIC-CTG JBR.10	**482**	**Cisplatin**	**50 day 1 and 8 every 4 weeks for 4 cycles**
		Vinorelbine	**25 every week for 16 cycles**
ANITA	**840**	**Cisplatin**	**100 every 4 weeks for 4 cycles**
		Vinorelbine	**30 every 4 weeks for 4 cycles**

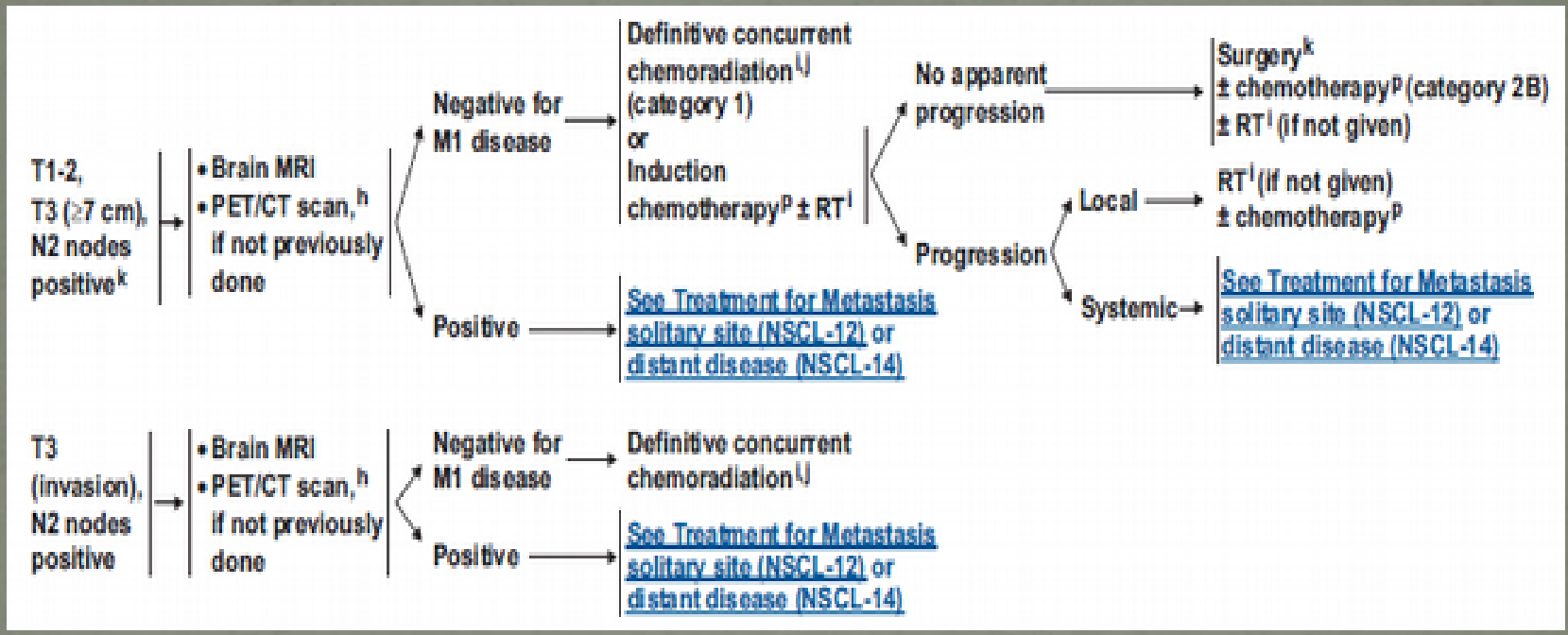
NOTE. Regimens displayed in bold were associated with statistically significant survival results.
Abbreviations: ALPI, Adjuvant Lung Project Italy; IALT, International Adjuvant Lung Cancer Trial; CALGB, Cancer and Leukemia Group B; AUC, area under the curve 6 mg/mL·minute; NCIC-CTG JBR.10, National Cancer Institute of Canada Clinical Trials Group JBR.10; ANITA, Adjuvant Navelbine International Trialist Association trial.
*27% of patients received vinorelbine and cisplatin.
†11% of patients received vinblastine and cisplatin.
‡57% of patients received etoposide and cisplatin.

NSCLC IIIA

Stage IIIA (**N2**) NSCLC

Multidisciplinary treatment

NSCLC III A (N2)

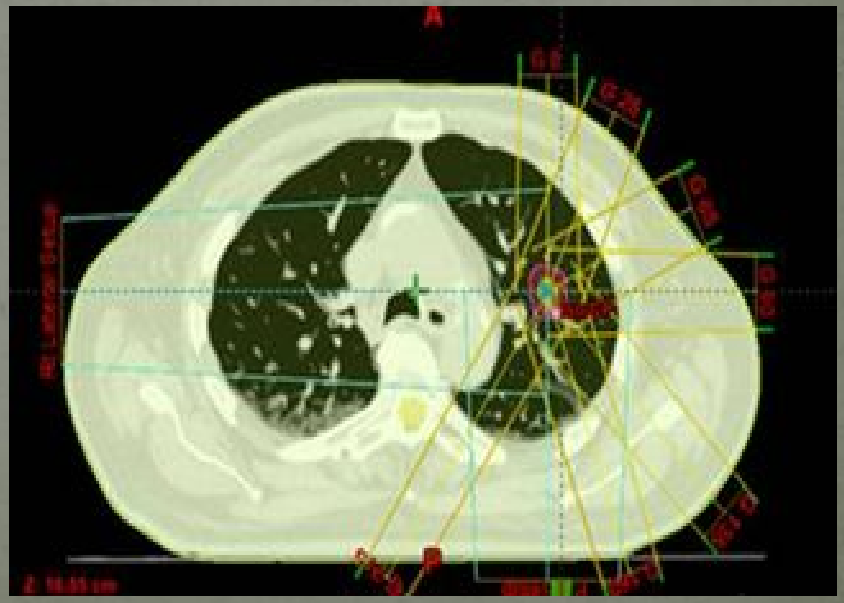


NCCN National Comprehensive Cancer Network®

NSCLC – Stage IIIB

Stage III B

Chemoradiotherapy



NSCLC

Stage IIIB chemoradiation

Concurrent

- Better outcomes outcomes
- Higher toxicity

Sequential

- Worse
- Lower toxicity

NSCLC – palliative chemotherapy

Stage IV – metastatic disease

Palliative chemotherapy

NSCLC – palliative chemotherapy

Table 1. Comparison of two-drug combinations

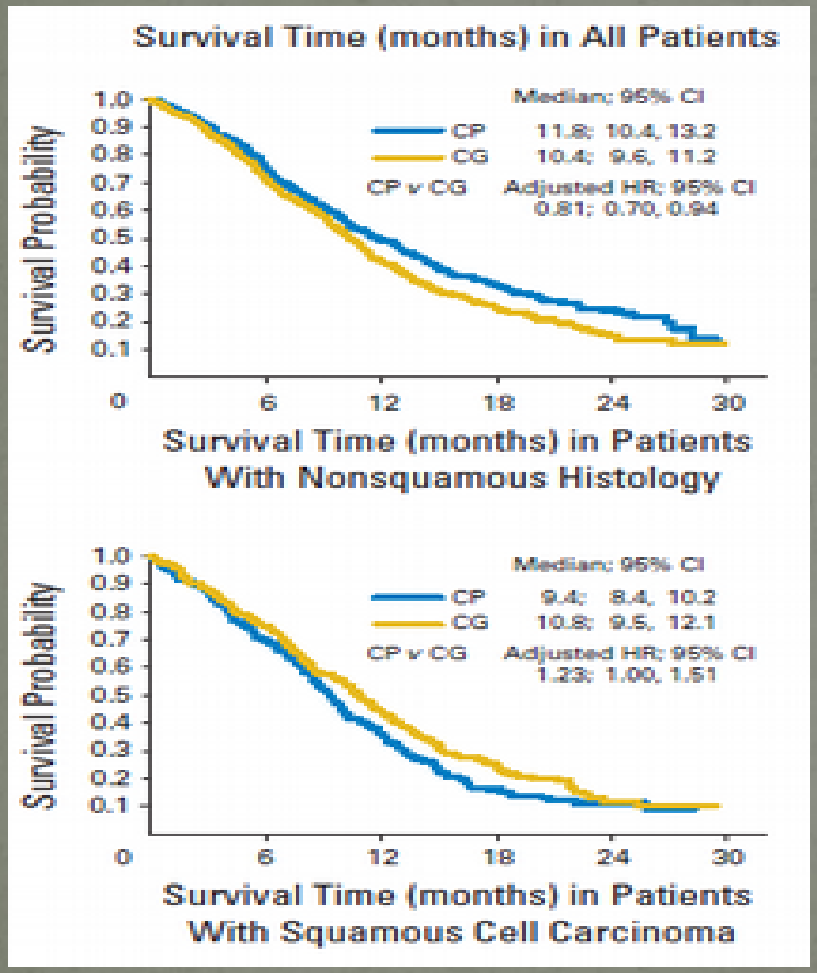
Study	Regimen	Response rate	Median survival (months)	1-Year survival
Belani et al. [41], $n = 369$	Cisplatin + etoposide	15%	9.0	37%
	Carboplatin + paclitaxel	23%	7.8	32%
Schiller et al. [10], ECOG 1594, $n = 1,155$	Cisplatin + paclitaxel	21%	7.8	31%
	Cisplatin + gemcitabine	21%	8.1	36%
	Cisplatin + docetaxel	17%	7.4	31%
	Carboplatin + paclitaxel	16%	8.1	34%
Fossella et al. [22], TAX 326, $n = 1,218$	Cisplatin + vinorelbine	25%	10.1	41%
	Cisplatin + docetaxel	32%[a]	11.3	46%
	Carboplatin + docetaxel	24%	9.4	38%
Kelly et al. [11], SWOG 9509, $n = 408$	Cisplatin+ vinorelbine	28%	8.1	36%
	Carboplatin + paclitaxel	24%	8.6	38%

[a] $p = .029$.

- Two – drugs combinations in patients in good general condition
- The basic drug –

  CISPLATIN
- Similar outcomes

What kind of regimen to use?



- Pemetrexed + cisplatin better in non-squamous cell group
- Gemcitabin + cisplatin better in squamous cell group

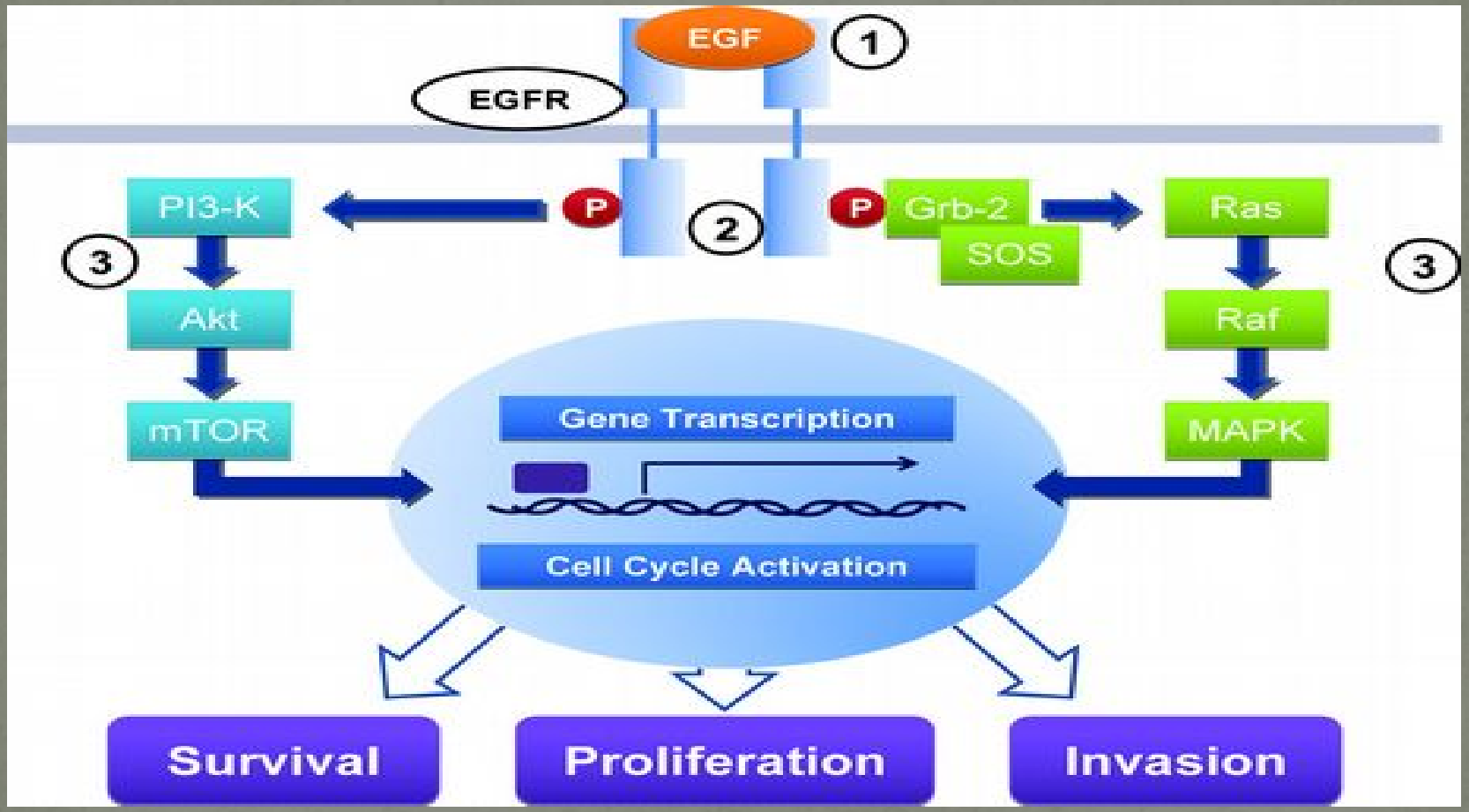
NSCLC – palliative systemic treatment

Erlotinib and gefitinib – tyrosine kinase inhibitors (TKIs)

Clinical predictive factors of response:

- Female
- Asian
- Never-smokers
- Adenocarcinoma

NSCLC – palliative systemic treatment



1 – anti-EGFR Ab

2 – **TKI**

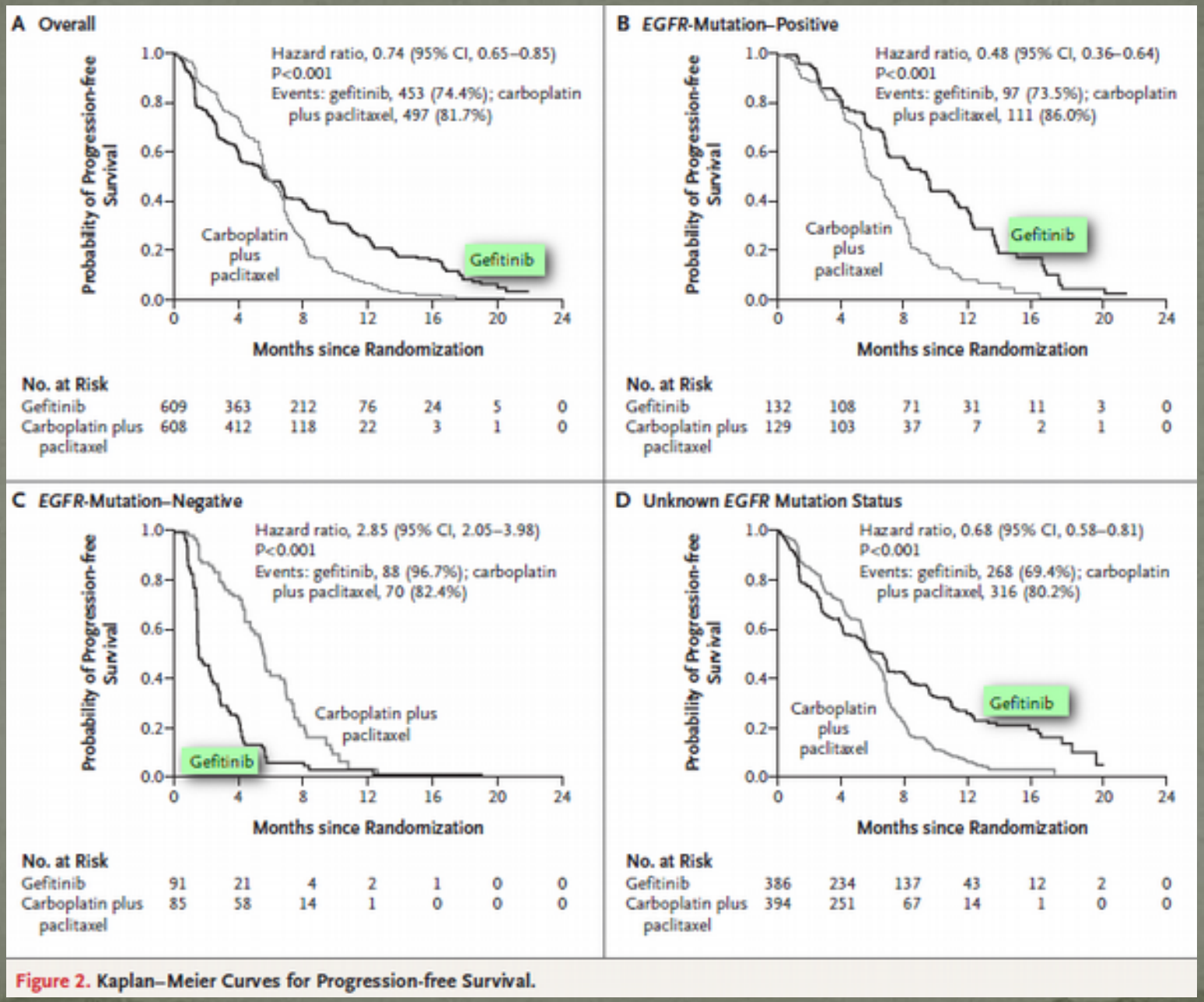


Figure 2. Kaplan–Meier Curves for Progression-free Survival.

TKI in NSCLC

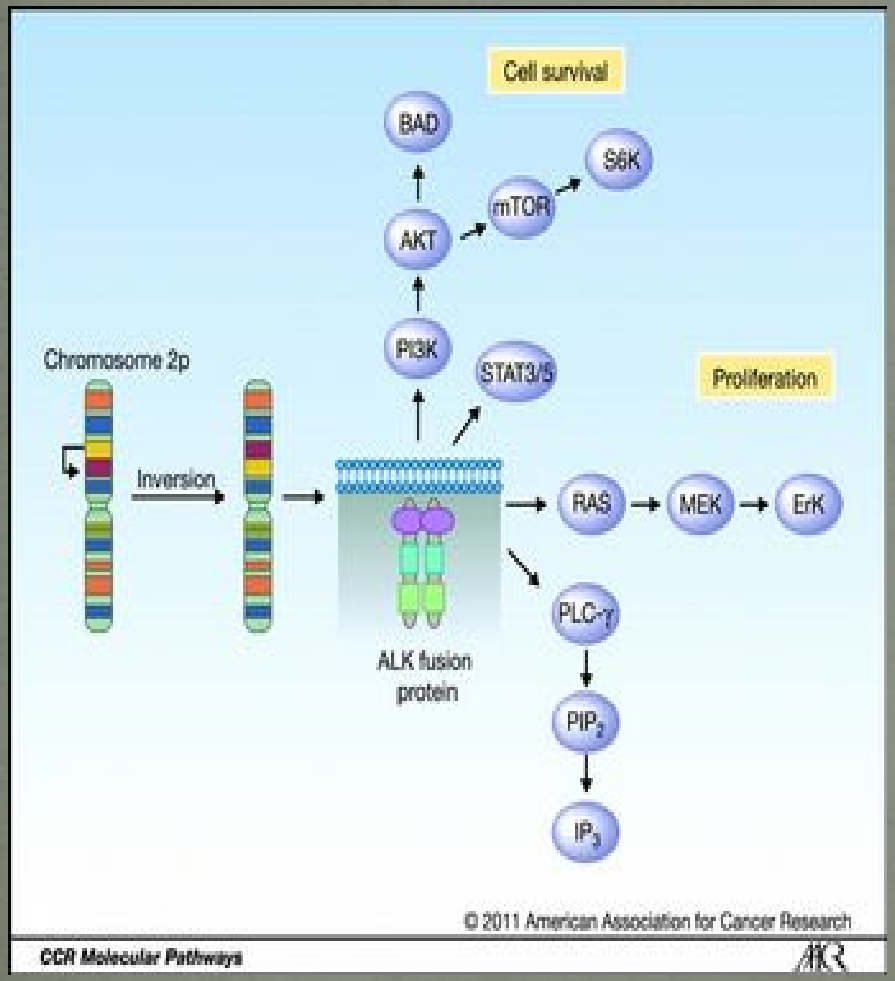
AFATYNIB

- ↑ OS in 1st line!

- **LUX-LUNG 3 TRIAL**: afatynib vs cisplatin&pemetreksed
  HR=0,54; p=0,0015

- **LUX-LUNG 6 TRIAL**: afatynib vs cisplatin&gemcitabine
  HR=0,64; p=0,0229

NSCLC – targeted therapy



- Fusion gene
- EML4-ALK
- 2-7% NSCLC patients

Crizotinib – oral ALK inhibitor

NSCLC – targeted therapy crizotinib

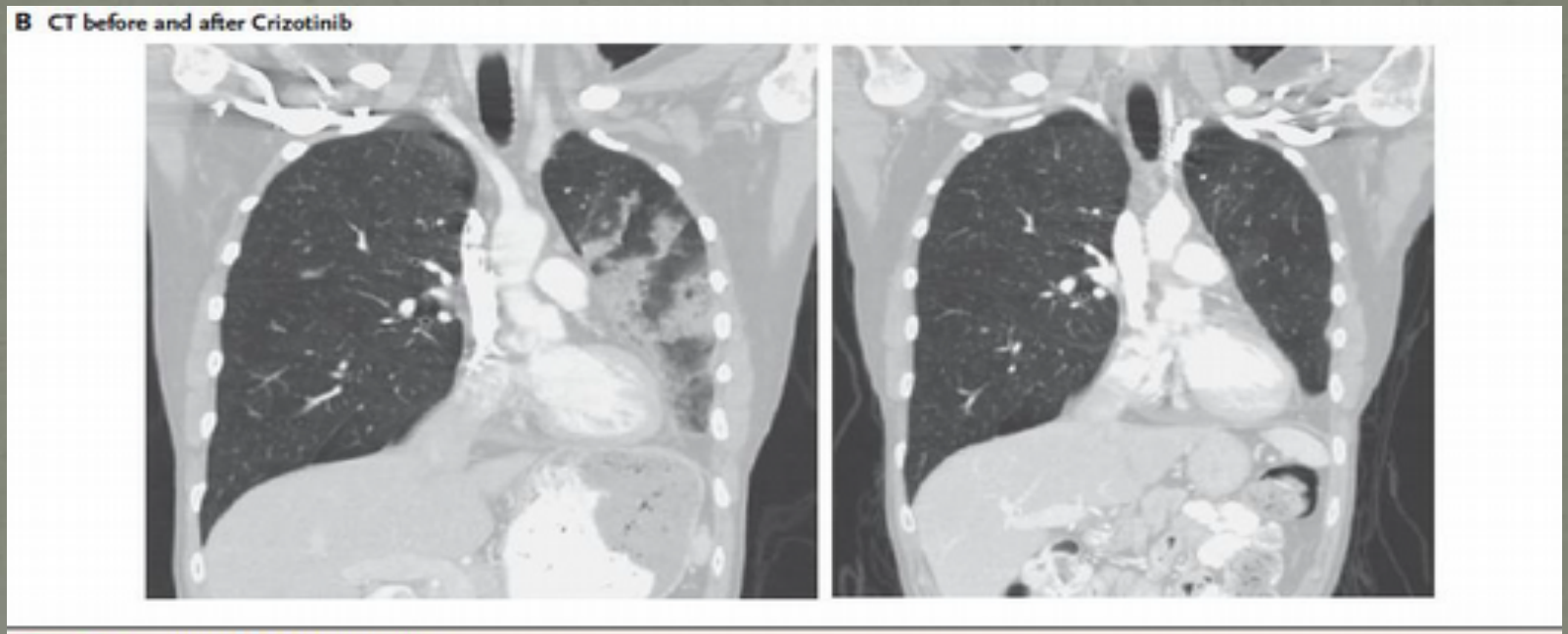


Figure 2. Response to ALK Inhibition.

Panel A shows the best response of patients with *ALK*-positive tumors who were treated with crizotinib, as compared with pretreatment baseline. Numbers along the x axis indicate arbitrarily assigned subject numbers from 1 to 79. The bars indicate the percent change in tumor burden from baseline. Three study patients are not included in this plot: one patient was clinically assessed as having had a partial response, although the response was primarily in areas of nonmeasurable disease, so the patient was classified as having stable disease; two patients with abrupt clinical deterioration could not be assessed. Four patients had complete resolution of their target lesions but were classified as having had a partial response on the basis of stability in nontarget lesions. Eight patients had tumor shrinkage of more than 30% but were classified as having stable disease either because confirmatory scans were not available by the data-cutoff point (for five patients) or early restaging was performed at 6 weeks after crizotinib initiation (for three patients). The dashed line indicates a tumor reduction of 30% from baseline, the minimal percent decrease that constitutes a partial response, according to Response Evaluation Criteria in Solid Tumors. Panel B shows the results of CT with coronal reconstruction in a representative patient at baseline (left) and after two cycles of therapy (right). This patient had undergone previous left lower lobectomy.

Anty PD-1

NIVOLUMAB

- Humanized IgG4 monoclonal antybody
- Antybody enhancing autoimmune response of the „host”
- Checkpoint inhibitor
- Proved to be effective in 2nd line treatment of NSCLC
- Both squamous and non-squamous NSCLS
- 12.2 months vs 9.4 (docetaxel monotherapy)
- 19% of patient experienced complete or partial tumor shrinkage, effect lasted an avarage 17 mo (in dtx group response lasted an avarage 6 mo only!)

NSCLC – early palliative care

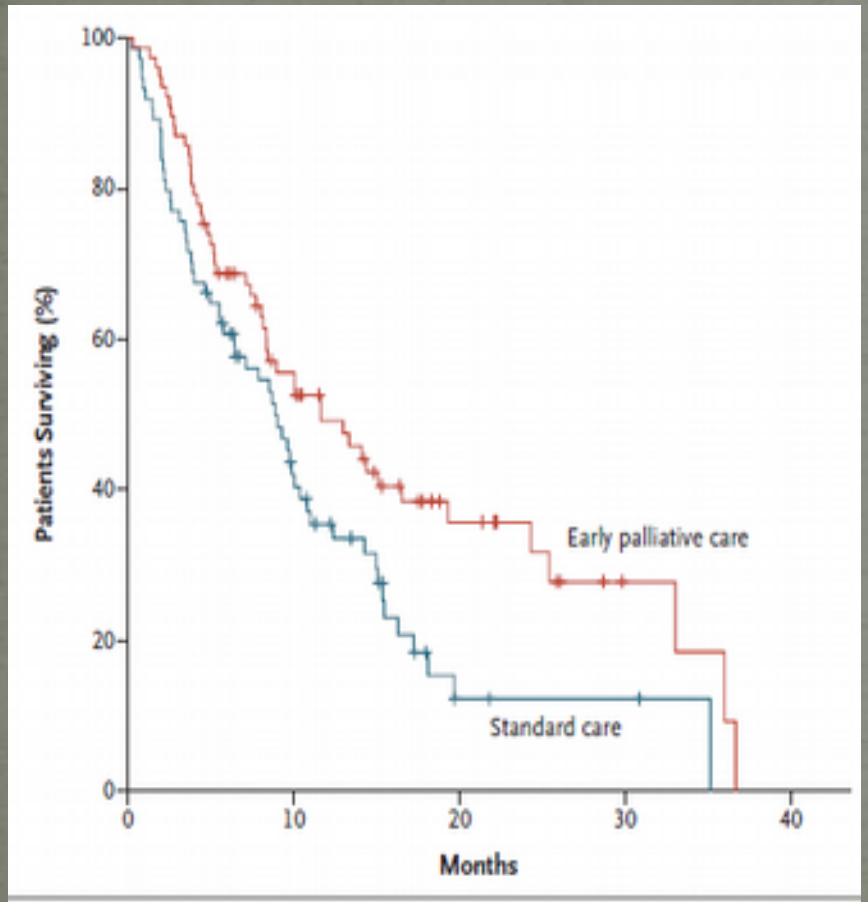


Figure 3. Kaplan–Meier Estimates of Survival According to Study Group.

- Early palliative care added to chemotherapy improves overall survival and quality of life.

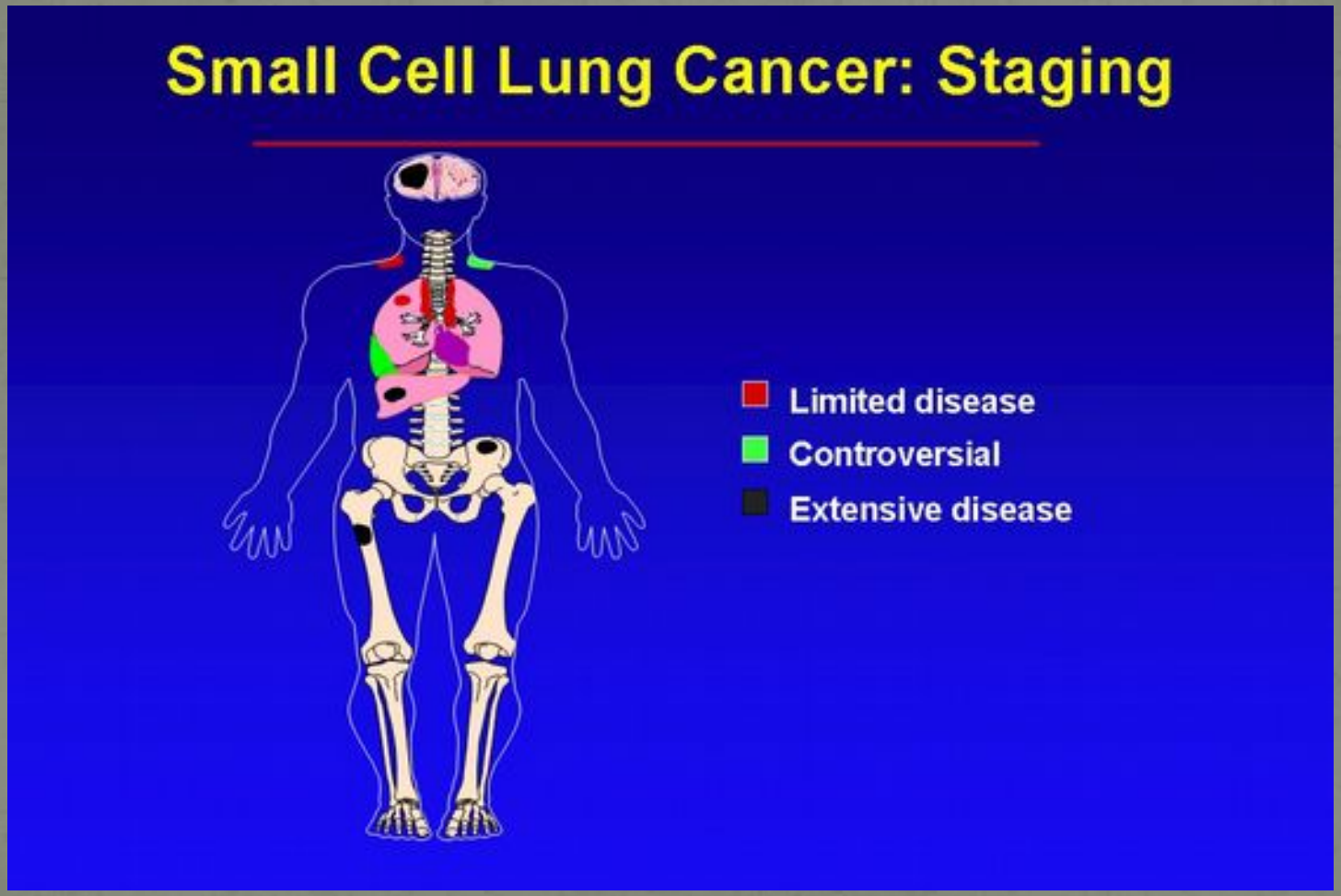
Small cell lung cancer – SCLC

- 13% of lung cancer cases
- Neuroendocrine differentiation: possitive staining for chromogranine, synaptophisine, NSE
- Paraneoplastic syndromes due to neuroendocrine activity (Cushing’s syndrome, SIADH)

- Large mass, hilar and mediastinal adenopathy
- - In most cases primary systemic disease (very high metastatic potential)

LS vs ES

Limited Stage (Limited Disease) – tumor doesn't exceed half of the chest



SCLC – LD Treatment

Chemoradiotherapy

[ChT regimen: EP (cisplatin + etoposide)]

Concurrent

- Better outcomes
- Higher toxicity

Sequential

- Worse outcomes
- Lower toxicity

SCLC – LD Treatment

Surgical treatment:

- Very rare cases of tumor surrounded by lung tissue -> histology after surgical excision
- If histology assessed before surgery and negative lymph nodes -> surgery + adj. chemotherapy

SCLC – LD Treatment

Prophylactic Cranial Irradiation (PCI)

- After chemoradiation
- Partial or Complete Response (PR/CR) in CT scan
- PS 0-1
- 3-5 weeks after last week of chemotherapy

3-year OS PCI group: 20,7%
No-PCI group:15,3%

SCLC – ED Treatment

- 70% of patients
- Treatment – chemotherapy cisplatin + etoposide
- 4 – 6 cycles
- If any response -> PCI
- Decrease in incidence of symptomatic CNS metastases
- Prolongs survival

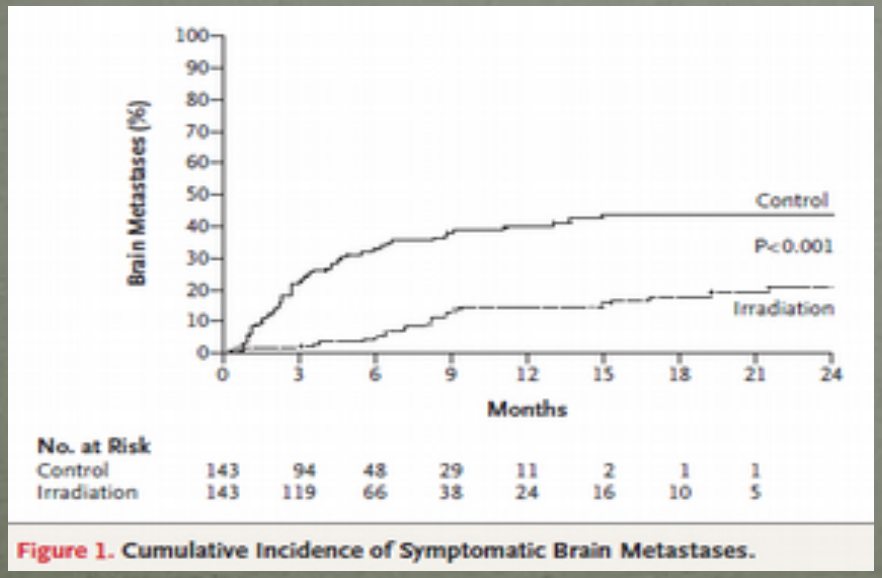


Figure 1. Cumulative Incidence of Symptomatic Brain Metastases.

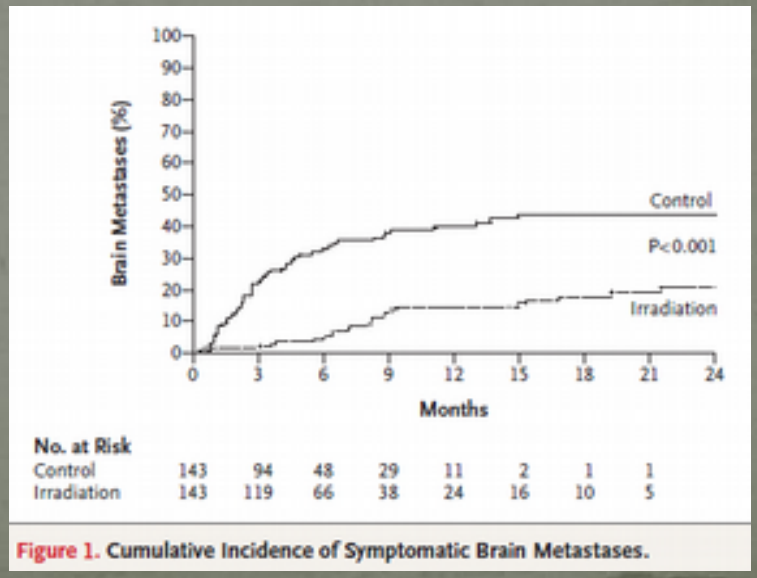


Figure 1. Cumulative Incidence of Symptomatic Brain Metastases.

SCLC – ED Treatment

2 nd line chemotherapy:

- PD within 3 months: refractory disease

- PD after 3 months:
  - topotecan
  - CAV (cyclophosphamide, doxorubicin, vincristine)

Thank You for Your Attention!