Lung Cancer in Young and Elderly Patients

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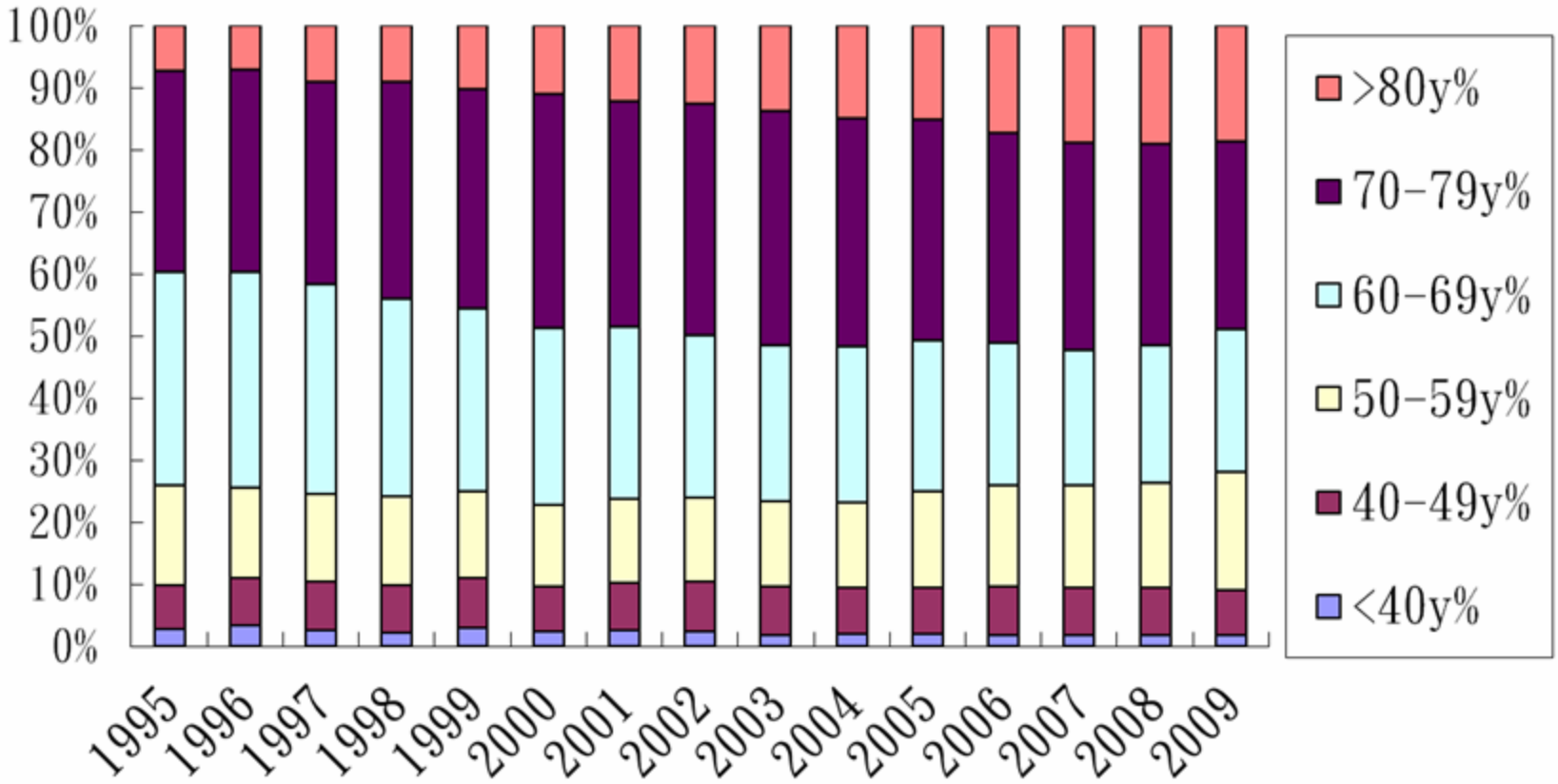
2011年台灣地區主要癌症死亡原因

癌症部位	人數	死亡率*
肺癌	8541	36.8
肝癌	8022	34.6
結腸直腸癌	4921	21.2
乳癌	1852	16.0
口腔癌	2463	10.6
胃癌	2288	9.9
總計	42558	183.5

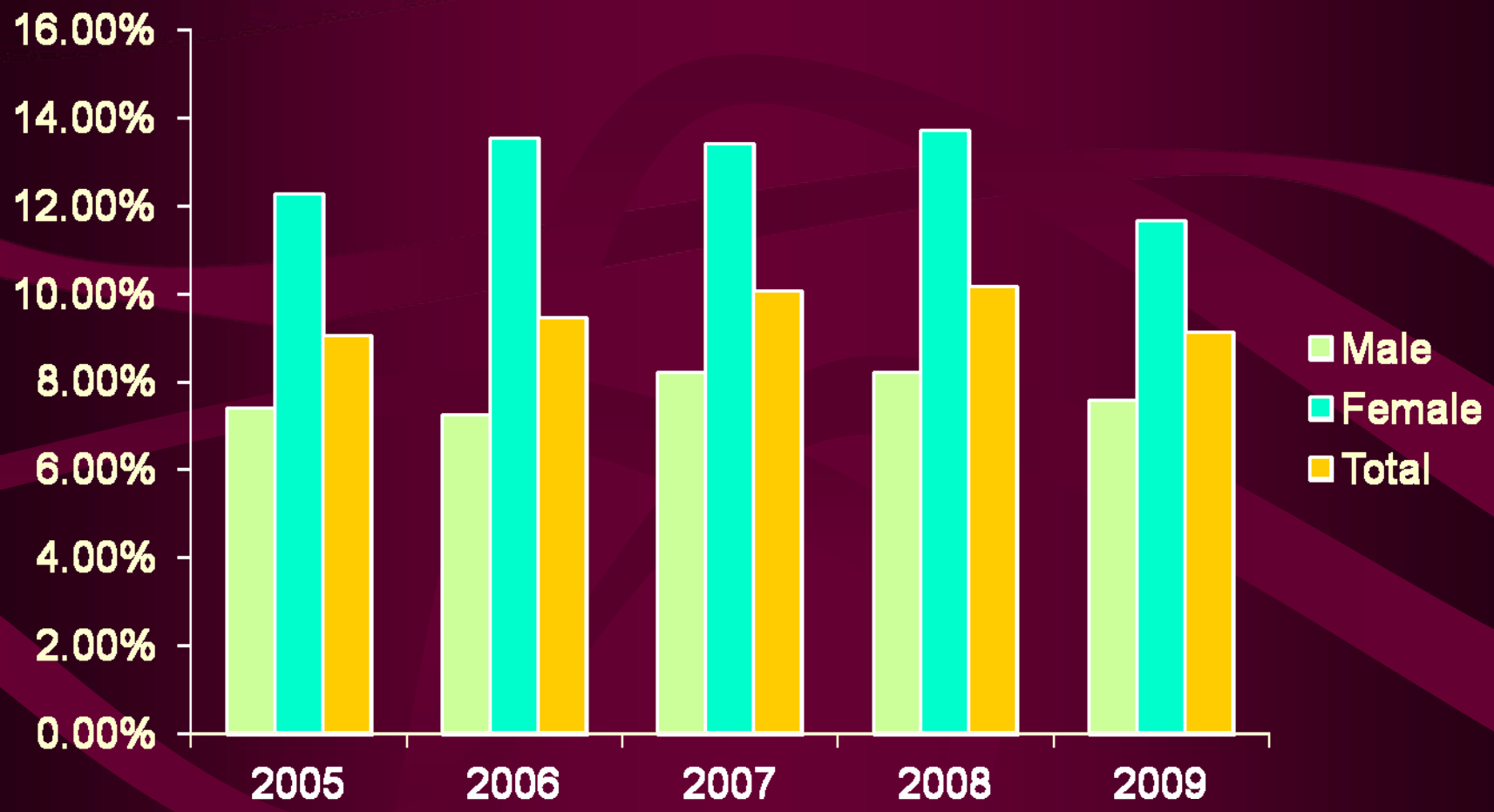
*每十萬人口死亡率

1995-2009台灣地區肺癌各年齡成百分比



Lung Cancer in Young Adults

Time Trend of Lung Cancer in Age < 50 y/o in Taiwan



Taiwan Cancer Registry
http://tcr.cph.ntu.edu.tw/main.php?Page=A5#t01

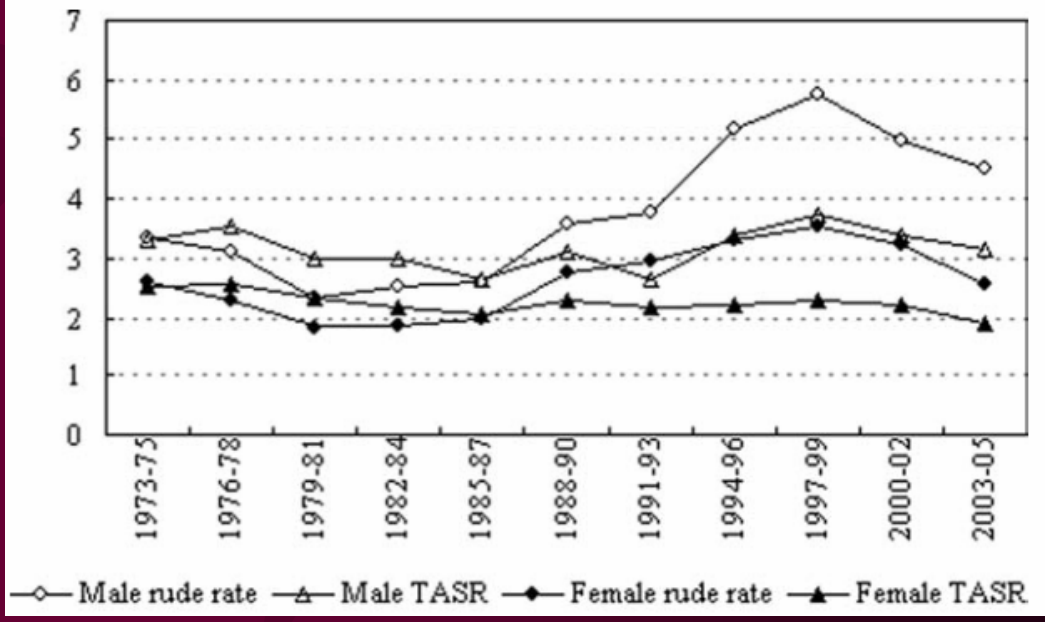
Incidence of NSCLC in young patients

Table 1. The Time Trend of Lung Cancer Incidence in Patients Between 15 and 45 Years Old in Shanghai (1973-2005)

Rate	Sex	APC	95% CI		t	*P*
Crude rate	Male	2.46	1.59	3.34	5.81	<.01
	Female	1.57	0.51	2.63	3.04	<.01
Adjusted rate	Male	0.17	−0.43	0.77	0.58	.57
	Female	−0.52	−1.32	0.30	−1.30	.20

APC indicates annual percentage change; CI, confidence interval.

Age < 45 y/o



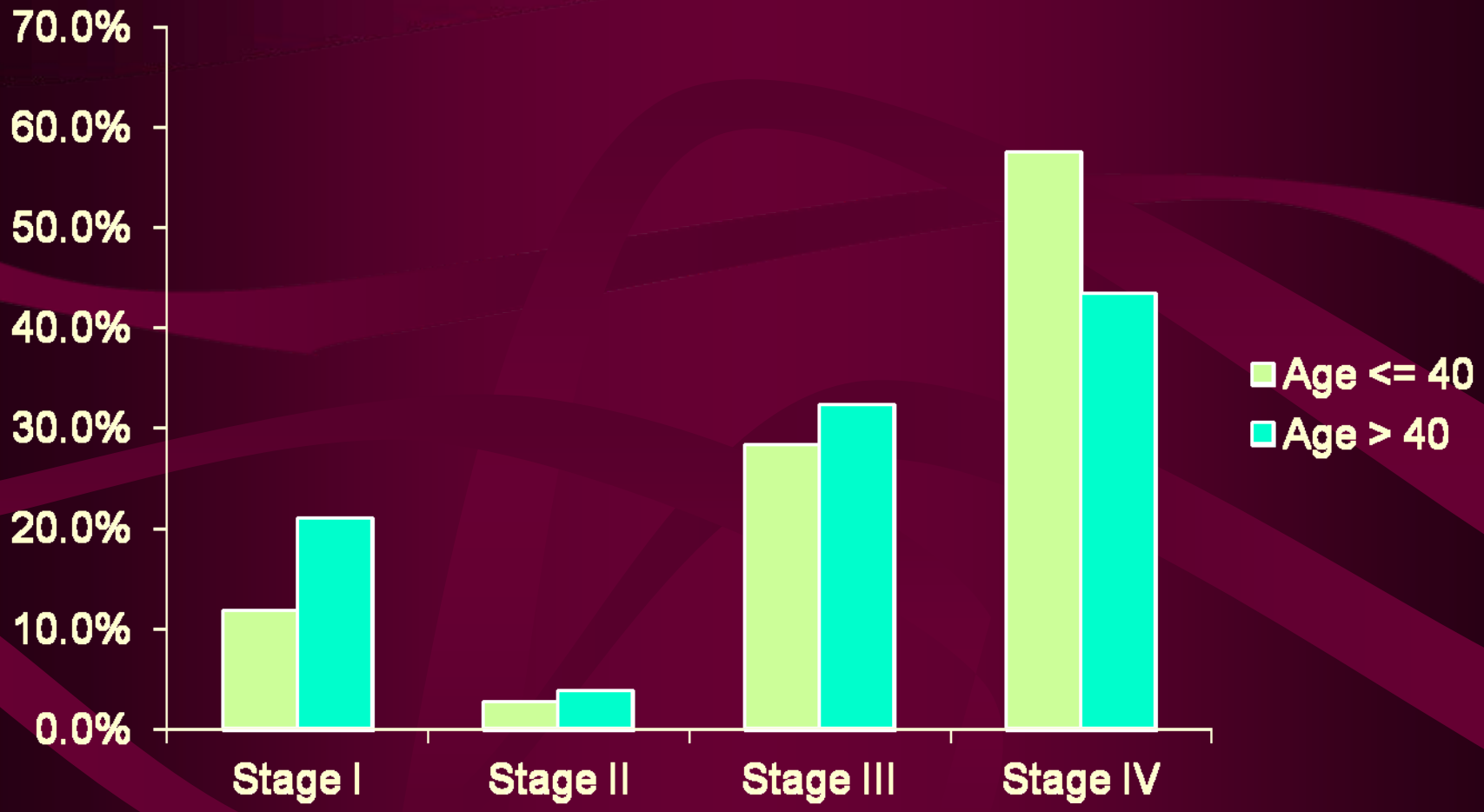
Zhang J, *et al. Cancer*. 2010 Aug 1;116(15):3656-62.

Clinical characteristics in young patients

- Fewer smoker
- More adenocarcinoma
- More aggressive treatment
- More in African Americans and Asian
- More female
- More advanced stage
- Better survival?

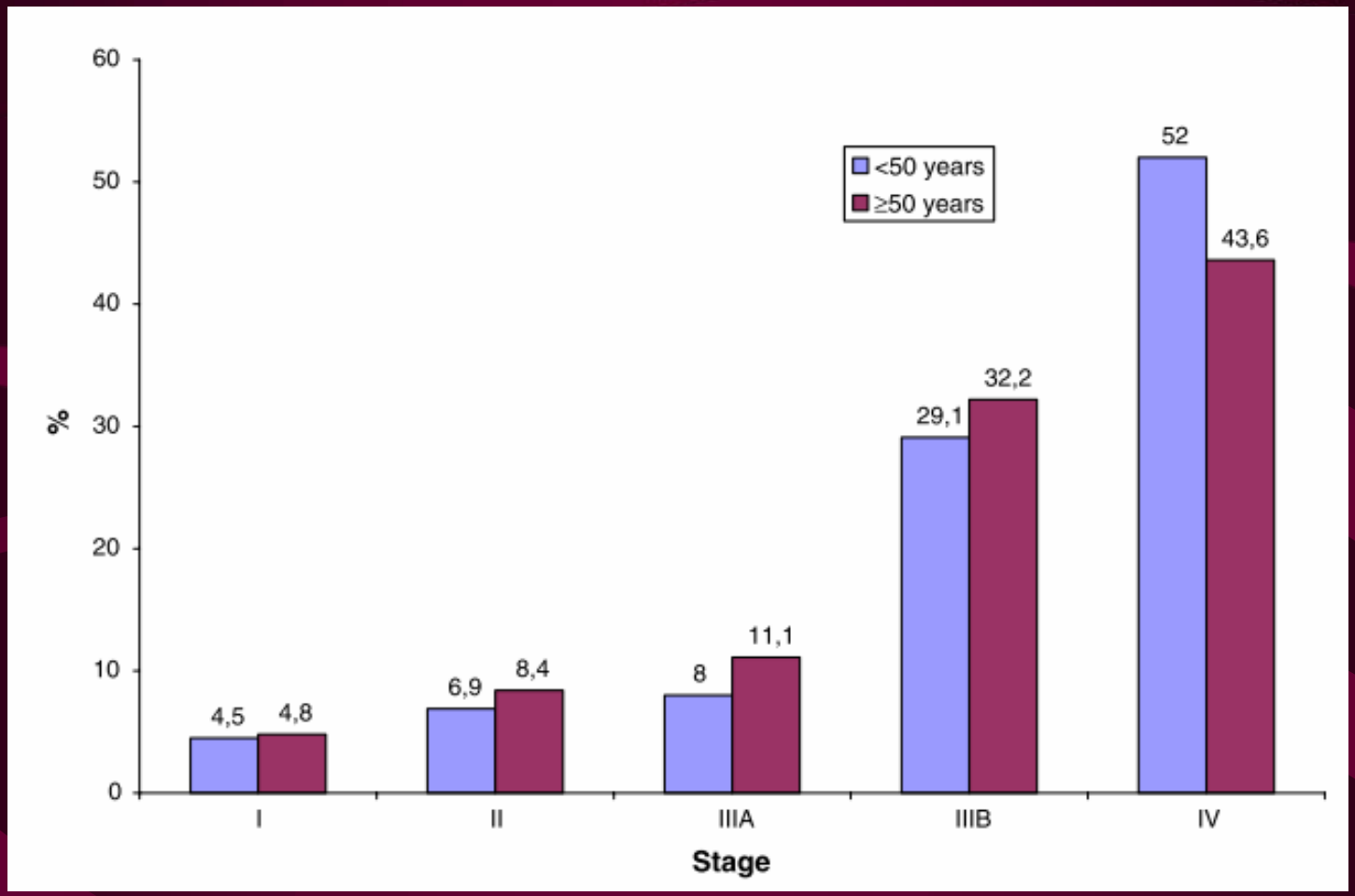
Liam CK, *et al. Respirology*. 2000 Dec;5(4):355-61.
Kuo CW, *et al. Chest*. 2000 Feb;117(2):354-7.
Subramanian J, *et al. J Thorac Oncol*. 2010 Jan;5(1):23-8.
Zhang J, *et al. Cancer*. 2010 Aug 1;116(15):3656-62.

Stage distribution (USA)



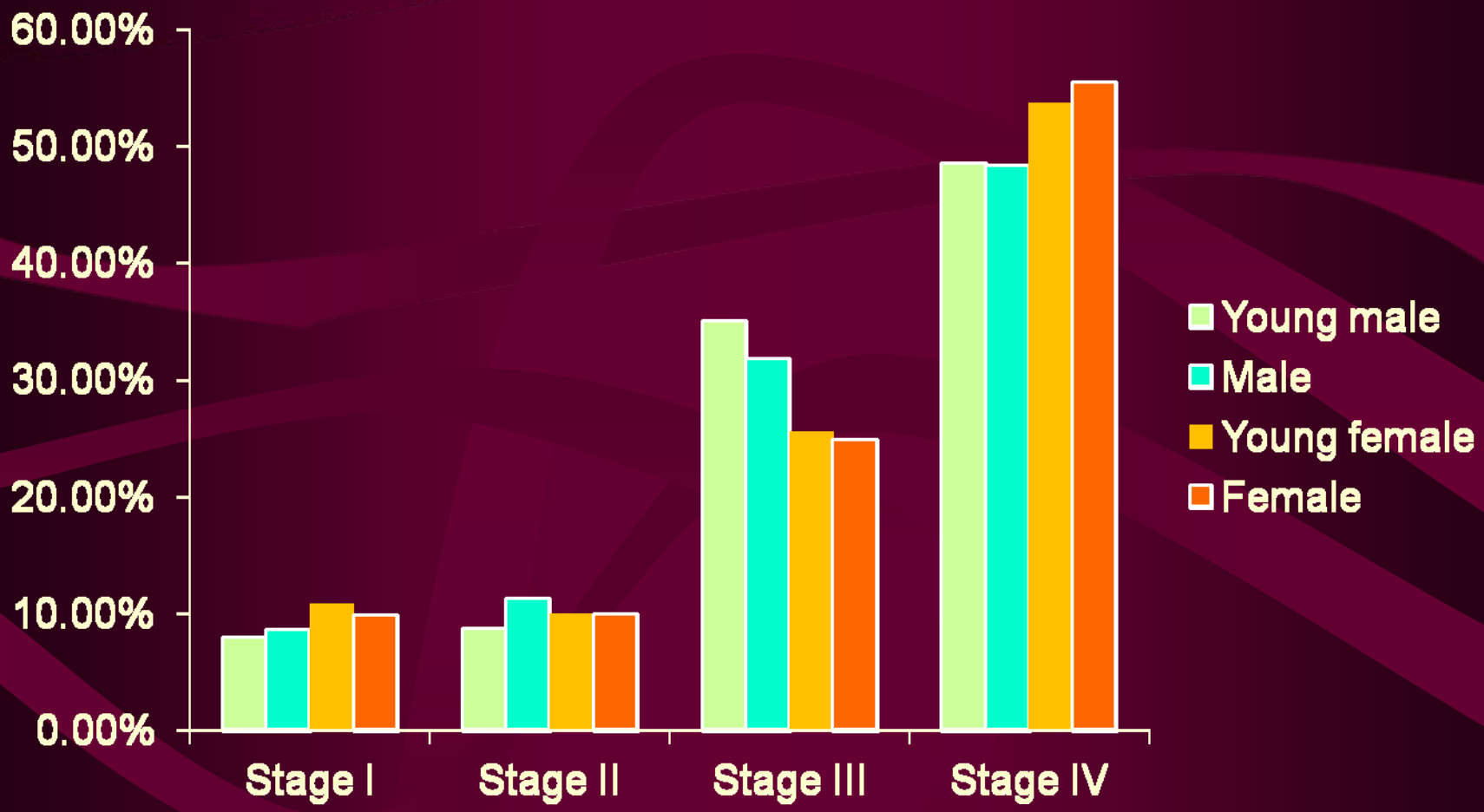
Subramanian J, *et al. J Thorac Oncol*. 2010 ;5(1):23-8.

Stage distribution (Turkey)



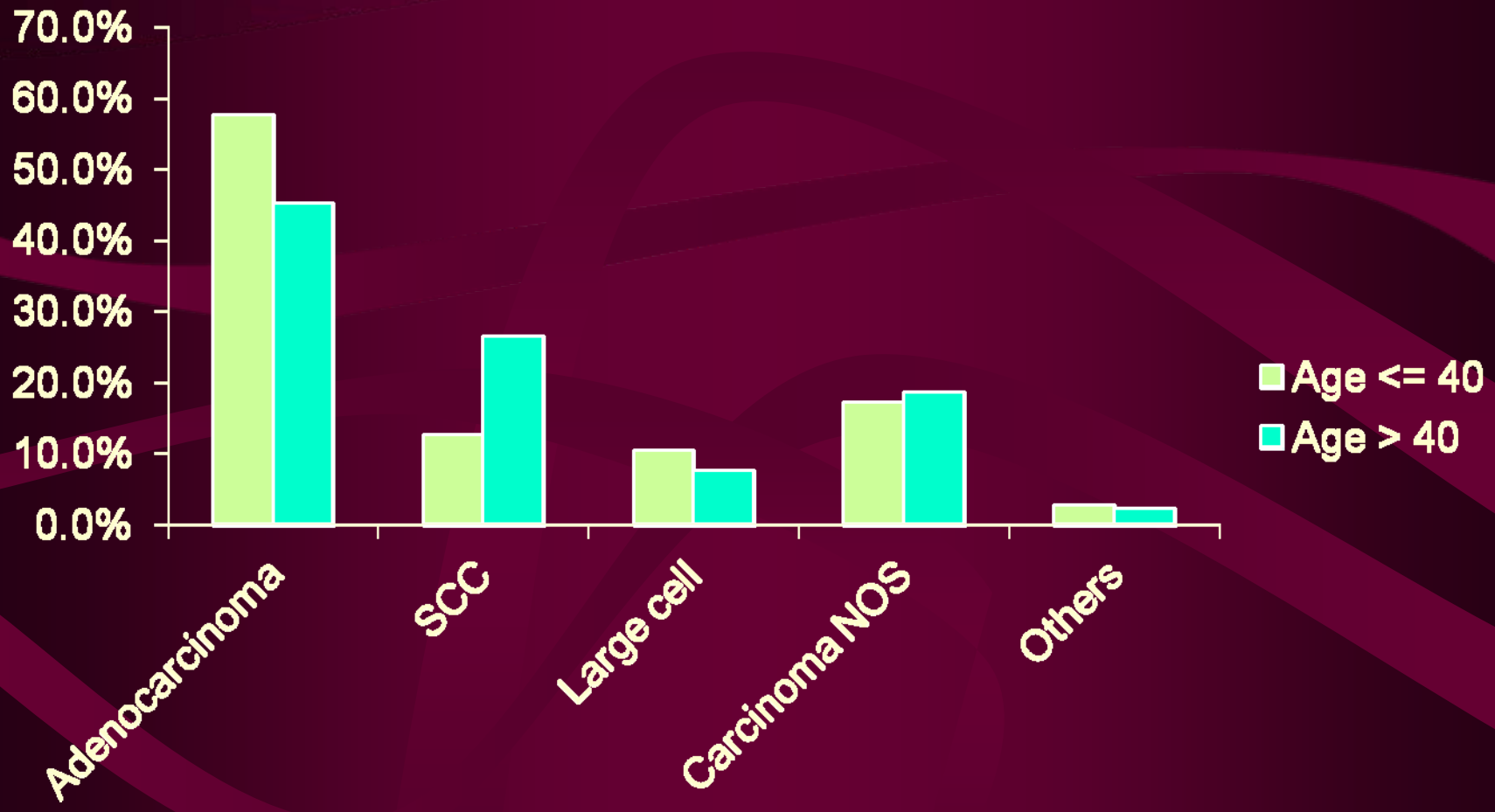
Ak G, *et al. Lung*. 2007;185(5):279-86.

Stage distribution (China)



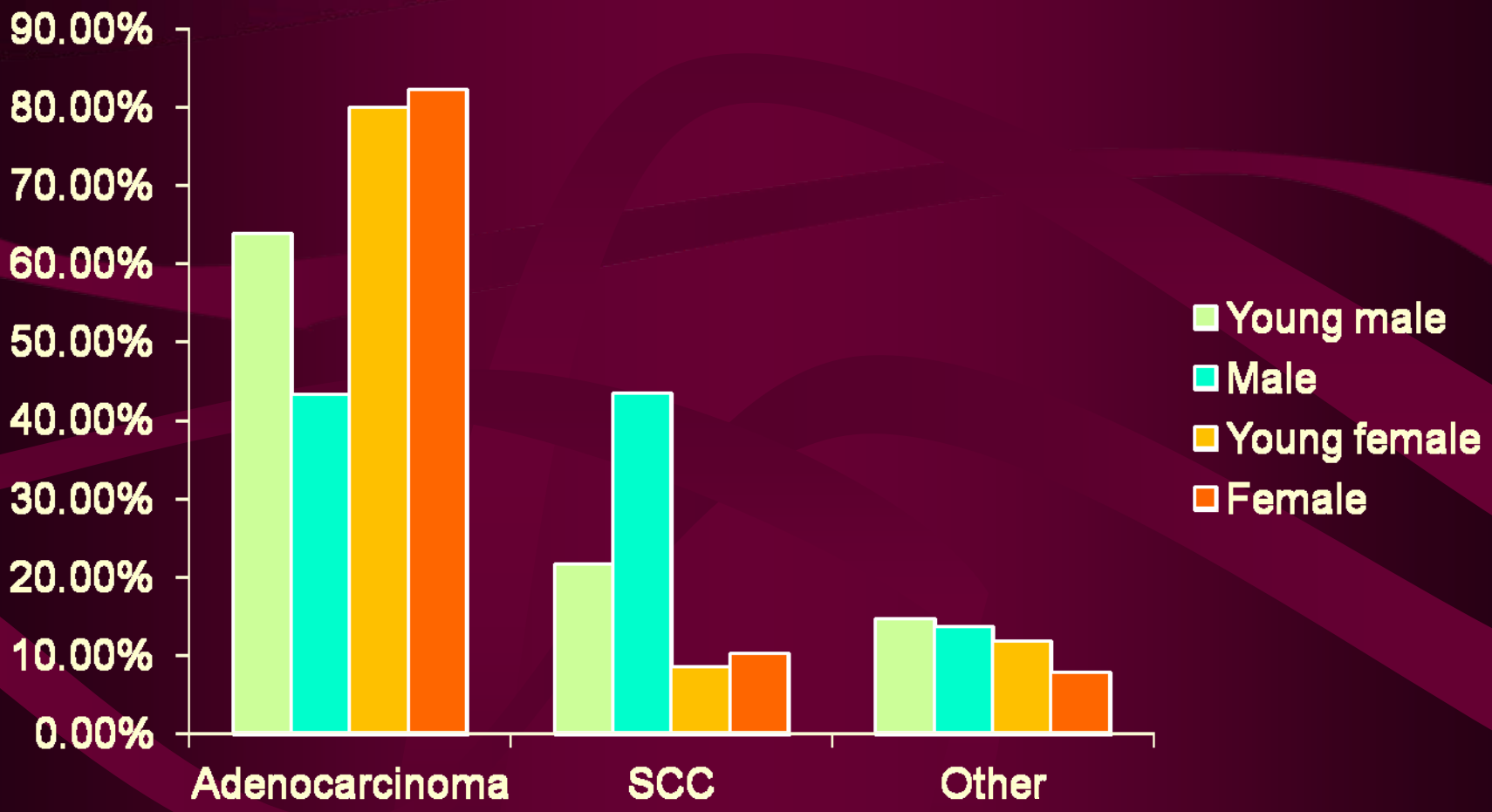
Zhang J, *et al. Cancer*. 2010 Aug 1;116(15):3656-62.

Histology distribution (USA)



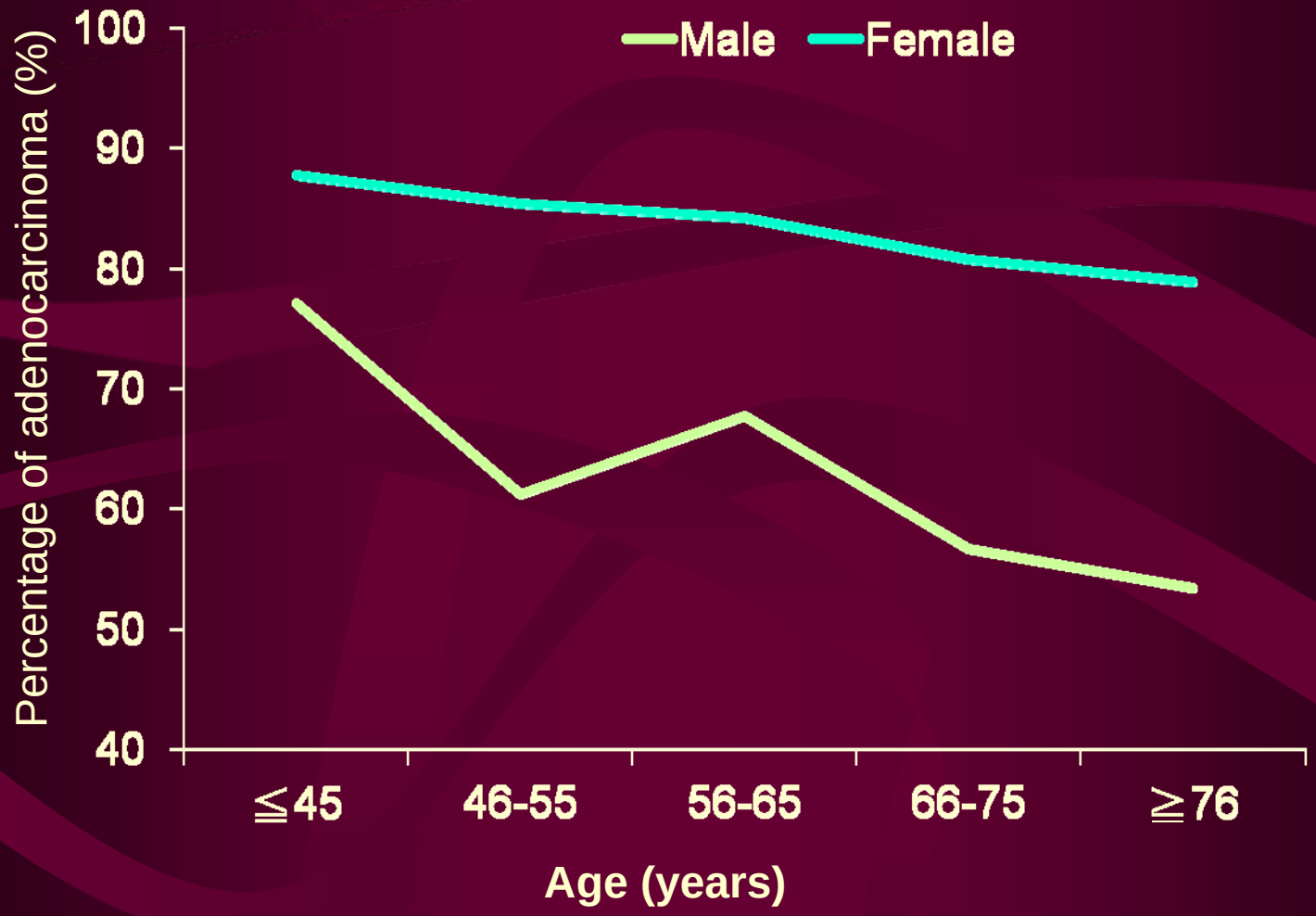
Subramanian J, *et al. J Thorac Oncol*. 2010 Jan;5(1):23-8.

Histology distribution (China)



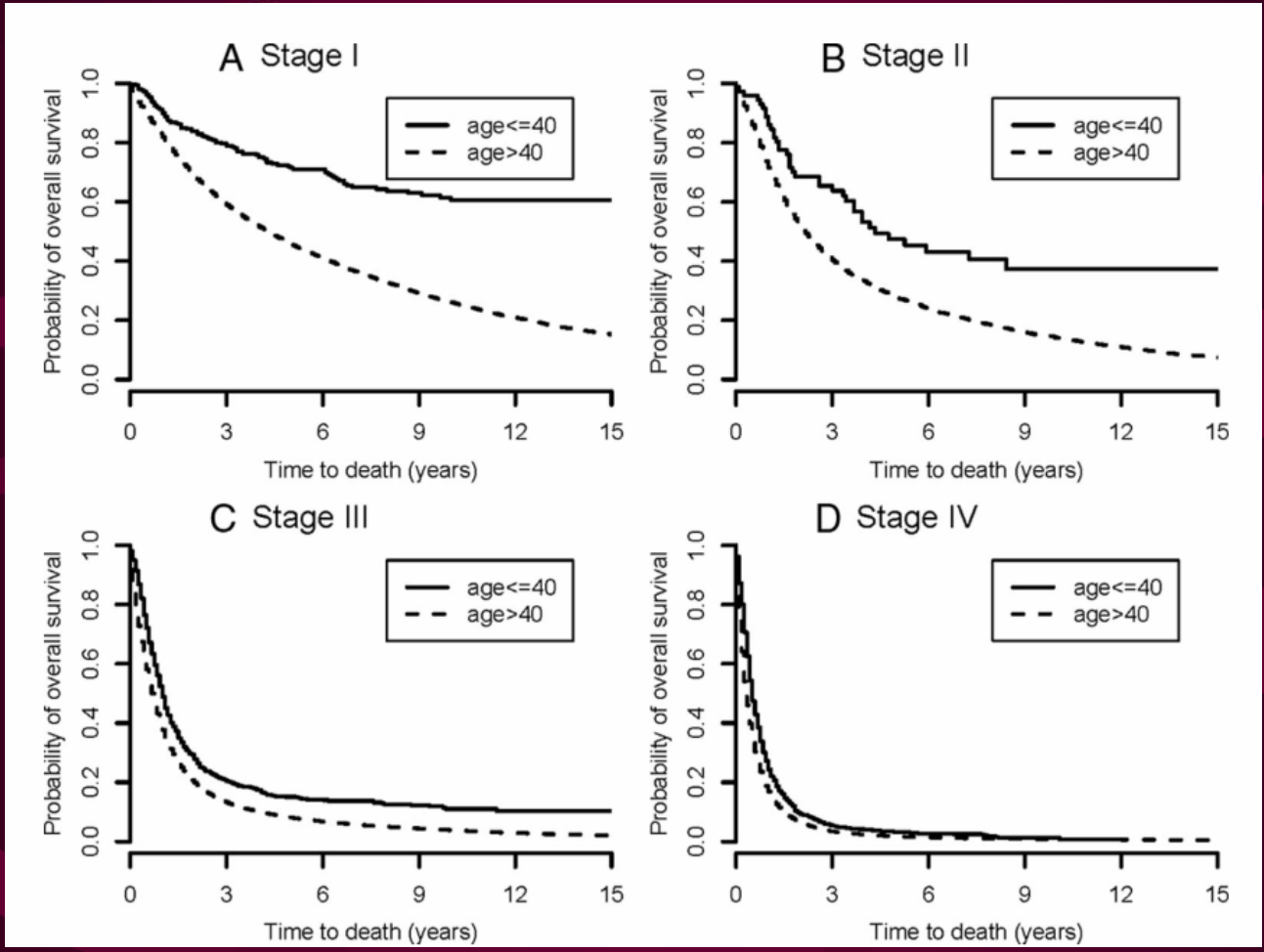
Zhang J, *et al. Cancer*. 2010 Aug 1;116(15):3656-62.

Trends of Incidence of Adenocarcinoma (NTUH)



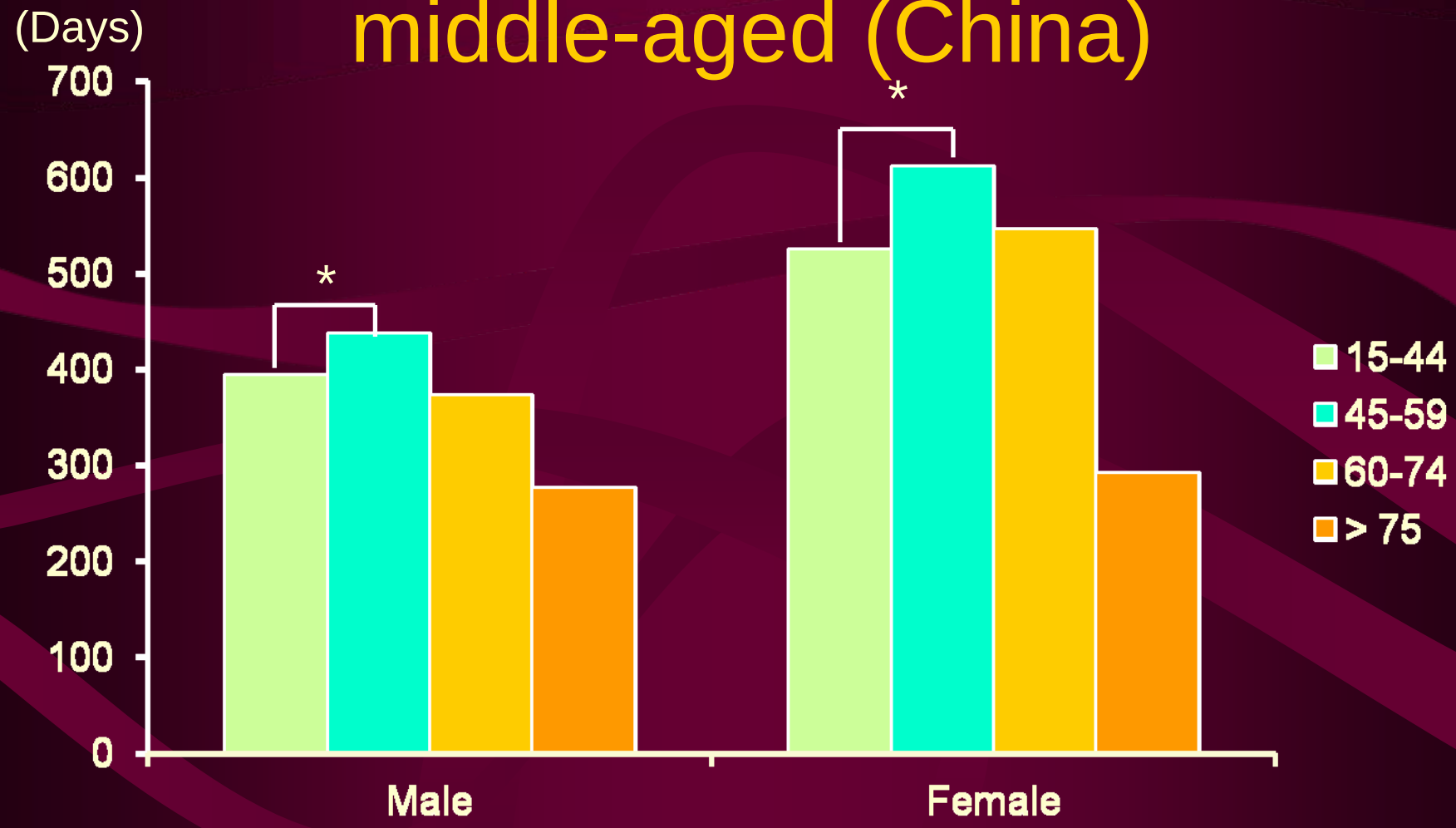
Hsu CL, *et al. BMC Cancer*. 2012 Jun 13;12:241.

Survival analysis in different stages of NSCLC (USA)



Subramanian J, *et al. J Thorac Oncol*. 2010 Jan;5(1):23-8.

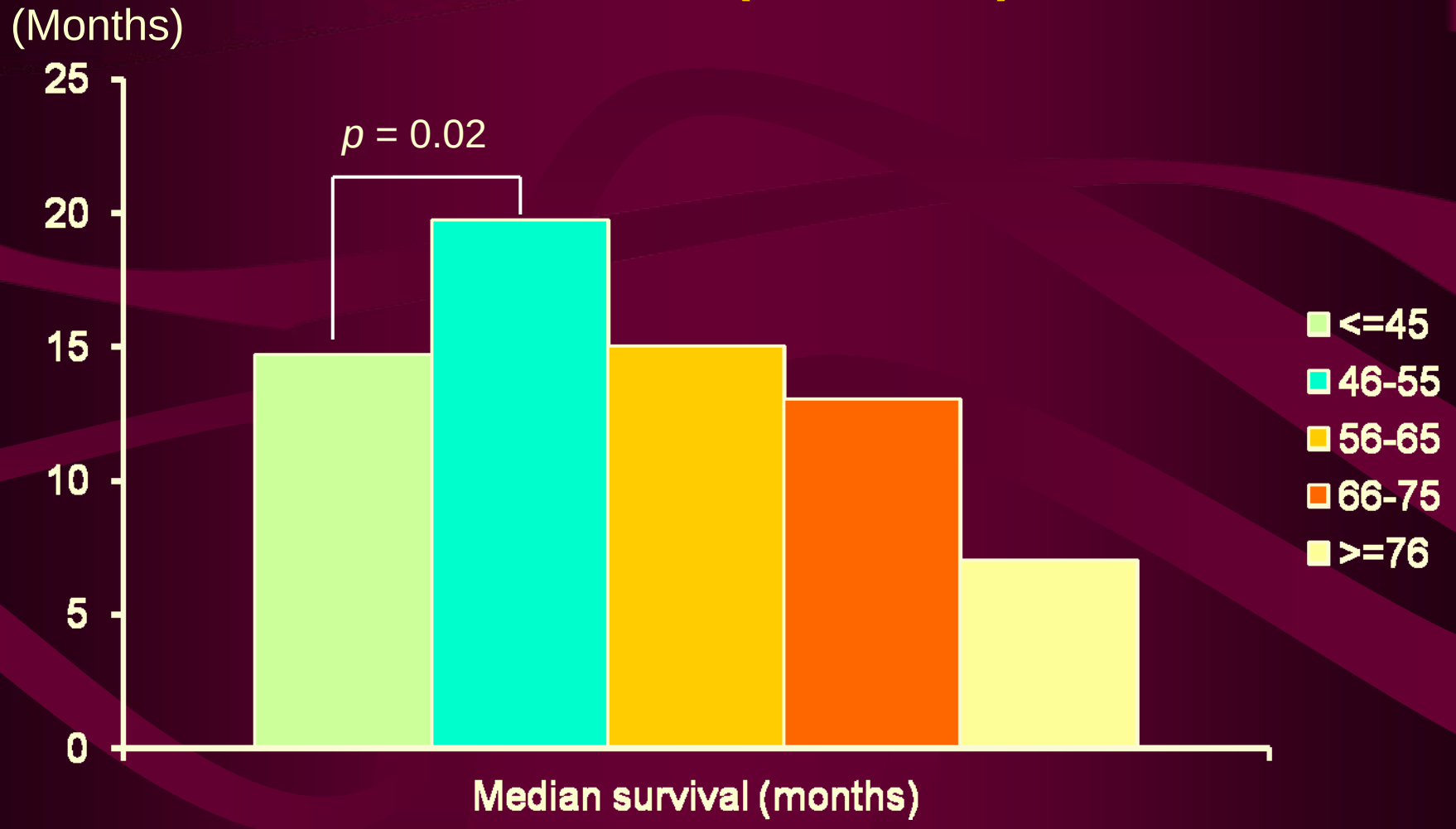
Longest median survival in middle-aged (China)



* p <0.05

Zhang J, *et al. Cancer*. 2010 Aug 1;116(15):3656-62.

Survival analysis in advanced NSCLC (NTUH)



Hsu CL, *et al. BMC Cancer*. 2012 Jun 13;12:241.

Prognostic factors in young advanced NSCLC (NTUH)

	Hazard Ratio (95% CI)	*p* value
Male gender	1.70 (1.08–2.68)	*0.02*
BMI < 25 kg/m^2	2.72 (1.39–5.30)	*0.003*
Disease stage		
IIIB	1	
IV	2.62 (1.50–4.57)	*0.001*
Performance status		
0-1	1	
2-4	1.59 (0.96–2.63)	0.08
Laboratory data		
Anemia (hemoglobin<11 g/dL)	2.08 (1.15–3.77)	*0.02*
Leukocytosis (> 10,000 cells/μL)	1.62 (0.94–2.78)	0.08

Hsu CL, *et al. BMC Cancer*. 2012 Jun 13;12:241.

Conclusions

- Young patient is a small subpopulation in lung cancer
- Higher adenocarcinoma percentage is noted in most studies, especially in Asia population
- Histology and stage distribution may be different in different ethnicities
- Better survival outcome in middle-aged population is noted in Taiwan and China

Lung Cancer in Elderly

Lung Cancer Has Become a Disease of Elderly

- In the 90's, >50% of patients with advanced NSCLC at diagnosis were > 65 y/o.
- According to SEER data, the median age of lung cancer patients was 71(M: 70, F: 71).
- In Taiwan, the median age of lung cancer patients were 71 in males and 68 in females.

Eur J Cancer 1997;332313-4
http://seer.cancer.gov/csr/1975_2005/
http://crs.cph.ntu.edu.tw/crs_c/annual.html

Treatment of Lung Cancer in the Elderly

- Lack of elderly-specific clinical trial.
- Most data come from subset analysis of existed trial.
- The efficacy and toxicity of newer therapies in older populations are poorly understood.

BMJ 1999;319:309-12
Arch Intern Med 1990;150:1485-90

Treatment of Lung Cancer in the Elderly

- Surgical operations and radiotherapy: physiological changes in cardiovascular and respiratory systems are the major concerns.
- Chemotherapy: Decreases of drug clearance and reduces of bone marrow, liver and renal function, which may limit the use.

Pharmacol Rev 2004; 56:163-84

Treatment of Small Cell Lung Cancer in Elderly

- Limited stage: concurrent chemoradiotherapy
- Extensive stage: chemotherapy
- Less likely to receive local therapy
- Less intensive chemotherapy regimen, fewer cycles, lower total doses, less PCI.
- The overall survival is worse.

Cancer 2010;116:1192-1200

Current Treatment of NSCLC: 2012

Stage	Primary treatment	Adjuvant therapy
IA	Surgery	
IB		
II		C/T
IIIA (resectable)	Neoadjuvant C/T → Surgery	C/T or RT
IIIA (unresectable)	CCRT or C/T → R/T	None
IIIB (N3)		
IV	C/T (with targeted therapy); EGFR-TKI in selected population	Maintainence therapy

Selection of Elderly NSCLC Patients for Surgery

- 30% of pts >75 y/o with early stage NSCLC did not receive curative surgery, whereas 8% of pts <65 y/o did not.
- The selection of patients for surgical resection: comorbidities (cardiopulmonary disease) and predicted post-OP pulmonary function (FEV1 and PaO2).
- Age should not be included as a criterion.

Chest 2003;123(1 Suppl):105S–14S.
Am J Respir Crit Care Med 1999;159(5 Pt 1):1450–6.
Chest 2005;128(1):237–45.
Eur J Cardiothorac Surg 2002; 22: 35-40

Outcomes in Elderly Patients Underwent Surgery for NSCLC

- Older (>76 yr) patients with ECOG PS 0-2 and no co-morbidities
  - similar perioperative mortality and long-term survival compared with younger patients.
- In a nested case-control study matched for FEV1%, ECOG PS, stage, type of tumor, and type of pulmonary resection,
  - no differences in short-term morbidity and mortality between >70 years and <70 years patients.

Chest 2005; 128(3):1557–63.
Ann Thorac Surg 2006;82(2):424–9

Predictors for Surgery in Elderly Patients with NSCLC

- Dementia is an independent poor prognostic factor.
- Dementia and disability in performing ADL were associated with postoperative complications.
- CHF and prior MI might be associated with an increased mortality in octogenarian.

BMJ 1990;300(6719):239–40.
N Engl J Med 2001;344(15):1111–6.
Chest 2005;127(3): 886–91.
Ann Thoracic Surg 2006;82:1175-9

Radiotherapy for NSCLC in the Elderly

- Stage I patients, 5 yr survival: 45% (vs. no treatment, 12%)
- Potential alternative treatment option: Radiofrequency ablation and Stereotactic body radiation therapy.

Int J Radiat Oncol Biol Phys 1988;15:69-73
Cancer 2004;101:1623-31
Oncology 2006;20:899-905
Int J Radiat Oncol Biol Phys 2004;60:186-96

Adjuvant Chemotherapy for NSCLC in the Elderly

- Subset analysis of Canada BR. 10.
- Vinorelbine+cisplatin vs. observation in resected NSCLC (IB/II).
- For patients aged >65, absolute improvement 10% in 5 yr survival (p=0.04)
- Further analysis of patients aged >=75 did not show the same benefit (n=23).

J Clin Oncol 2007;25:1553-61

Current Treatment of NSCLC: 2012

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IIIB (N3)		
IV	C/T (with targeted therapy); EGFR-TKI in selected population	Maintainence therapy

Treatment for Locally Advanced NSCLC in the Elderly

- Stage IIIA disease: remains controversial
- Stage IIIB : CCRT improved survival with more severe neutropenia, renal toxicity, and esophagitis

Cancer 2002;94:181-7

Proceedings of American Society of Clinical Oncology 2003;22:621a

Current Treatment of NSCLC: 2012

Stage	Primary treatment	Adjuvant therapy
IA	Surgery	
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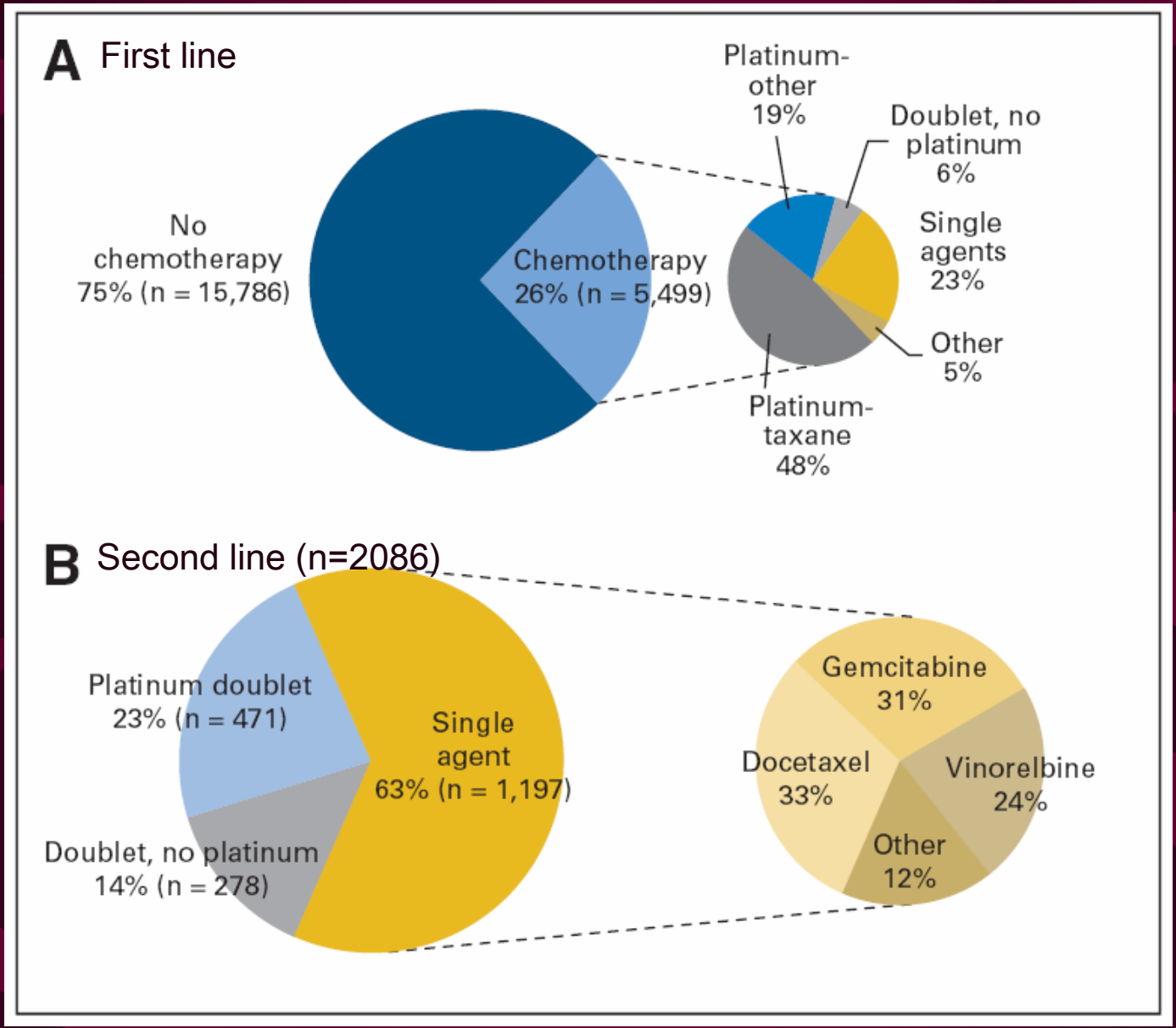
IIIB (N3)		
IV	C/T (with targeted therapy); EGFR-TKI in selected population	Maintainence therapy

Chemotherapy and Survival Benefit in Elderly Patients With Advanced NSCLC

- 21,285 patients ≥ 66 years with advanced NSCLC (1997- 2002)
- Receipt of any chemotherapy: (HR: 0.558; 95% CI, 0.547-0.569) and an increase in adjusted 1-year survival from 11.6% to 27.0%.
- Platinum-doublet receipt increased adjusted 1-year survival over single agents, from 19.4% to 30.1%.

J Clin Oncol 2010; 28:2191-2197

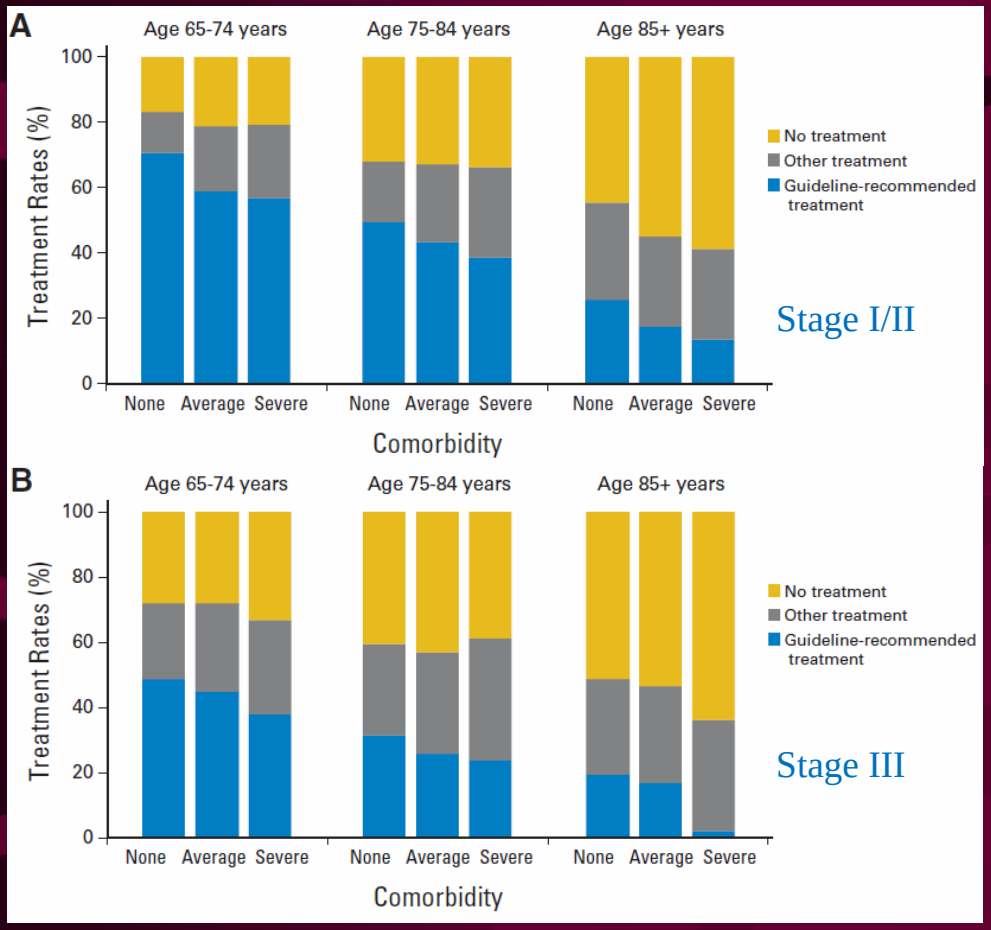


J Clin Oncol 2010; 28:2191-2197

Impact of Age and Comorbidity on Non–Small-Cell Lung Cancer Treatment in Older Veterans

- 20,511 patients ≥ 65 years with advanced NSCLC (2003-2008)
- Patients were stratified by age (65 to 74, 75 to 84, 85 years), CCI score (0, 1-3, 4), and AJCC stage (I - II, IIIA-IIIB, IIIB with malignant effusion - IV).
- Treatment rates decreased more with advancing age than with worsening comorbidity for all stages, such that older patients with no comorbidity had lower rates than younger patients with severe comorbidity.

J Clin Oncol 2012; 30:1447-1455



In NSCLC, age remained strong negative predictors of treatment for all stages, whereas comorbidity and nonclinical factors had a minor effect

J Clin Oncol 2012; 30:1447-1455

TABLE 1. The Clinical Characteristics of 203 Patients Aged 80 Years or Older with Advanced Non-small Cell Lung Cancer

Clinical Characteristics	*n* (%)
Median age (range)	83 (80–96)
Male	114 (56.2)
Performance status	
0–1	85 (41.9)
2	31 (15.2)
3–4	87 (42.9)
Histology	
Adenocarcinoma	140 (69.0)
Squamous cell carcinoma	37 (18.2)
Undifferentiated carcinoma	21 (10.3)
Large cell carcinoma	5 (2.5)
Clinical stage	
IIIB	57 (28.1)
IV	146 (71.9)
Ever smoker	83 (40.9)
Comorbidity	
Hypertension	115 (56.7)
Cardiac diseases	49 (24.1)
Diabetes mellitus	40 (19.8)
Chronic obstructive pulmonary disease	27 (13.3)
Renal insufficiency[a]	25 (12.3)
CNS diseases	11 (5.5)
Initial treatment modalities	
Supportive care only	93 (45.8)
Chemotherapy	17 (8.4)
Palliative radiotherapy	28 (13.8)
EGFR-TKI therapy	65 (32.0)

- NTUH experience
- From Jan 2000 to Dec 2006: 3639 patients with lung cancer.
- 410 patients aged $\geqq 80$
- Among them, 203 with advanced stages NSCLC were included.
- The fear of side effects of chemotherapy might be the major reason to choose supportive care.

J Thorac Oncol 2010; 5:82-9

Cisplatin-based Chemotherapy for Advanced NSCLC in Elderly

Chemotherapy for Advanced NSCLC in the Elderly

- Retrospective age-specific analysis of the randomized trial of four different doublet regimens. (Cis+Tax, Cis+Gem, Cis+Doc, Car+Tax) (n=1155)
- 227 patients aged 70 or older.
- MS: 8.2 months. (younger patients: 8.1 months)
- 1-yr survial: 35%(>=70 y/o) vs. 33% (<70 y/o)
- Toxicity were similar.
- For age 80 and older (n=9), only one patient could complete more than 3 cycles of therapy, with no response

N Engl J Med 2002;346:92-8
PASC 2003;22:2572

Chemotherapy for Advanced NSCLC in the Elderly

- Taxol+Carbo with/without Bevacizumab (n=878)
- Retrospective analysis of 224 patients aged 70 or older.
- RR 29% vs. 17%, p=0.067
- Median PFS: 5.9 vs. 4.9 months, p=0.063
- MS: 11.3 vs. 12.1 months, p=0.4
- Severe treatment-related toxicity was more common with bevacizumab (87% vs. 61%, $p<0.001$)

J Clin Oncol 2008; 26: 60-65

Non-platinum-based Chemotherapy for Advanced NSCLC in Elderly

Chemotherapy for Advanced NSCLC in the Elderly

- ELVIS study: VNB > BSC (OS: 28 vs. 21wk)
- MILES study: VNB = GEM = VNB/GEM (but more toxic)

Docetaxel vs. Vinorelbine in the Elderly

	WJTOG	
	Tax (60 mg/m^2) q 3 wk	Vnb (25 mg/m^2) d 1, 8 q 3 wk
No. pts	88	91
ORR, %	22.7*	9.9
Median PFS/TTP, mo	5.5†	3.1
Median OS, mo	14.3	9.9
Neutropenia (Gr3/4), %	82.9**	69.2

***p* = .019 †*p* < .001 ***p*= .031**

J Clin Oncol. 2006;24(22):3657-63

Single-agent gemcitabine, vinorelbine, or docetaxel in patients with advanced NSCLC with poor PS and/or are elderly

- A randomized phase II trial
- Of the 134 patients, 43 received gemcitabine, 45 vinorelbine, and 46 docetaxel. The response rate was 16%, 20%, 22% for gemcitabine, vinorelbine, and docetaxel, respectively.
- No differences in OS and PFS.

J Thorac Oncol. 2007;3: 230–236

Chemotherapy for Advanced NSCLC in Elderly
Doublets vs. Single Agent

Comparison of efficacy and safety of single-agent and doublet chemotherapy in advanced NSCLC in the elderly

- A meta-analysis
- Eight eligible studies included 1804 patients (mean age 73; 1362 men and 368 women; 461 stage IIIB and 1114 stage IV; 600 epidermoid cancers, 565 adenocarcinomas, 410 other pathological types).

Des Guetz G et al, J Clin Oncol 28:15s, 2010

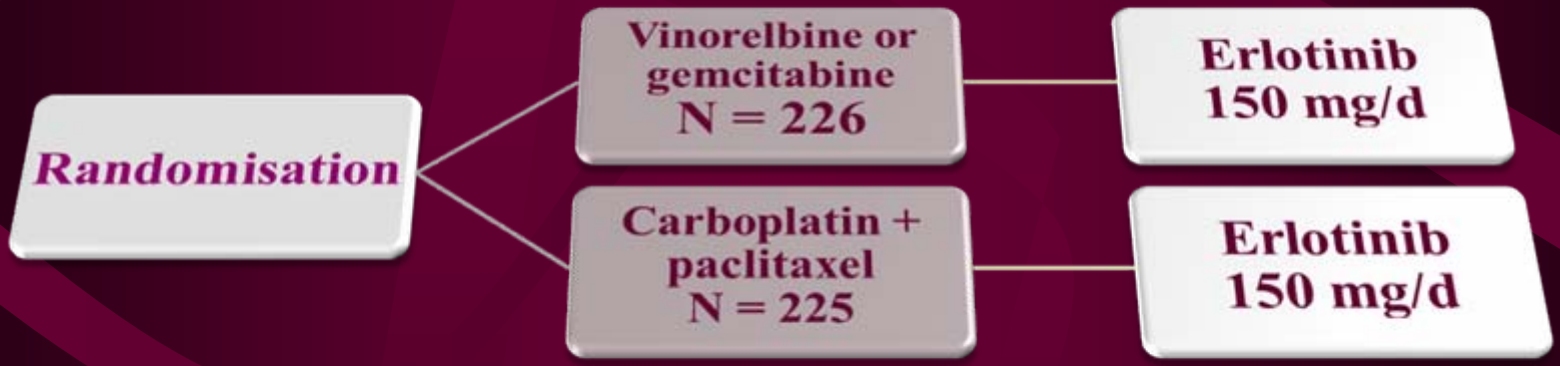
Comparison of efficacy and safety of single-agent and doublet chemotherapy in advanced NSCLC in the elderly

- 1-year OS was similar for single-agent and doublets (HR 0.98; 95% CI: 0.92-1.05), RR was significantly improved (HR 1.31; 95 % CI 1.08-1.58; p=0.005).
- HRs for nausea/vomiting, neutropenia, thrombopenia and anemia were significantly higher for doublets than for single agent

Des Guetz G et al, J Clin Oncol 28:15s, 2010

Weekly paclitaxel combined with monthly carboplatin versus single agent therapy in patients aged 70 to 89:

- IFCT-0501 randomized phase III study in advanced non-small cell lung cancer
- 451 chemo-naiive patients, stage IIIB/IV NSCLC, age 70-89, PS 0-2



Quoix E et al, Lancet 378:1079-88, 2011

Result

- Median PFS: doublet vs. single agent : 6.0 vs. 2.8 months ($p<0.001$)
- Median OS doublet vs. single agent : 10.3 vs. 6.2 months ($p<0.001$)

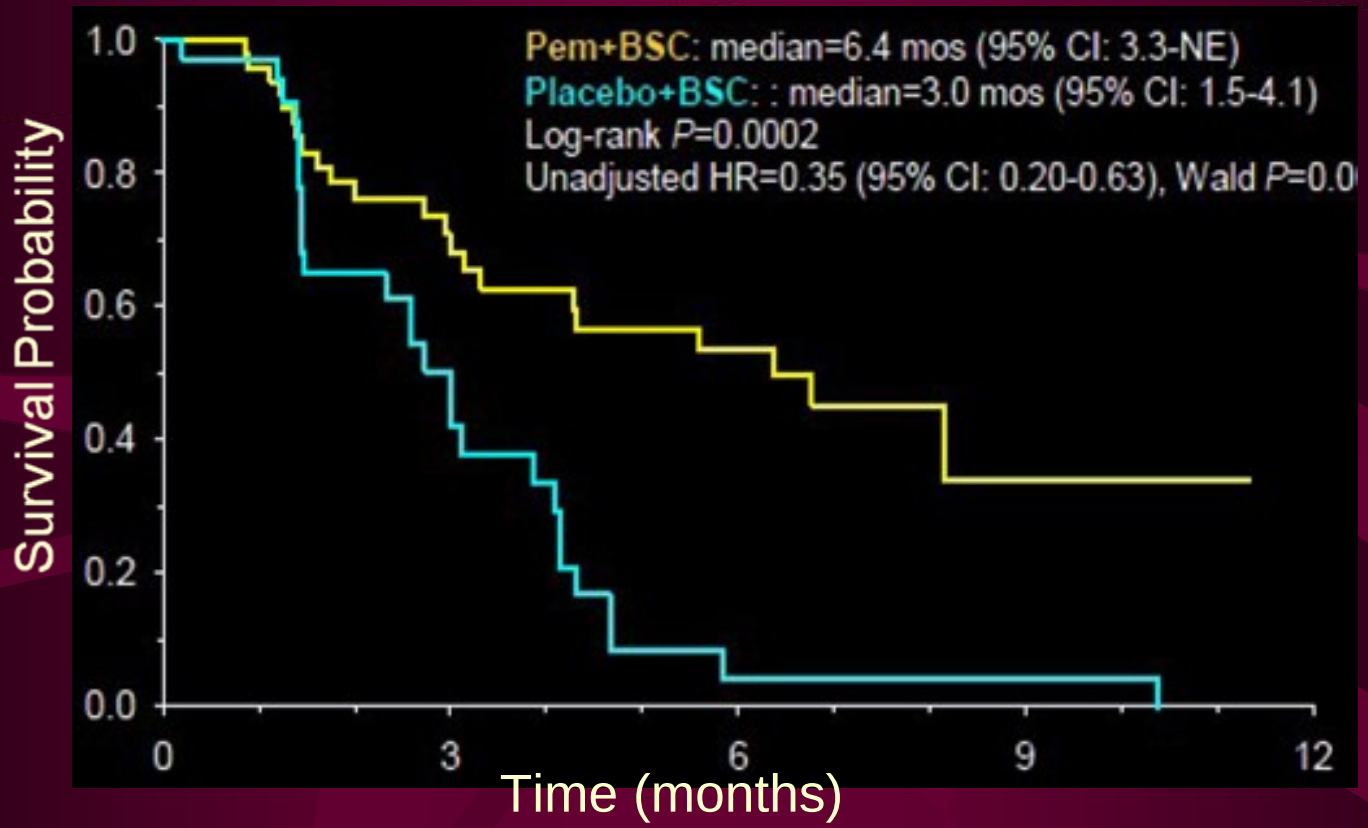
Quoix E et al, Lancet 378:1079-88, 2011

	Monotherapy group (n=225)			Doublet chemotherapy group (n=223)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
Haematological						
Decreased neutrophil count	28 (12·4%)	15 (6·7%)	13 (5·8%)	108 (48·4%)	69 (30·9%)	39 (17·5%)
Decreased haemoglobin concentration	10 (4·4%)	10 (4·4%)	0	21 (9·4$)	21 (9·4)	0
Febrile neutropenia	6 (2·7%)	3 (1·3%)	3 (1·3%)	21 (9·4%)	12 (5·4%)	9 (4·0%)
Decreased platelet count	2 (0·9%)	2 (0·9%)	0	15 (6·7%)	11 (4·9%)	4 (1·8%)
Non-haematological						
Asthenia	13 (5·8%)	13 (5·8%)	0	23 (10·3%)	20 (9·0%)	3 (1·3%)
Anorexia	2 (0·9%)	2 (0·9%)	0	9 (4·0%)	9 (4·0%)	0
Worsening general condition	4 (1·8%)	4 (1·8%)	0	5 (2·2%)	4 (1·8%)	1 (0·4%)
Diarrhoea	2 (0·9%)	2 (0·9%)	2 (0·9%)	6 (2·7%)	6 (2·7%)	0
Nausea and vomiting	2 (0·9%)	2 (0·9%)	0	6 (2·7%)	6 (2·7%)	0
Pulmonary disorder	5 (2·2%)	5 (2·2%)	0	3 (1·3%)	3 (1·3%)	0
Sensory neuropathy	1 (0·4%)	1 (0·4%)	0	7 (3·1%)	7 (3·1%)	0
Mouth irritation	2 (0·9%)	2 (0·9%)	2 (0·9%)	2 (0·9%)	2 (0·9%)	0
Constipation	2 (0·9%)	2 (0·9%)	2 (0·9%)	1 (0·4%)	1 (0·4%)	0
Dyspnoea	1 (0·4%)	1 (0·4%)	0	1 (0·4%)	1 (0·4%)	0
Infection	1 (0·4%)	1 (0·4%)	0	1 (0·4%)	1 (0·4%)	0
Pulmonary embolism	0	0	0	2 (0·9%)	0	2 (0·9%)
Bronchitis	0	0	0	1 (0·4%)	1 (0·4%)	0
Raised γ-glutamyltransferase concentration	0	0	0	1 (0·4%)	1 (0·4%)	0
Superficial phlebitis	0	0	0	1 (0·4%)	1 (0·4%)	0

Table 5: Grade 3–4 toxic effects in patients who received at least one dose of first-line therapy

Chemotherapy for Advanced NSCLC in Elderly: Maintenance Therapy

Investigator-assessed Progression-free Survival: Age≧70 Cohort ＊



Pem+BSC(n)	52	25	14	4	0
Plcb+BSC(n)	40	10	1	1	0

EGFR-TKI for Advanced NSCLC in Elderly

Gefitinib Monotherapy in Chemotherapy-Naı¨ve Patients ≧ 75 Year Old with Advanced NSCLC

- A phase II trial with 49 patients
- ECOG PS of 0–2, and adequate organ functions received 250 mg/day of gefitinib.
- Median age (range) : 80 (75–90) yrs
- 32 female (65%) and 40 adenocarcinoma (82%).
- The objective RR was 25% (95%CI, 13–39%).
- Median survival time was 10 months (95%CI , 7–20) and 1-year survival rate was 50%.

J Thorac Oncol. 2008;3: 1166–71

Gefitinib Monotherapy in Chemotherapy-Naı¨ve Patients ≧ 75 Year Old with Advanced NSCLC with *EGFR* mutation

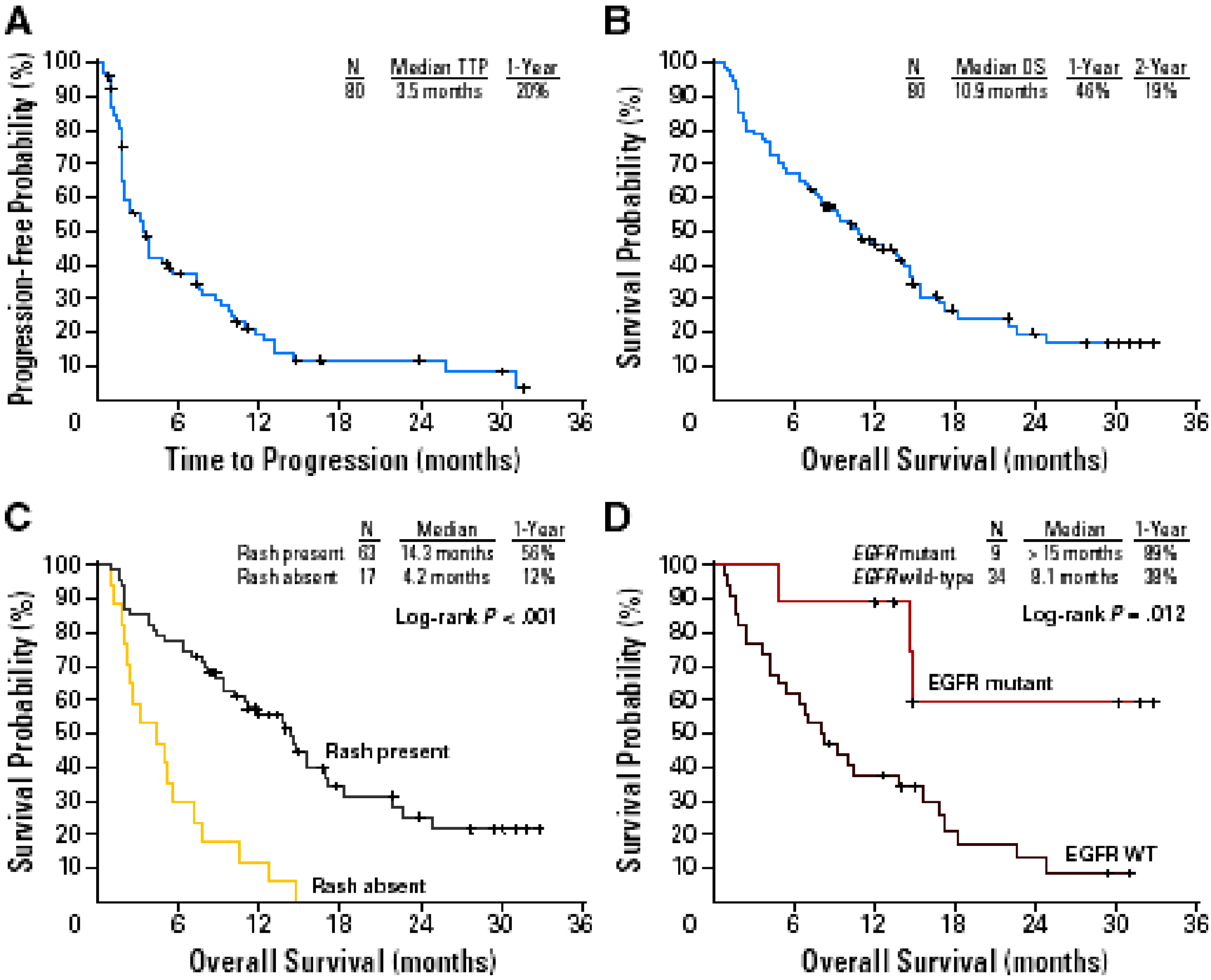
- A phase II trial with 31 patients
- ECOG PS of 0–2, *EGFR* mutation (+)
- Median age (range) : 80 (75–87) yrs
- 25 female (81%) and 30 adenocarcinoma (97%).
- The objective RR was 74% (95%CI, 58-91%).
- Median PFS was 13.6 months.

Minegishi et al, ASCO 2010 June

Erlotinib for Advanced NSCLC in Chemo-naïve Elderly patients

- A phase II, multicenter, open-label study
- 80 eligible patients >= 70 years.
- M: F= 1:1, adenocarcinoma: (64%)
- PR: 8, SD: 33 for >2 months
- Median TTP: 3.5 m. OS: 10.9 m
- 1 yr/2 yr survival: 46/19%
- *EGFR* mutation: 9/43

J Clin Oncol. 2007 Mar 1;25(7):760-6.

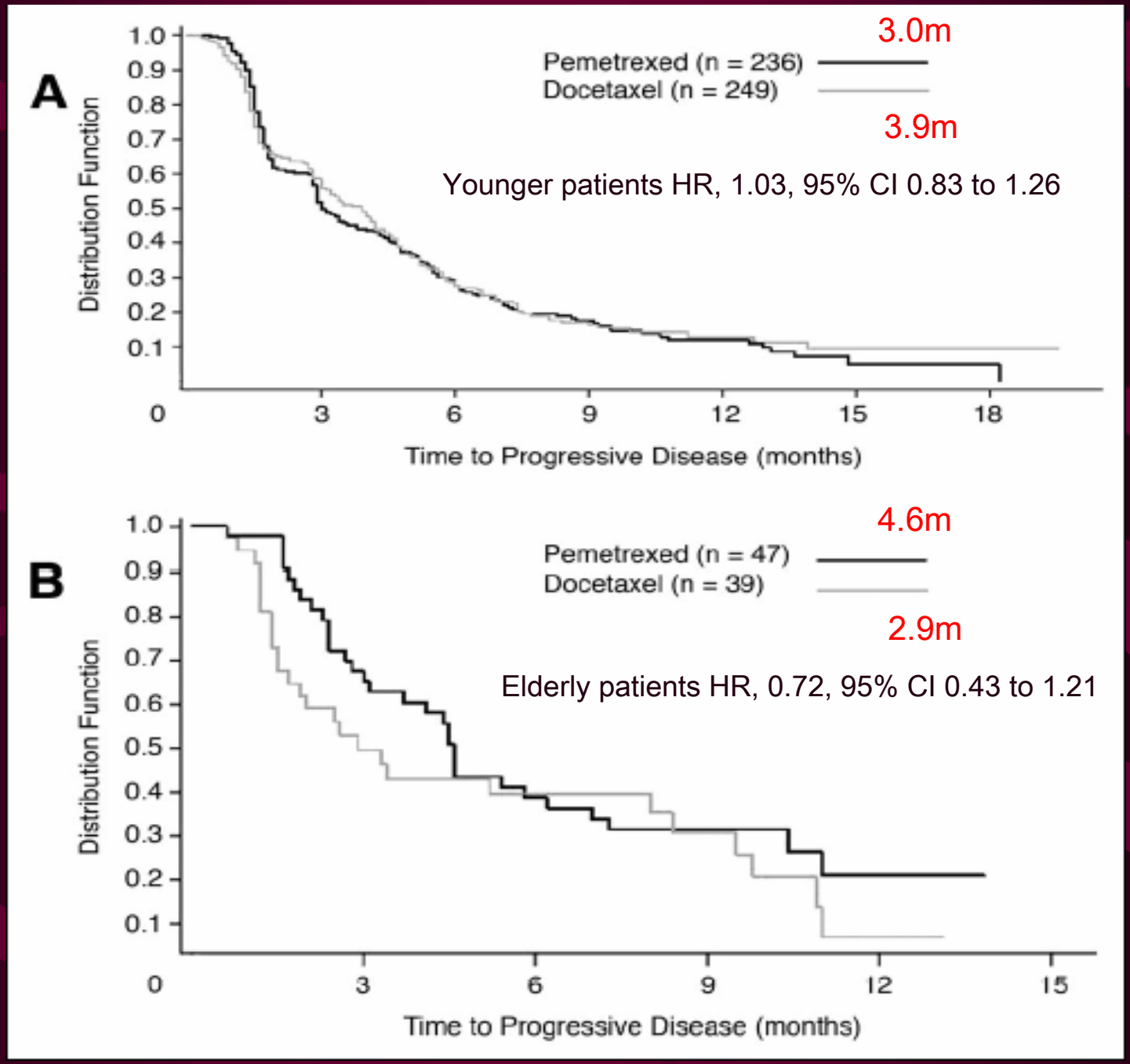

A
Progression-Free Probability (%)
N
80
Median TTP
3.5 months
1-Year
20%
Time to Progression (months)
B
Survival Probability (%)
N
80
Median OS
10.9 months
1-Year
46%
2-Year
19%
Overall Survival (months)
C
Survival Probability (%)
N
Median
1-Year
Rash present
63
14.3 months
56%
Rash absent
17
4.2 months
12%
Log-rank P < .001
Rash present
Rash absent
Overall Survival (months)
D
Survival Probability (%)
N
Median
1-Year
EGFR mutant
9
> 15 months
89%
EGFR wild-type
34
8.1 months
38%
Log-rank P = .012
EGFR mutant
EGFR WT
Overall Survival (months)

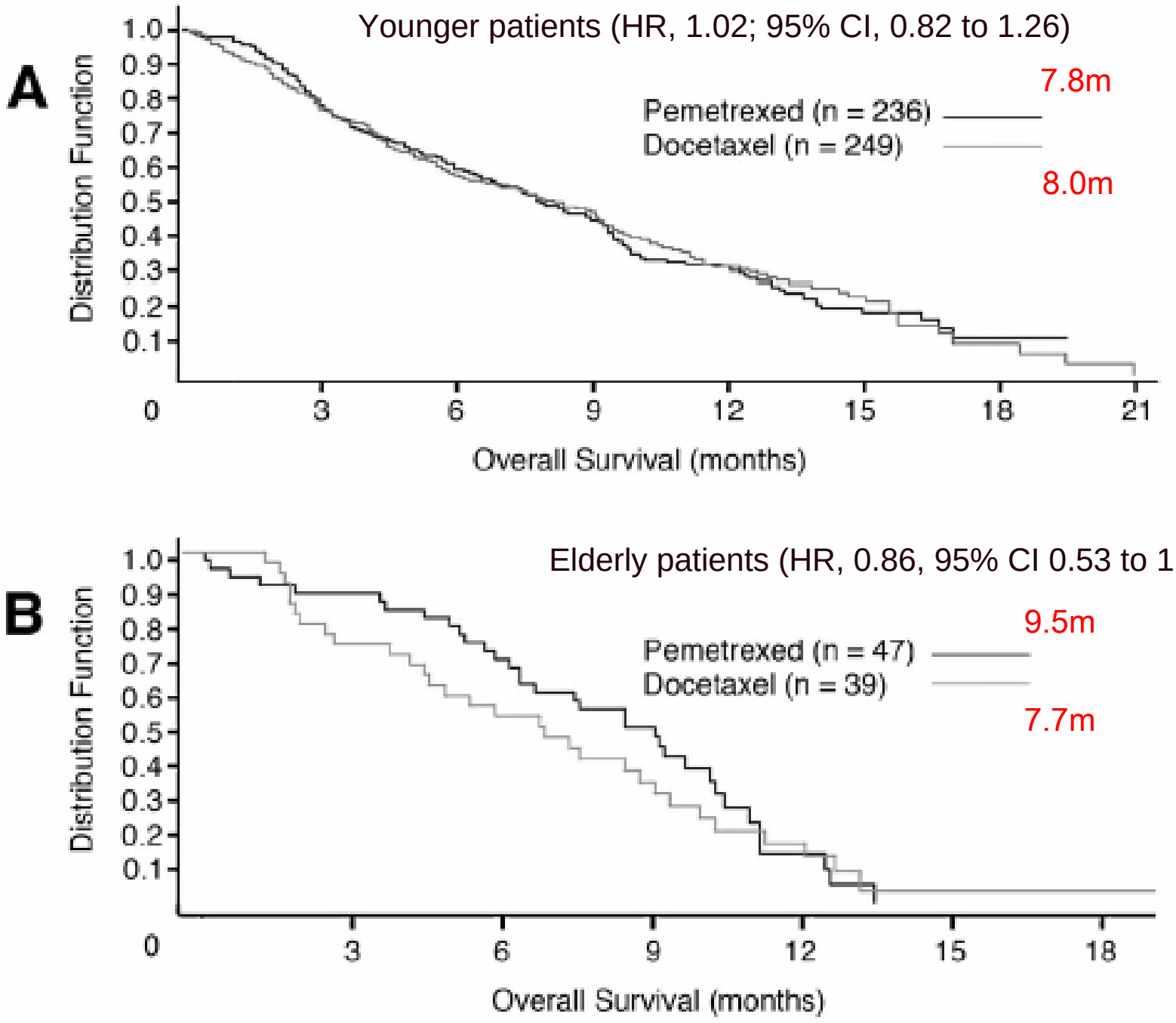
2nd line Therapy for Elderly Patients with Advanced NSCLC

Pemetrexed vs. Docetaxel in Elderly Patients With Previously Treated Advanced NSCLC

- Retrospective analysis of a large second-line trial.
- Docetaxel 75 mg/m^2 vs. pemetrexed 500 mg/m^2 every 3 weeks
- analyzed for efficacy and toxicity comparisons between age groups (>=70 and < 70) and treatment arms.
- 86 patients (15%) were 70 years old.

J Clin Oncol 2006, 24:4405-4411


A
Distribution Function
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
3
6
9
12
15
18
Time to Progressive Disease (months)
Pemetrexed (n = 236)
Docetaxel (n = 249)
3.0m
3.9m
Younger patients HR, 1.03, 95% CI 0.83 to 1.26
B
Distribution Function
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
3
6
9
12
15
Time to Progressive Disease (months)
Pemetrexed (n = 47)
Docetaxel (n = 39)
4.6m
2.9m
Elderly patients HR, 0.72, 95% CI 0.43 to 1.21


A
Younger patients (HR, 1.02; 95% CI, 0.82 to 1.26)
7.8m
Pemetrexed (n = 236)
Docetaxel (n = 249)
8.0m
Distribution Function
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
3
6
9
12
15
18
21
Overall Survival (months)
B
Elderly patients (HR, 0.86, 95% CI 0.53 to 1.42)
9.5m
Pemetrexed (n = 47)
Docetaxel (n = 39)
7.7m
Distribution Function
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
3
6
9
12
15
18
Overall Survival (months)

Pemetrexed vs. Docetaxel in Elderly Patients With Previously Treated Advanced NSCLC

- Febrile neutropenia was less frequent in elderly patients treated with pemetrexed (2.5%) compared with docetaxel (19%; p =.025), with only one death as a result of toxicity (docetaxel arm).

First-Line Systemic Therapy for advanced NSCLC in the Elderly

- Elderly with good performance
  - *EGFR* wild type: Single-agent vs. Platinum-base doublet
  - *EGFR* mutation:TKI therapy
- Elderly with PS ≧ 2 patients
  - EGFR-TKI therapy, single agent, supportive care
- Predictive marker for treatment response and prognosis
- Quality of life

Tolerance of Treatment in Elderly Patients with Advanced NSCLC

- Renal function: Ccr>60 for cisplatin, Ccr>45 for Pemetrexed
- Hematological Toxicity: Prophylatic G-CSF
- Reducing chemotherapy dose: No evidence based guideline
- Predictive scoring system for side effect

Drugs Aging 2011 28:885-894

Thank You for Your Attention