

Present and Future of Adjuvant Therapy in Early Stage NSCLC

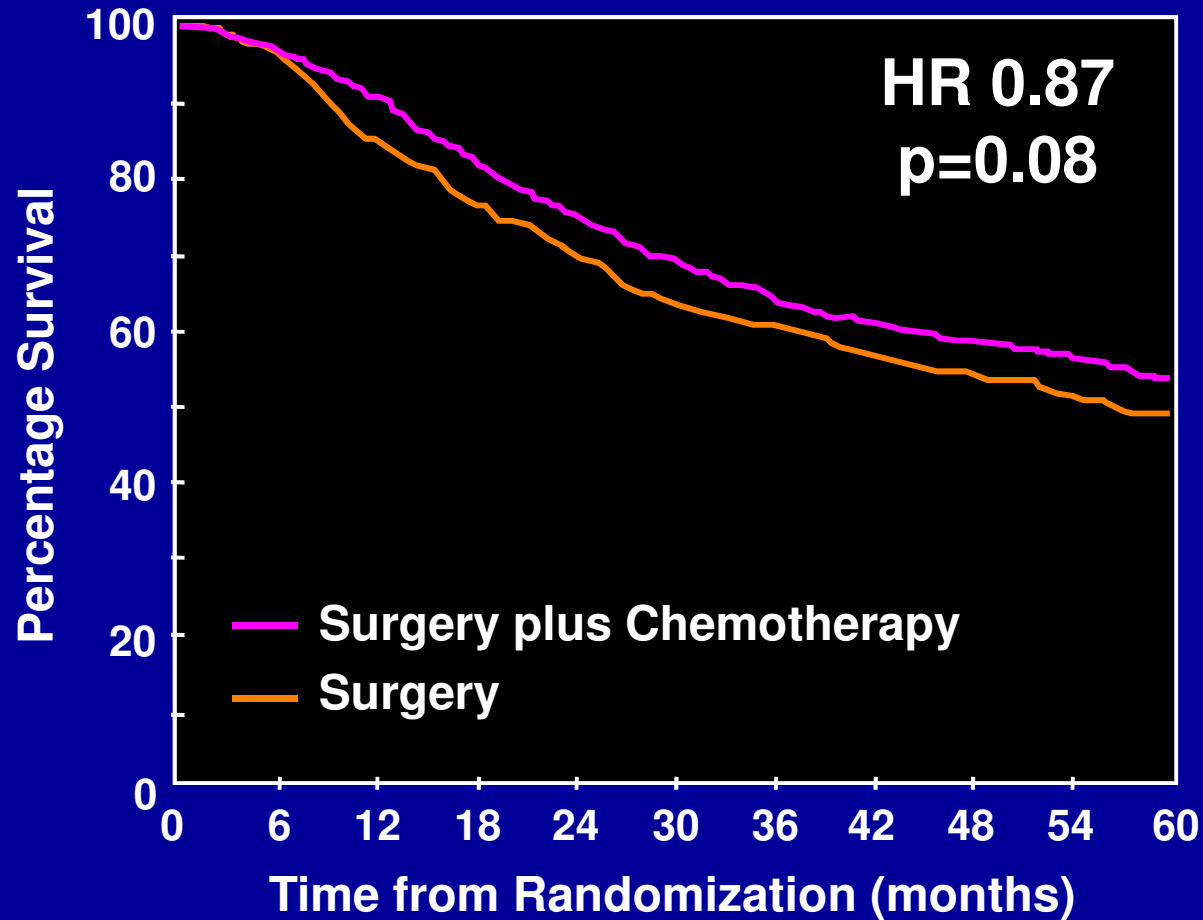
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Stanford University, Stanford Cancer Center

Post-operative (Adjuvant) Chemotherapy History

- 1957 VA 1002 pts Surgery +/- nitrogen mustard
No benefit
- 1970s Immunotherapy (BCG) - no benefit
- 1981 LCSG trial no benefit
- 1991 Consensus statement:
Adjuvant chemotherapy is experimental
- 1995 Meta-analysis 9387 pts/ 52 trials
Surgery +/- cisplatin chemo HR 0.87 (p=0.08)
13% decreased risk of death
5% absolute benefit at 5 years

1995 Meta-Analysis Adjuvant Cisplatin Trials n=1394



Post 1995 Meta-Analysis (HR 0.87, p.08): NSCLC Randomized Adjuvant Platinum Trials

Trial	Stage	n	Chemo	↑Survival
ECOG	II-III A	488	Cis/VP16	No
ALPI	I-III	1209	Cis/MVd	No
BLT	I-III	381	Cis/4 options	No
IALT	I-III	1867	Cis/Vinca or VP16	Yes
BR.10	IB-II	482	Cis/Vin	Yes
CALGB*	IB	344	Carbo/Pac	Yes → No
ANITA	I-III A	840	Cis/Vin	Yes

ECOG 3590

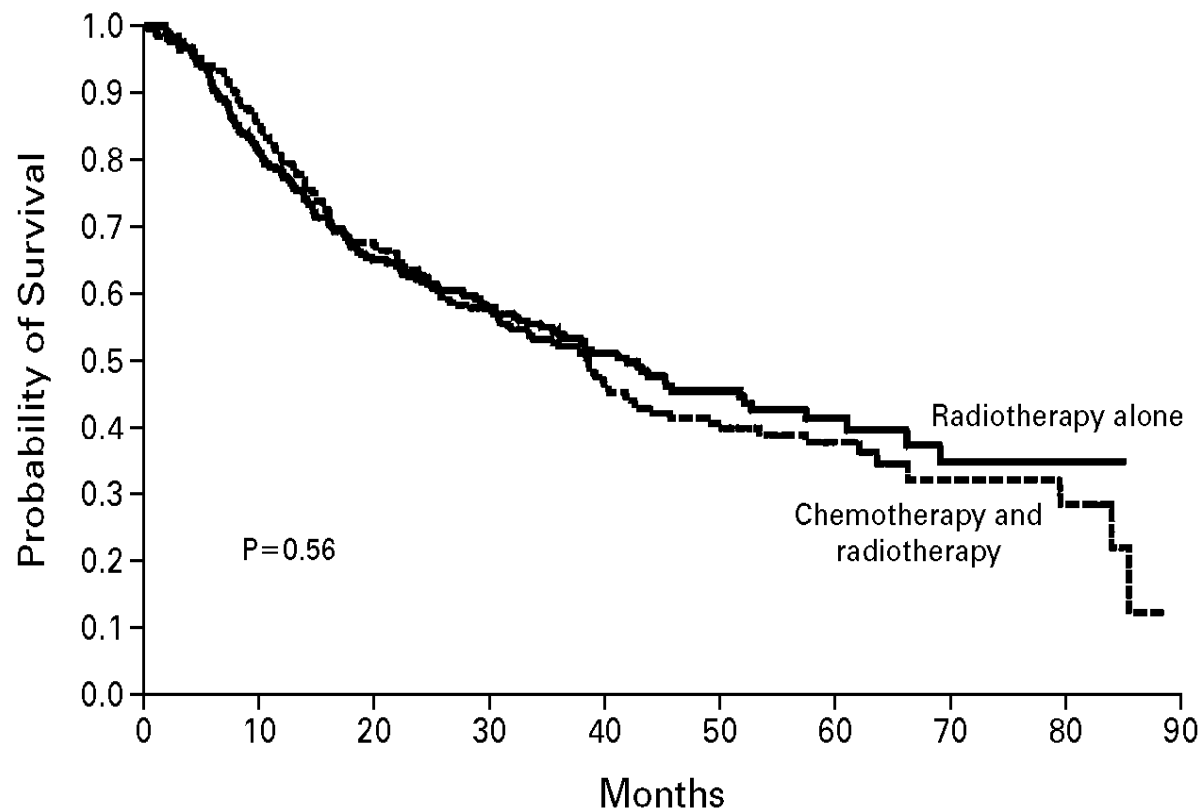
2000 - 488 Pts, Stage II-III A

- **Randomized to post-op radiation alone vs post-op radiation plus chemo***
- **Radiation therapy for all patients**
- **MST 38.8 mo vs 37.9 with chemo**
- **5 year survival 39% vs. 33% with chemo (p=.56)**

*cisplatin/etoposide

ECOG 3590 - 2000

Overall survival



	NO. OF PATIENTS	NO. OF DEATHS	MEDIAN SURVIVAL (mo)
Radiotherapy	242	132	38.8
Chemotherapy and radiotherapy	246	146	37.9

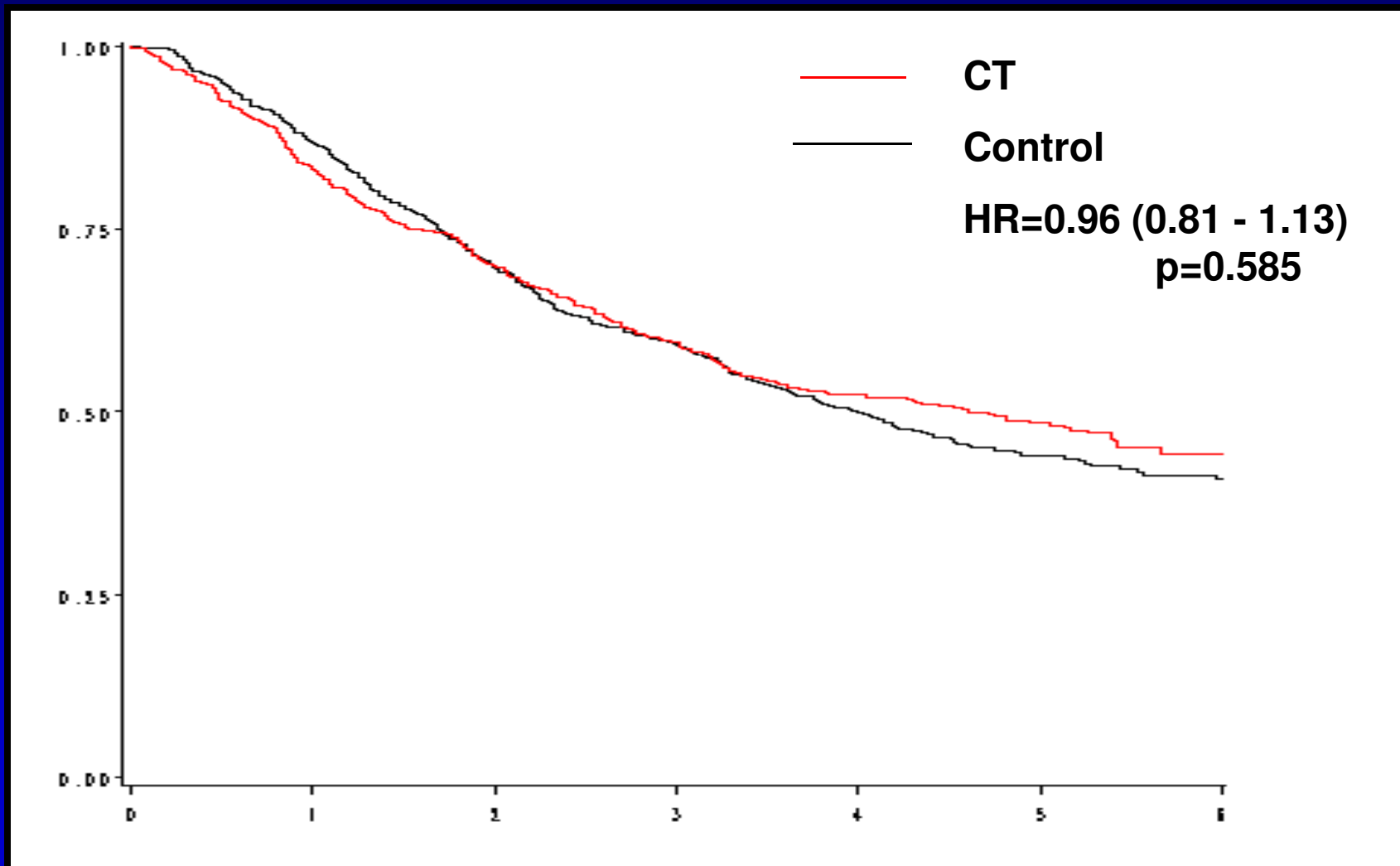
Adjuvant Lung Project: Italy (ALPI) 2002 - 1078 Pts, Stage I-III A

- Randomized to observation vs post-op chemo*
- Radiation therapy optional (~45%)
- Only 70% received all chemo (less if + XRT)
- Median f/u 64 months
- HR=0.96 (0.81 - 1.13), p=0.585

*mitomycin / vindesine / cisplatin

ALPI Overall Survival

PROBABILITY

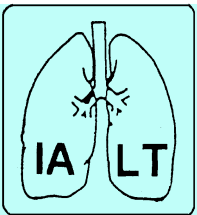


Scagliotti JNCI 95:1453-61, 2003

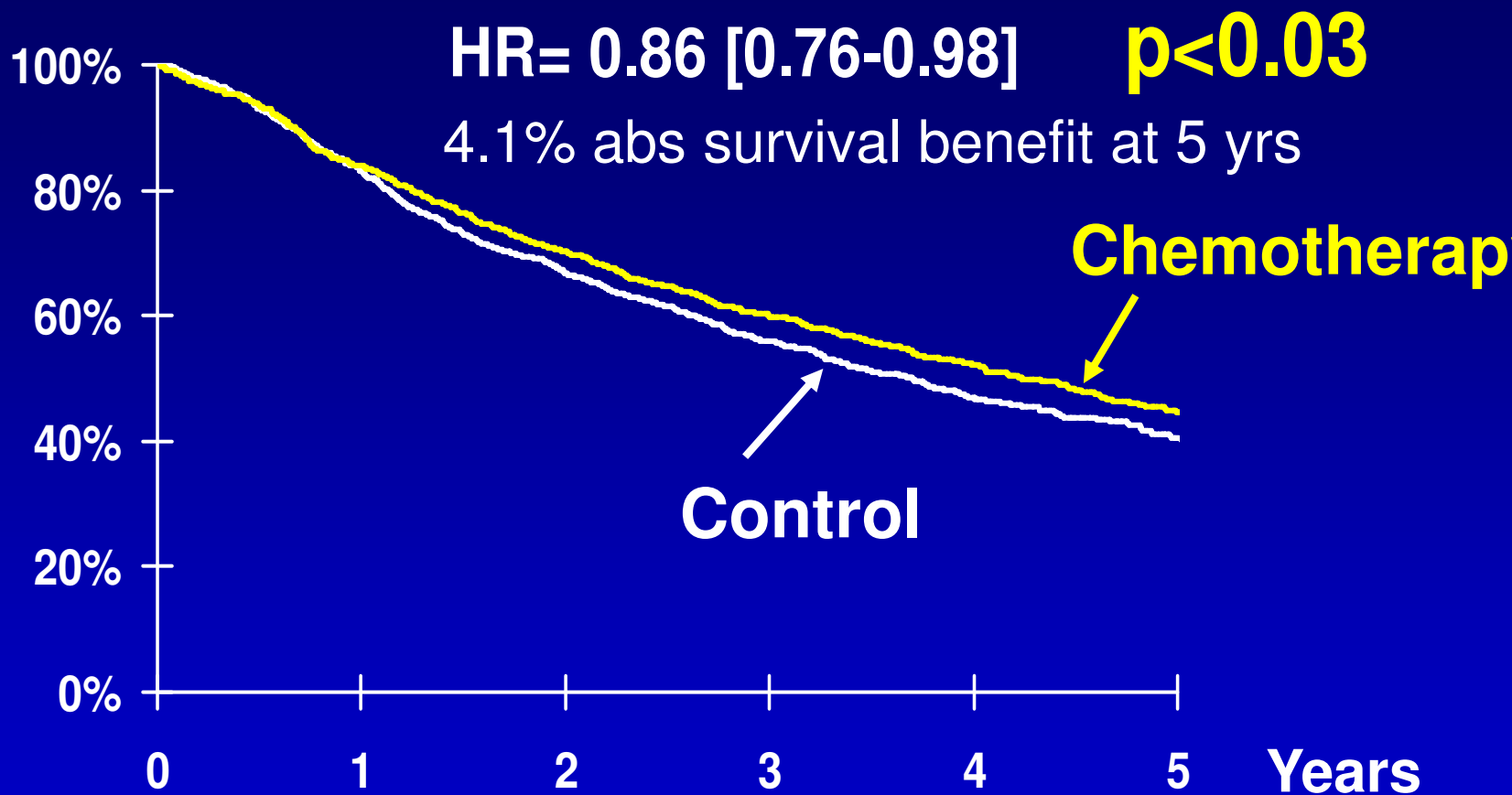
YEARS

Intl Adjuvant Lung Cancer Trial (IALT) 2003 - 1867 pts, I-III

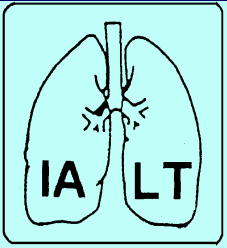
- Randomized to obs vs. post-op chemo*
- Radiation therapy optional (~30%)
- **4.1% absolute benefit at 5 years, $p < 0.03$**
- MST 40 mo vs 44 mo with chemo
- HR 0.86 [0.76-0.98]
- Stage III > Stage I benefit , $p = 0.4$



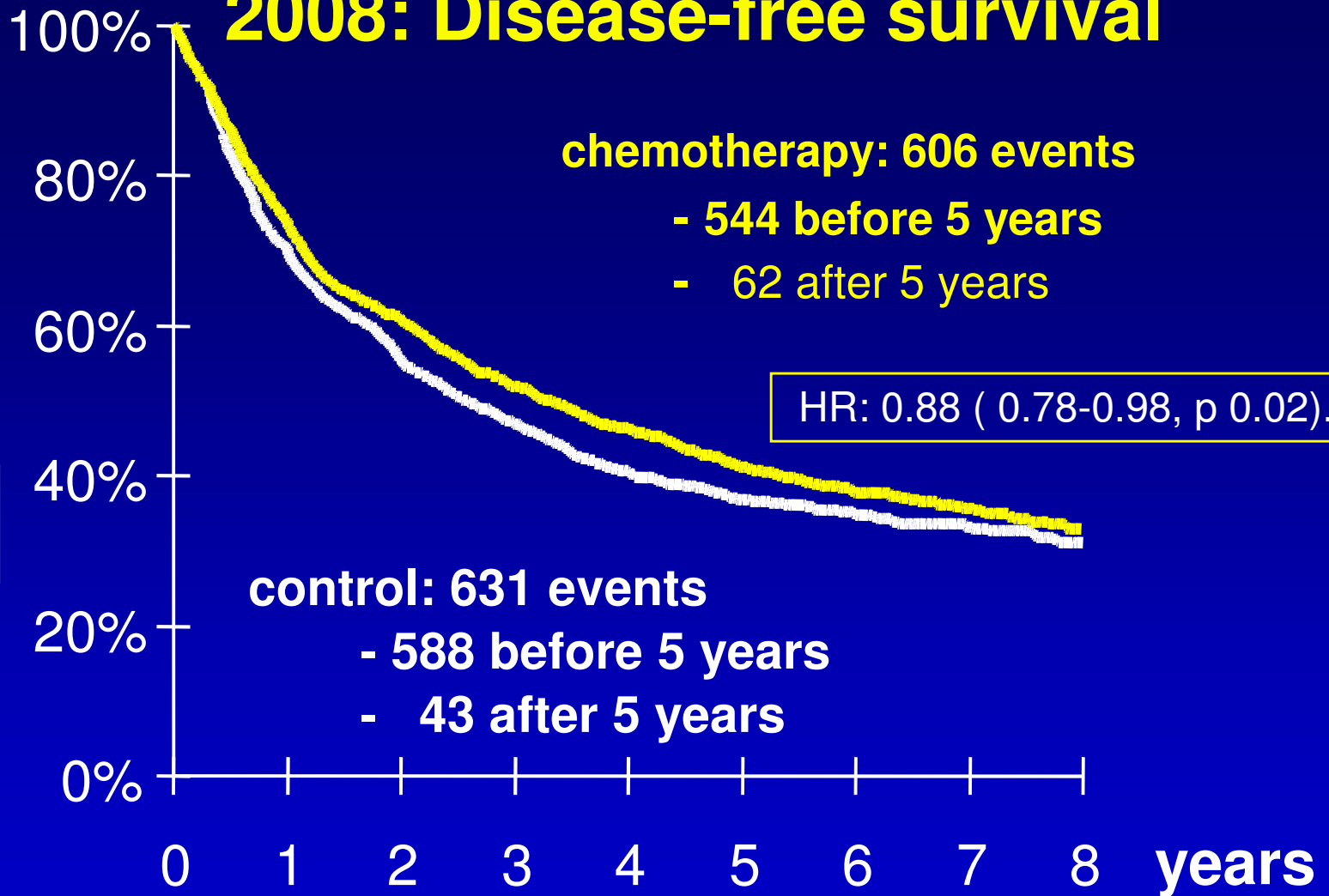
2004-IALT Overall Survival 1867 pts I-III



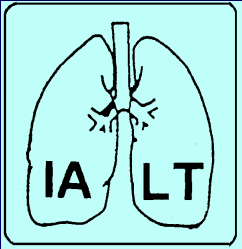
At risk	— 932	775	624	450	308	181
	— 935	774	602	432	286	164



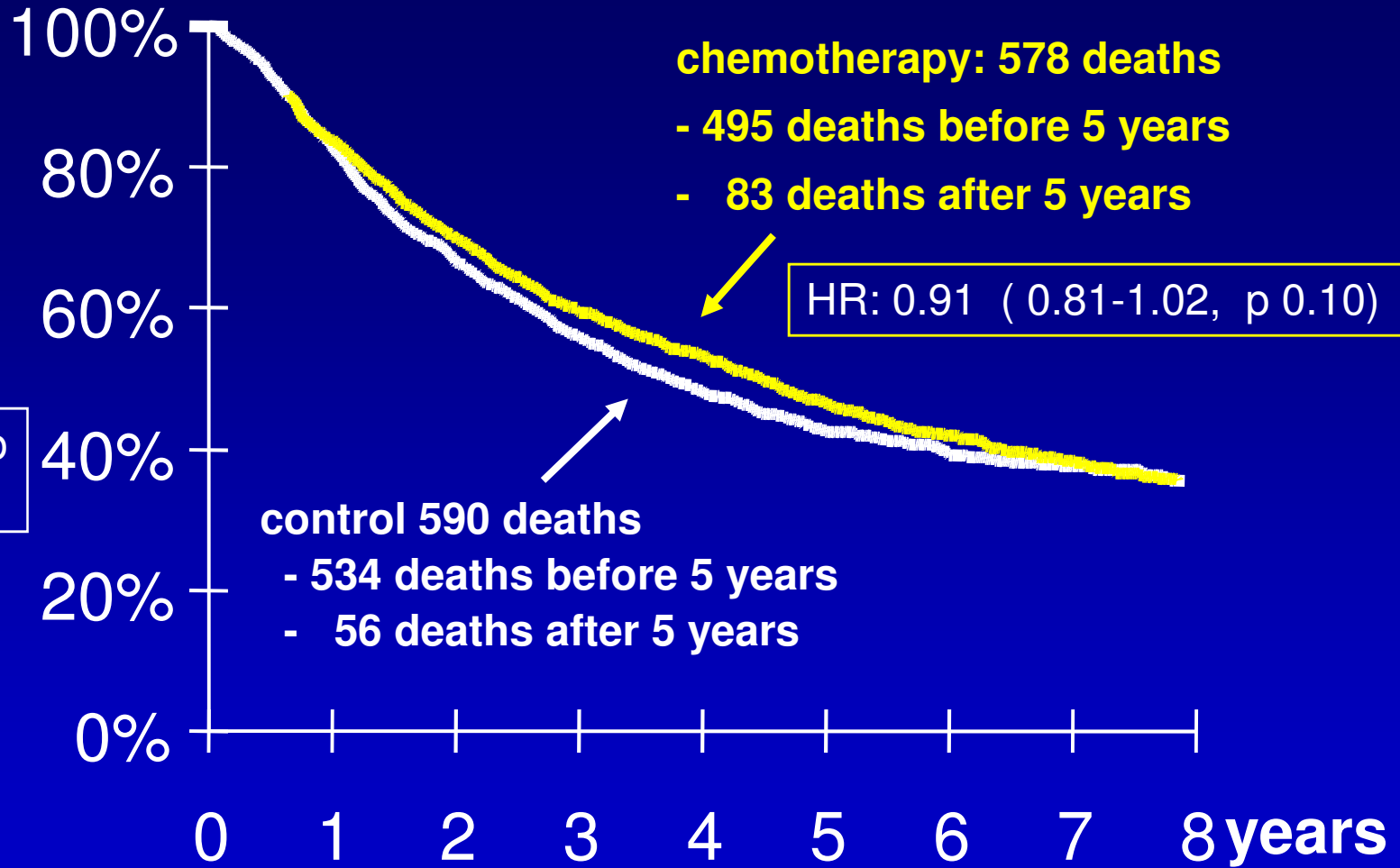
2008: Disease-free survival



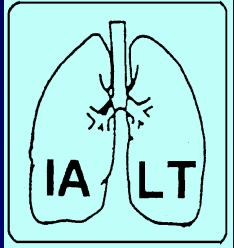
At risk	— 935	655	517	437	376	321	248	181	109
	— 932	686	565	480	423	354	267	190	123



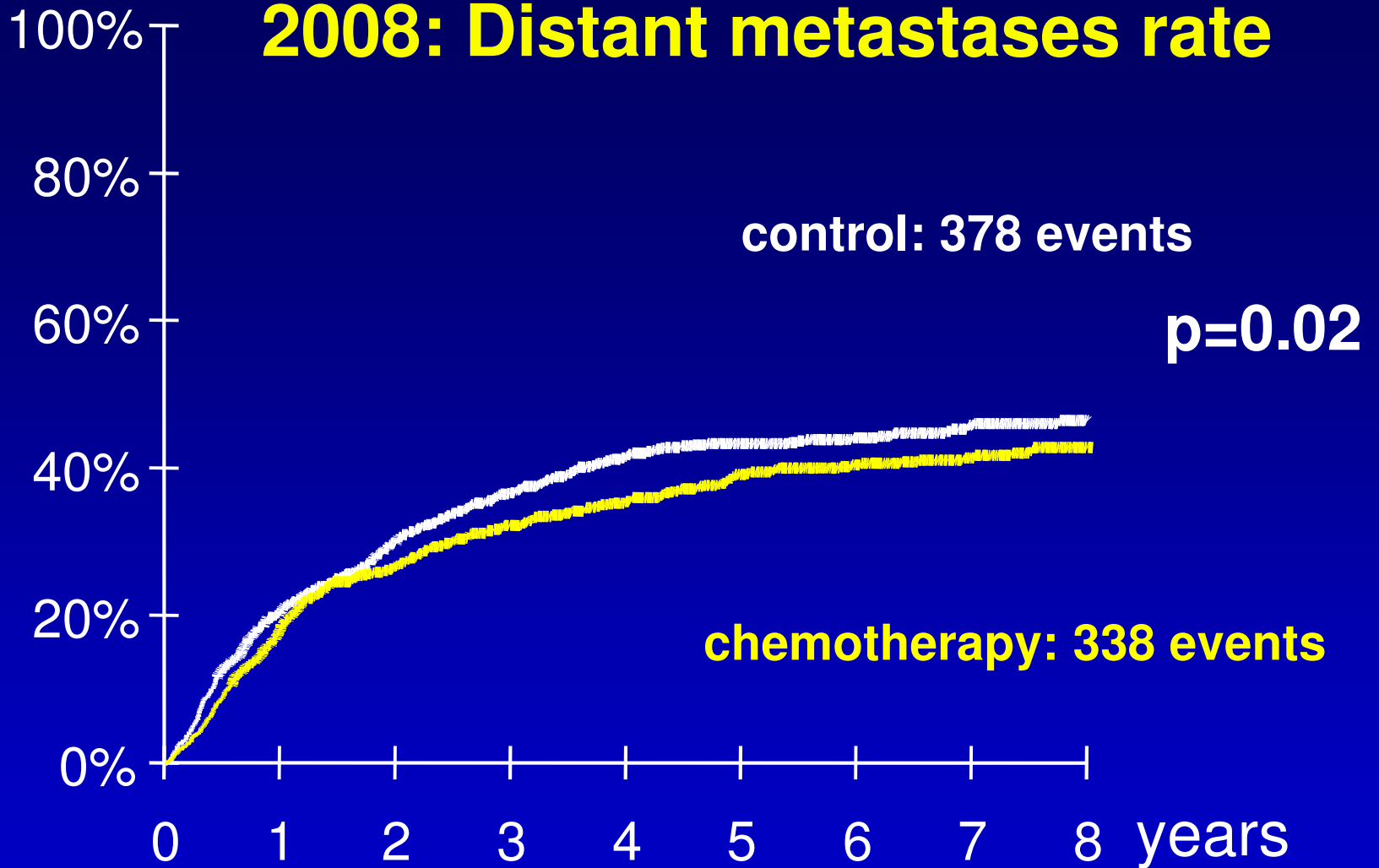
2008: Overall survival



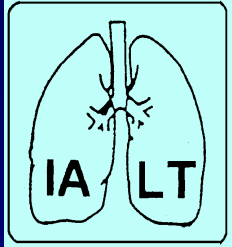
—	935	775	619	520	447	372	282	208	125
—	932	780	650	550	487	399	300	208	133



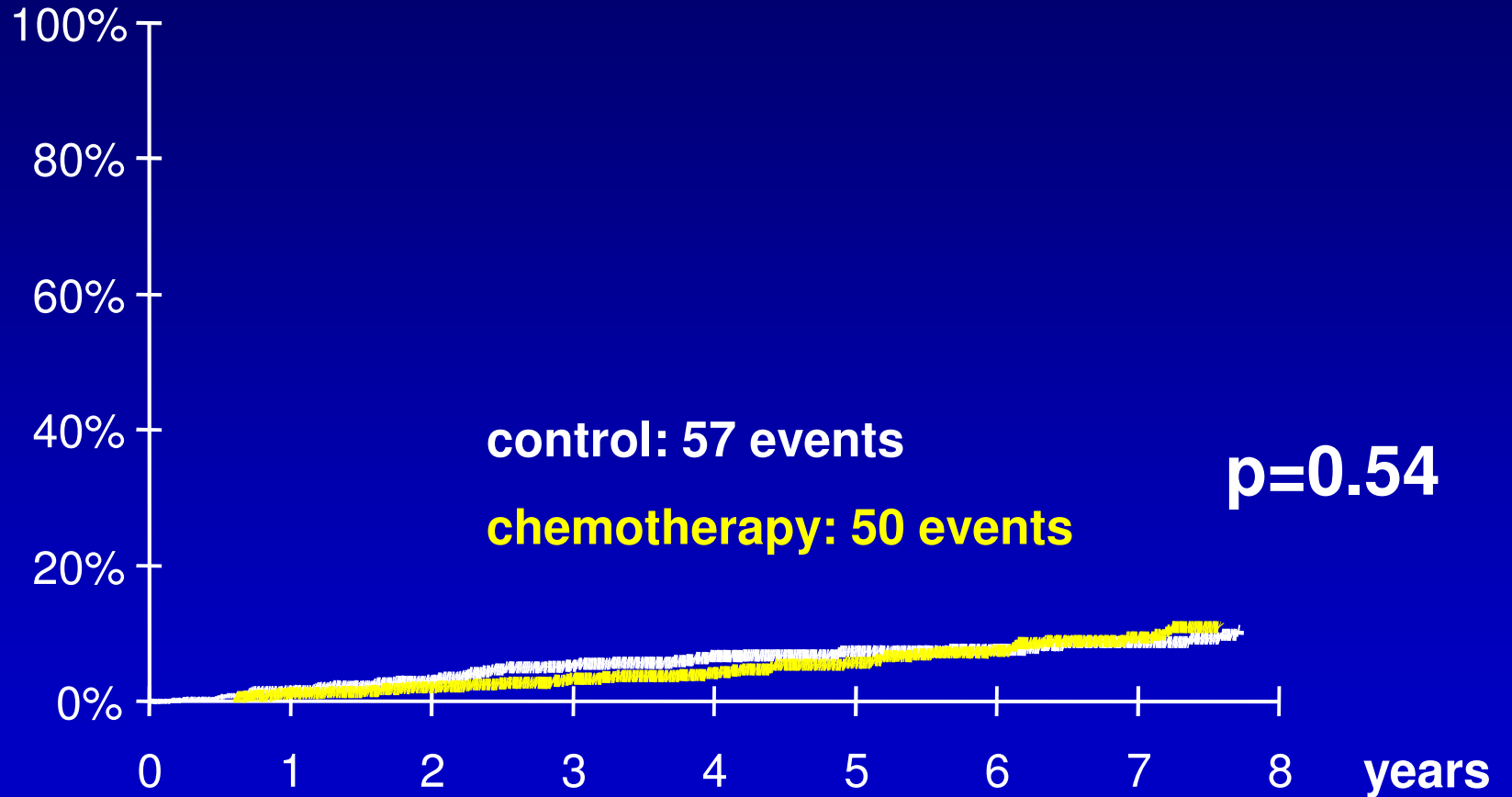
2008: Distant metastases rate



At risk	0	1	2	3	4	5	6	7	8
—	935	695	553	464	400	343	267	194	118
—	932	704	591	501	446	367	277	196	127

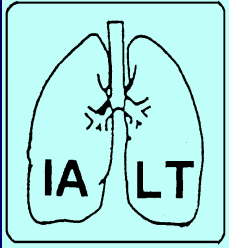


2008:Second malignancies

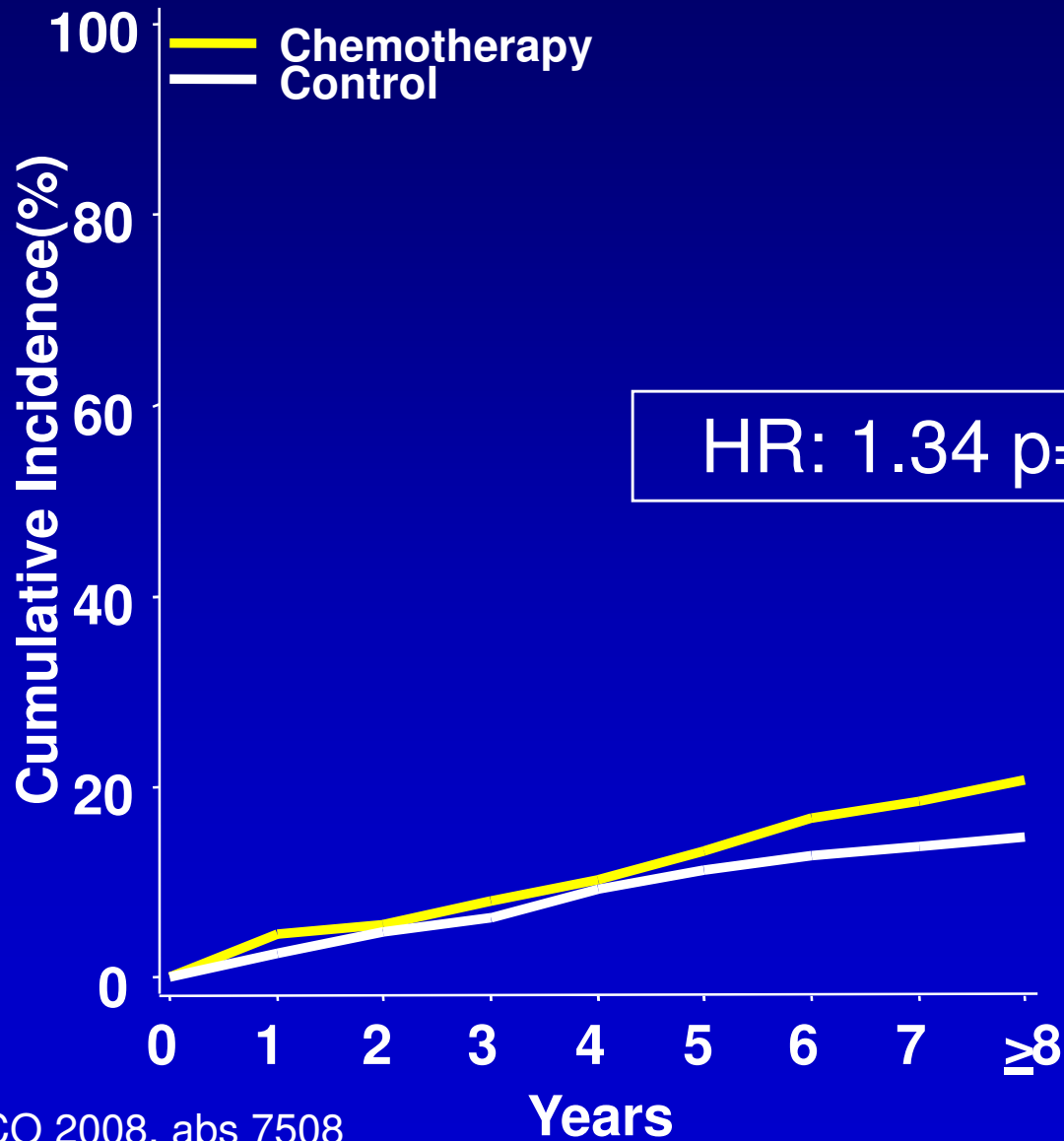


At risk	— 935	764	604	496	425	358	272	201	121
	— 932	772	639	539	474	383	282	193	123

Le Chevalier, PASCO 2008, abs 7508



2008: Non-lung cancer mortality



HR: 1.34 p=0.06

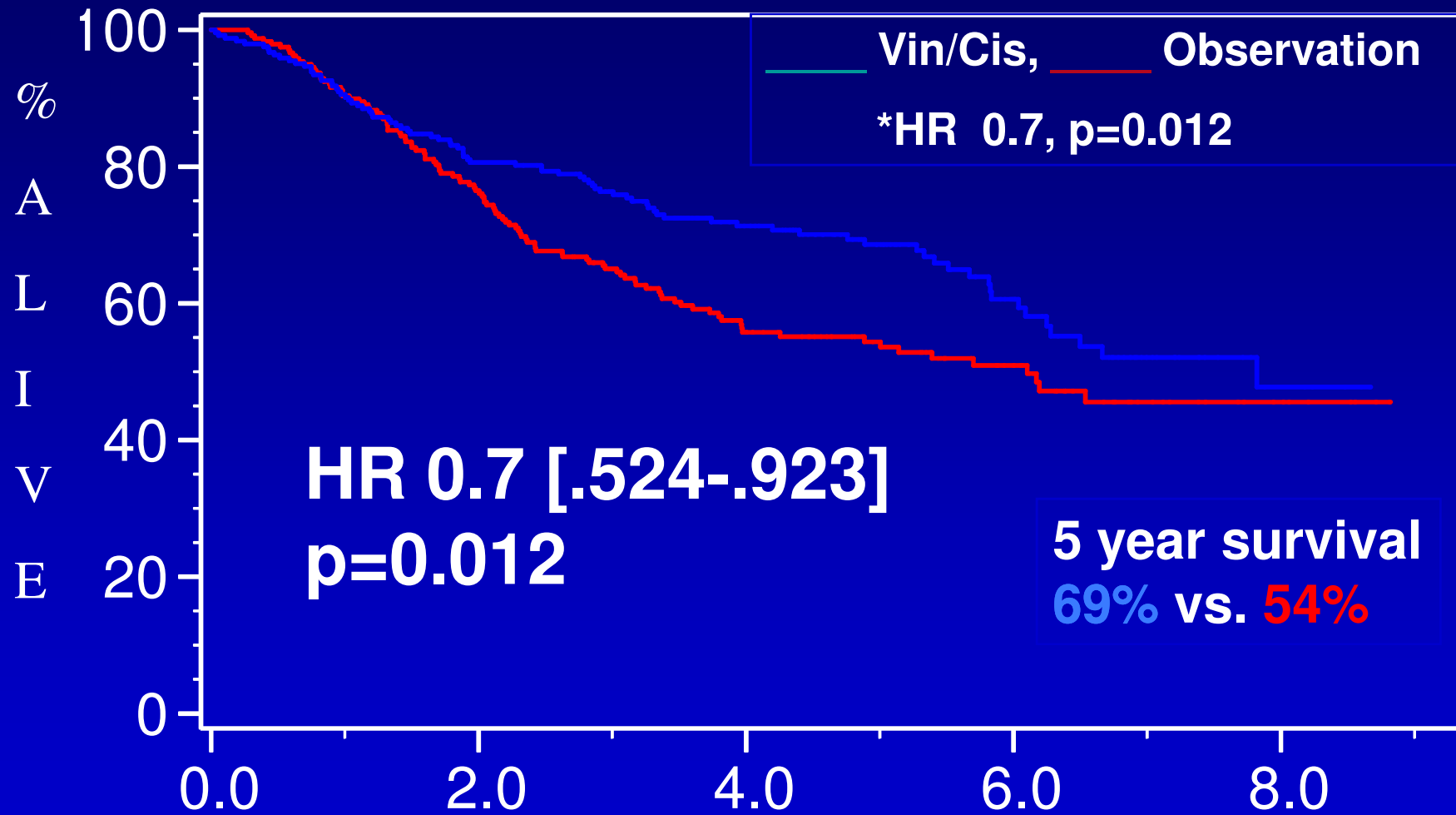
IALT updates summary

- Loss of survival benefit for group as a whole at 7.5 years
- Still improvement in lung cancer death rate
- Not due to second malignancies
- No clear explanation
- Increased non-cancer deaths, but why?
- How does this relate to other positive adjuvant trials?

NCIC-CTG JBR.10

- 482 pts, Stage IB-IIB only
- **15% survival advantage at 5 years**
- HR 0.7, $p=.012$
- Benefit only in stage II in subset analysis
- No data presented yet on longer term follow-up

JBR.10 - Overall Survival

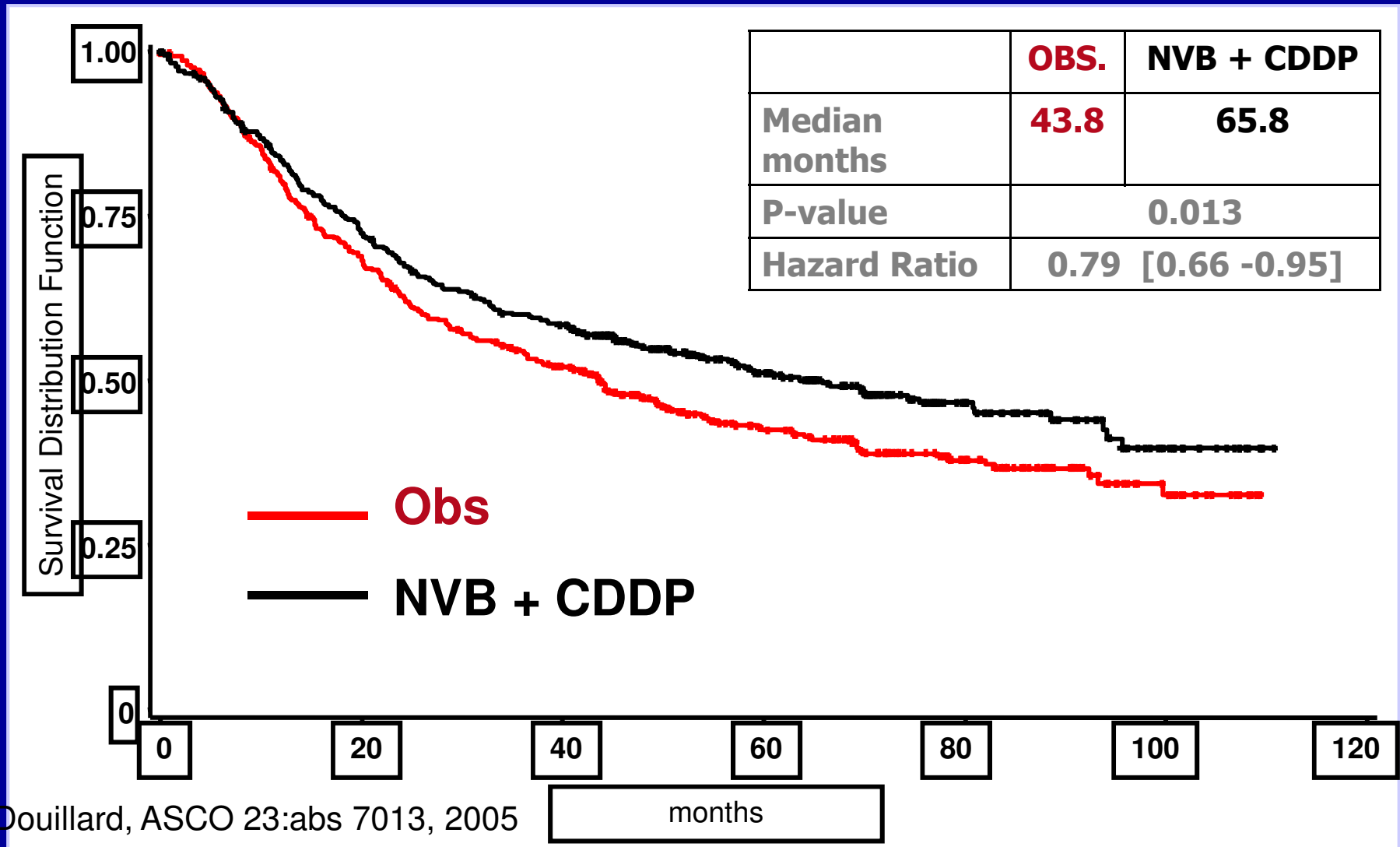


ANITA

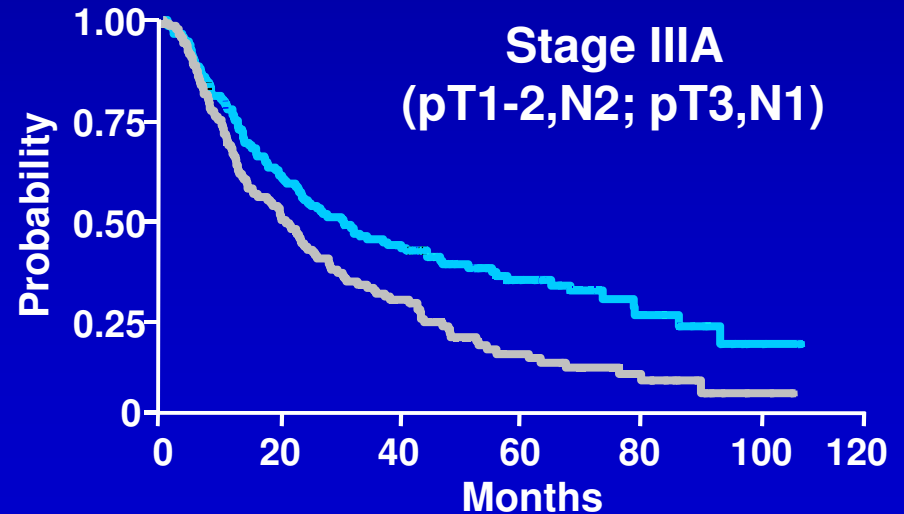
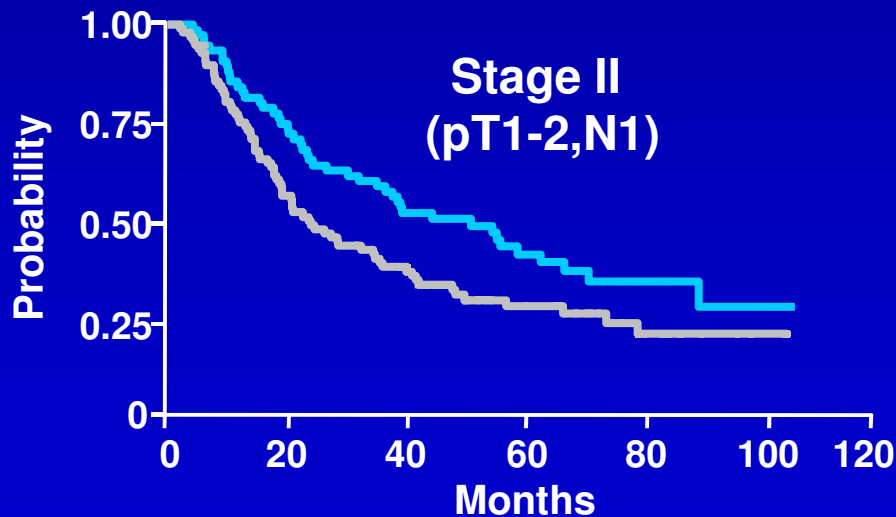
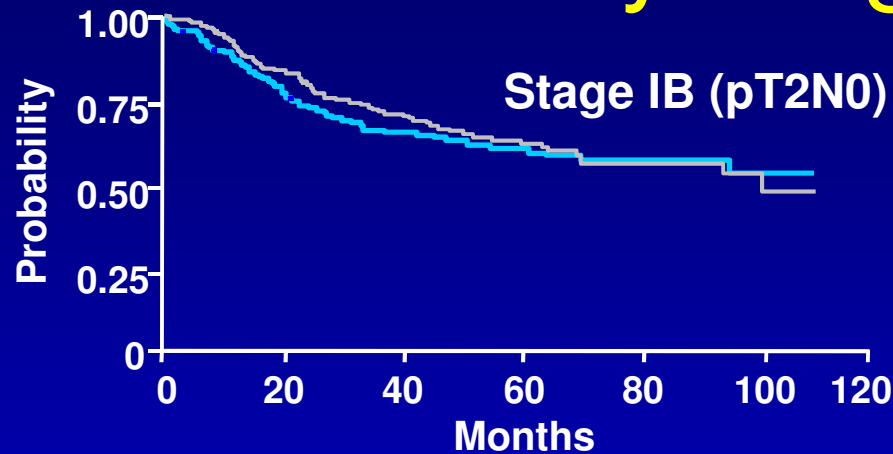
- ANITA 840 pts, stage IB-IIIA
- 8.6% survival advantage at 5 years
- **8.4% absolute survival benefit at 7 yrs**
- HR 0.7 [0.66-0.95], p =.013
- Benefit only in stage II and IIIA in subset analysis

ANITA Trial

Overall survival - ITT population



Adjuvant Vinorelbine/Cisplatin for Resected Stage I, II, or IIIA NSCLC: ANITA Survival by Stage Subset



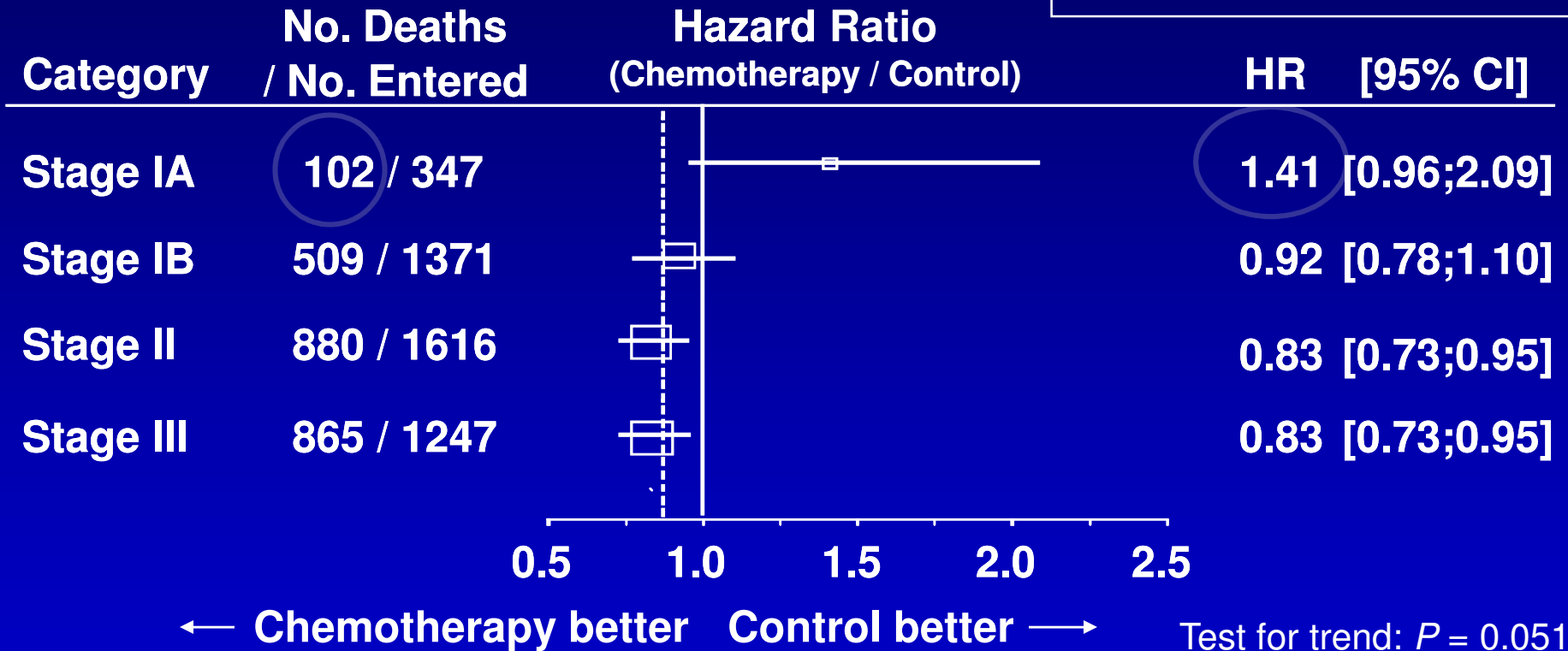
Lung adjuvant cisplatin evaluation (LACE)

- Individual patient data from cisplatin based adjuvant studies ALPI, ANITA, BLT, IALT, JBR10
- 5 trials including 4,584 patients
- Median follow-up: 5.1 years (3.1 – 5.9)

Adjuvant Chemotherapy for NSCLC

LACE Analysis by Stage

Overall Survival HR 0.89

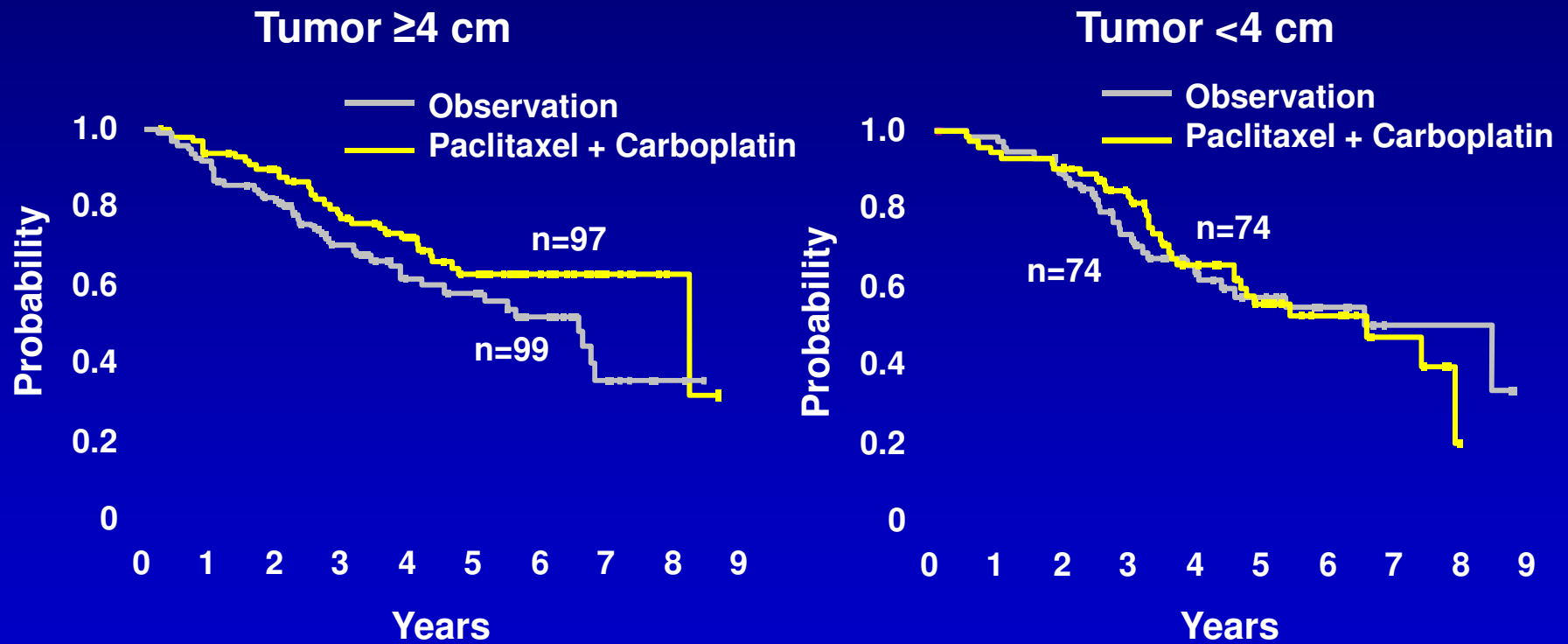


Adjuvant chemo has greatest benefit for stage II and III
and may be detrimental for stage IA
Longer follow-up warranted

CALGB 9633 - 344 pts, stage IB

- 4 cycles carboplatin/paclitaxel versus observation
- Overall Survival
- 2004 - HR 0.62 p =.028
- 2006 - HR 0.80 p=.1

CALGB 9633 Overall Survival by Tumor Size



HR = 0.66; 90% CI, 0.45-0.97; P=0.04 **HR = 1.02; 90% CI, 0.67-1.55; P=0.51**

Adjuvant UFT - Japan 2003, 978 pts, stage I

- Resected stage I, adenocarcinoma only
- Randomized to UFT vs placebo
 - UFT -fluoropyrimidine (Tegafur + uracil) po x 2 yrs
- Compliance
 - 79%-6mo, 71%-12mo, 64%-18 mo, 53%-24mo

% Alive at 5 yr

	UFT	Placebo	p =
Total	87.9	85.4	.035
T1	89	89	NS
T2	84.9	73.9	.00051

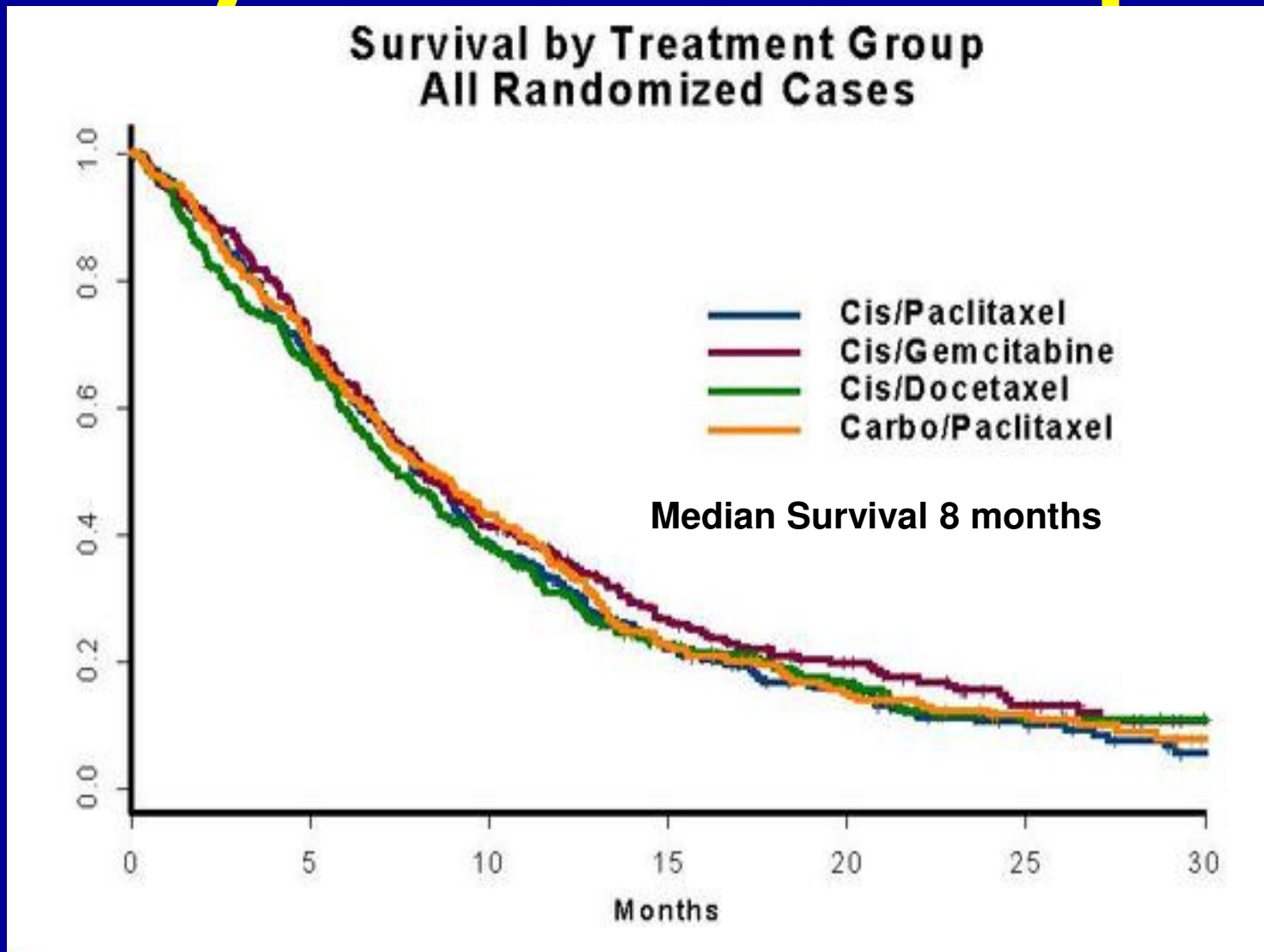
Japanese UFT Meta-Analysis 2004 - 2003 pts, stage I (95%)

- 6 randomized trials, 95% stage I
- Conducted in Japan
- 5 years follow-up
- OS HR 0.74 [0.61-0.88] $p = .001$,
curves separate after 3 years



Which Chemotherapy?

ECOG 1594: Overall Survival by Treatment Group



CISCA: Meta-analysis Cis vs Carbo 1st line NSCLC

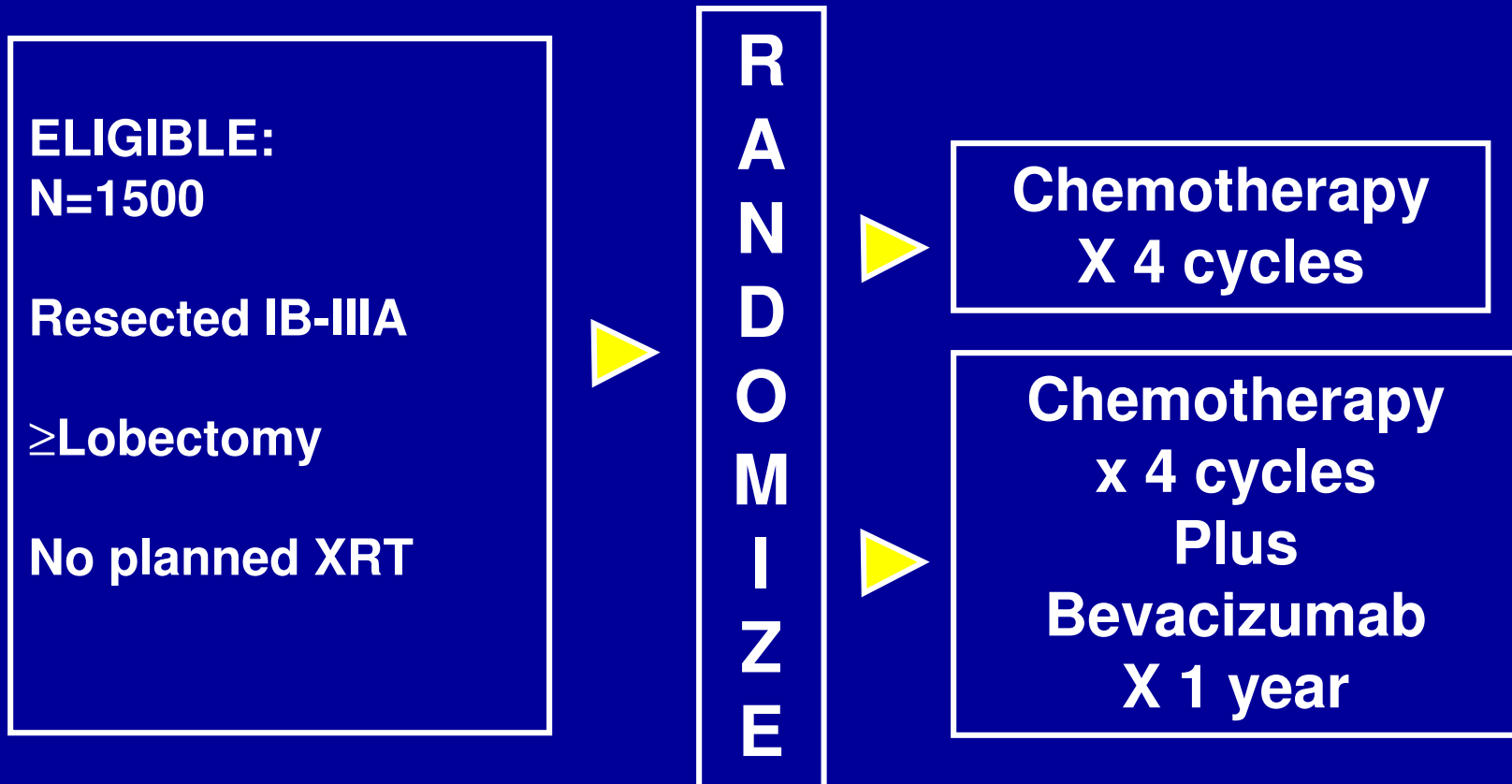
- **9 trials, 2968 patients, individual data**
- **Randomized comparisons of CIS vs CARBO with the same doublet agent in both arms**
- **Toxicity differences as expected**
- **RR ↑ with cisplatin (30% vs 24%)**
- **OS HR favored cisplatin-1.07 [.99-1.15]**
- **Significant if restricted to 3rd gen agents (n=2330) -HR 1.11 [1.01-1.21]**
 - (excludes 1 study)

Which Chemotherapy in the Adjuvant Setting?

- All 3 positive trials used cisplatin (2 with vinorelbine)
- Carboplatin may not be equivalent to cisplatin
- Cisplatin is the optimal choice
- Carboplatin only if cisplatin contraindicated
- Vinorelbine can probably be substituted with docetaxel or gem or paclitaxel or pemetrexed
- The role of ERCC1 and other predictors of chemotherapy response in development

ECOG 1505

Adjuvant NSCLC Chemo+/- Bevacizumab



- Investigator Choice of chemo regimens
- Cis/Vin, Cis/Docetaxel, Cis/Gem, soon Cis/Pem

Overall Survival
Primary Endpoint

Special Patient Groups: Elderly Analysis

JBR.10 Adjuvant Elderly Analysis

- Analyzed young ≤ 65 yo (n=327) vs elderly > 65 (n=155)
- Overall Survival HR 0.61 [0.38-0.98], p = .04 in elderly
- Overall Survival HR 0.77 [0.54-10.9], p = 0.14 in young

LACE Adjuvant Elderly Analysis

- Overall Survival **HR 0.90** [0.7-1.16], **≥ 70 yo** (n=414)
- Overall Survival **HR 1.01** [0.85-1.21], **65-69 yo** (n=901)
- Overall Survival **HR 0.86** [0.78-0.94], **≤ 65 yo** (n=3269)
- Elderly received less chemotherapy overall
- Toxicity differences not seen by age group, but more non-lung cancer deaths in elderly groups in the LACE analysis
- Adjuvant chemotherapy should be offered to the fit elderly

Patient preferences - adjuvant therapy

- **Meta-analysis 23 papers -1987-2003**
- **Patients accept adjuvant therapy more if:**
 - **larger benefits (10% vs. 5% significant)**
 - **less toxicity**
 - **having dependents at home**
- **Age did not affect decisions**
- **Therapy acceptance higher if framed in terms of increased probability of survival versus survival prolongation**

How do we discuss the data with patients?

- **Study of decision-making for adjuvant therapy**
 - 203 preclinical medical students -breast CA adj chemo scenario
 - Presented data 4 equivalent ways in case scenarios -
 - RRR, Absolute RR, absolute survival benefit, # needed to treat
- **Initially only given 1 piece of data, then all 4**
 - If only RRR choose chemo 2x > vs ASB
- **Confusion scores went up with all 4 pieces of data**
- **RRR led to less accurate assessment**
 - overestimate absolute benefit
- **Absolute Survival Benefit least confusing (ie. % alive at 5 yrs)**
- **In breast research if 4% survival benefit, 50% choose chemo**

Pre vs Post-op chemo Meta-analysis 2008

- 31 trials fulfilled entry criteria
 - 21 post-op/ 10 pre-op chemotherapy
- Used indirect comparison meta-analysis
- **OS HR** of post- vs pre-operative chemo
0.99 [0.81-1.21, $P = 0.9$]
- **PFS HR** of post- vs pre-operative chemo
0.96 [0.74-1.26, $P = 0.77$]
- Await NATCH and ongoing trials in Asia to establish role of neo-adjuvant vs adjuvant

Adjuvant Chemotherapy

Conclusions

- IALT long term follow-up brings up questions of chemotherapy toxicity, but not true of all trials
- Better patient selection will be critical (molecular (Dr. Bepler), genomic (Dr. Potti), etc.)
- Better drugs are needed (targeted - Dr. Kris)
- Elderly can be treated
- Neo-adjuvant therapy likely equivalent - Dr. Pisters
- Adjuvant CISPLATIN chemotherapy remains the standard of care for patients with resected stage II/IIIA NSCLC (and larger IB)