Prognostic molecular models in early-stage lung cancer

14th Annual

Winter Lung Cancer Conference

Miami, Feb 12 2017

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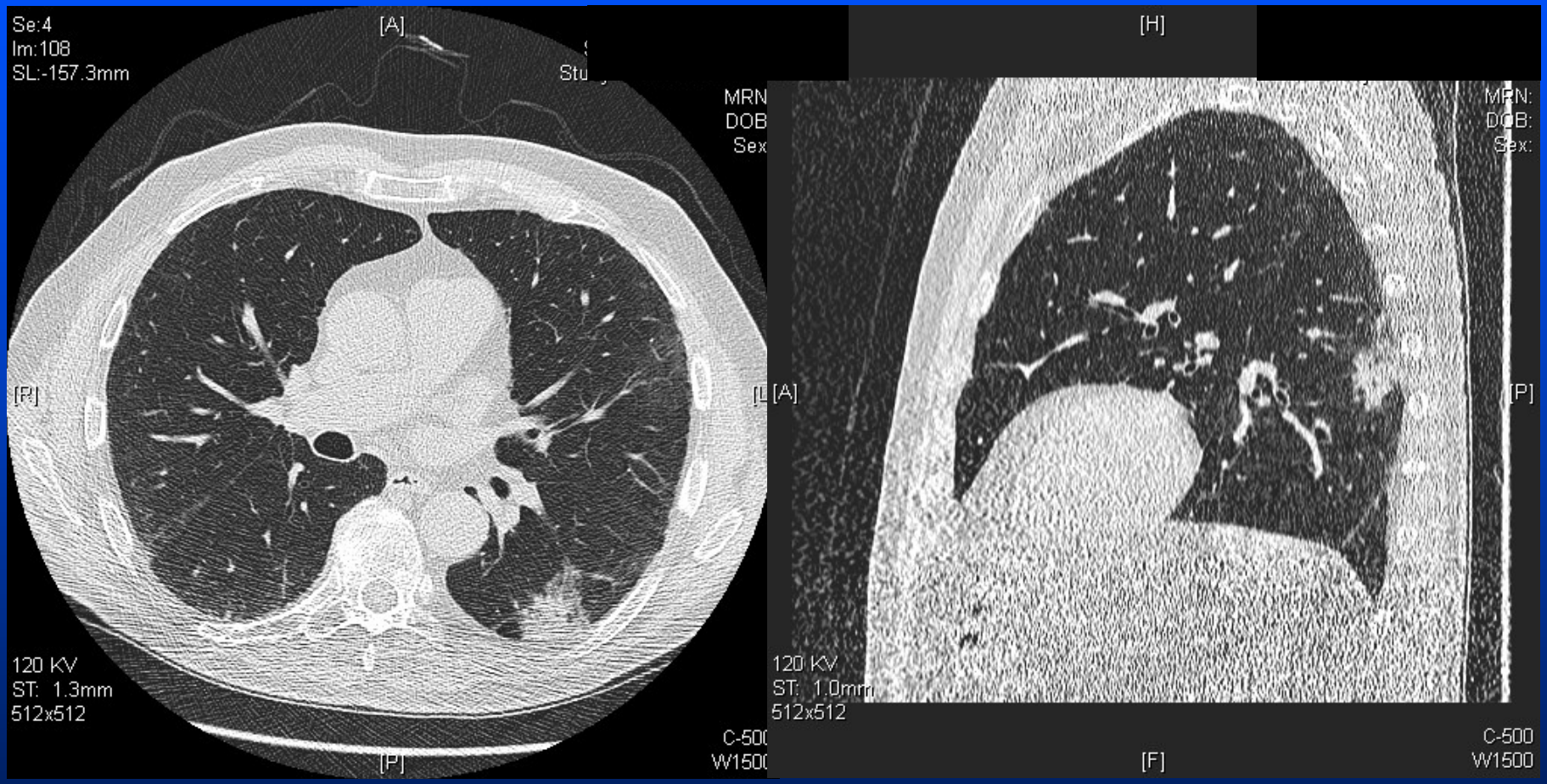
CASE I: AC OR NOT

- 73-year-old M former smoker
- Screening CT chest
- Excellent CP reserves (FEV1 90%/84 DCO 84%)
- No significant co-morbidities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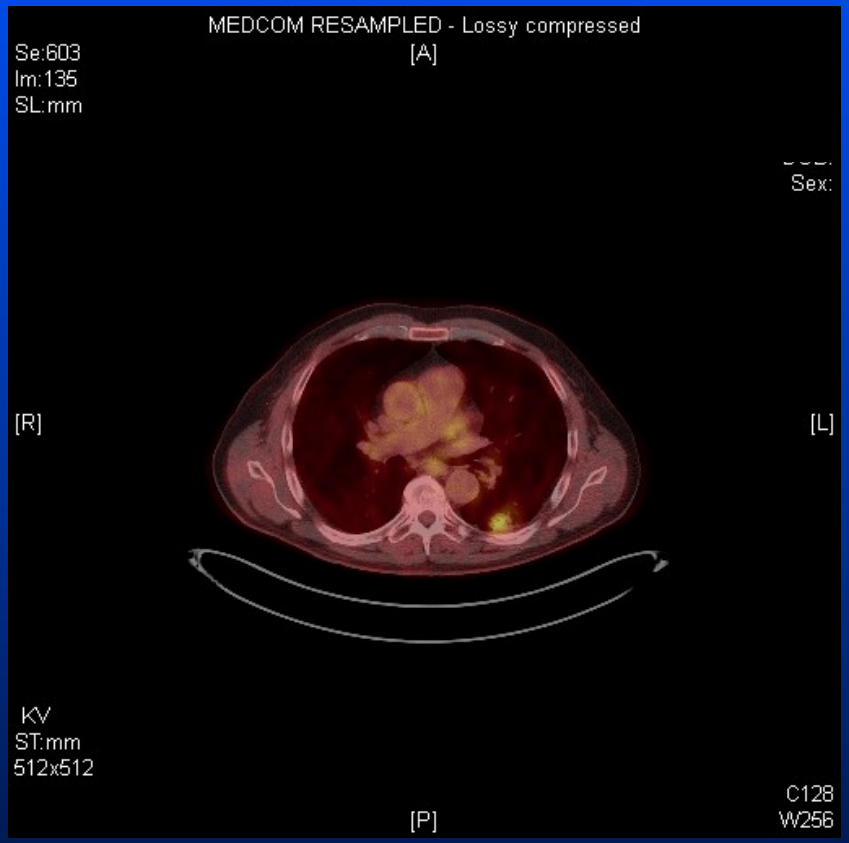


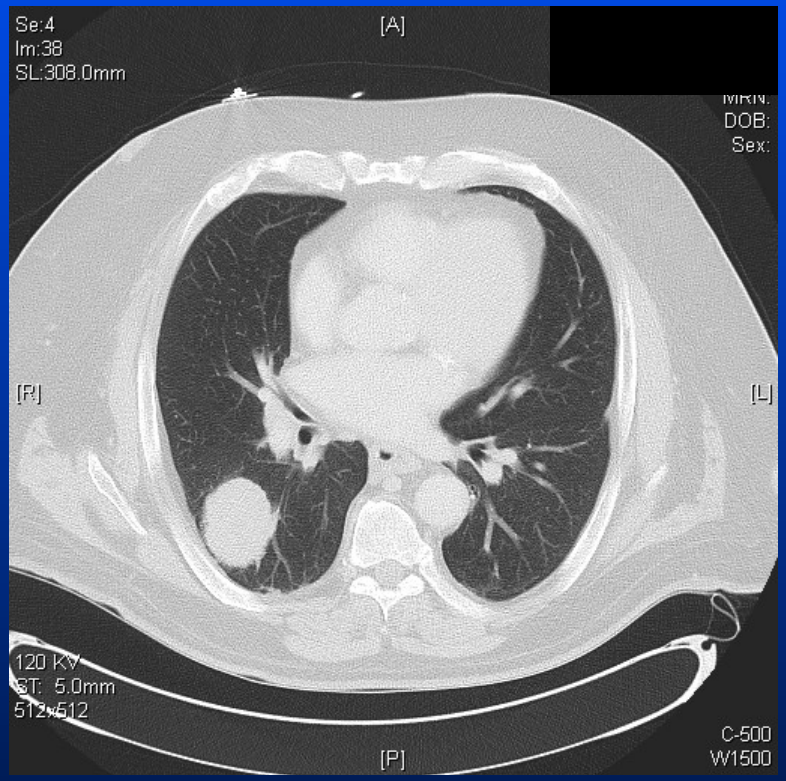
cT2aN0M0 adenocarcinoma
37 mm
Max SUV 3.8

Uneventful med/VATS LLL, HD 3
pT2aN0M0R0 adenocarcinoma
37 mm, G2, LVI+

AC or not?

CASE 2: adjuvant TKIs?

- 65-year-old M never smoker
- Abdominal pain > imaging = RLL mass
- Significant comorbidities: CAD, a fib, IDDM, related CKD 3, DM related neuropathy, sedentary
- New onset clubbing
- FEV1 79%, DCO 60%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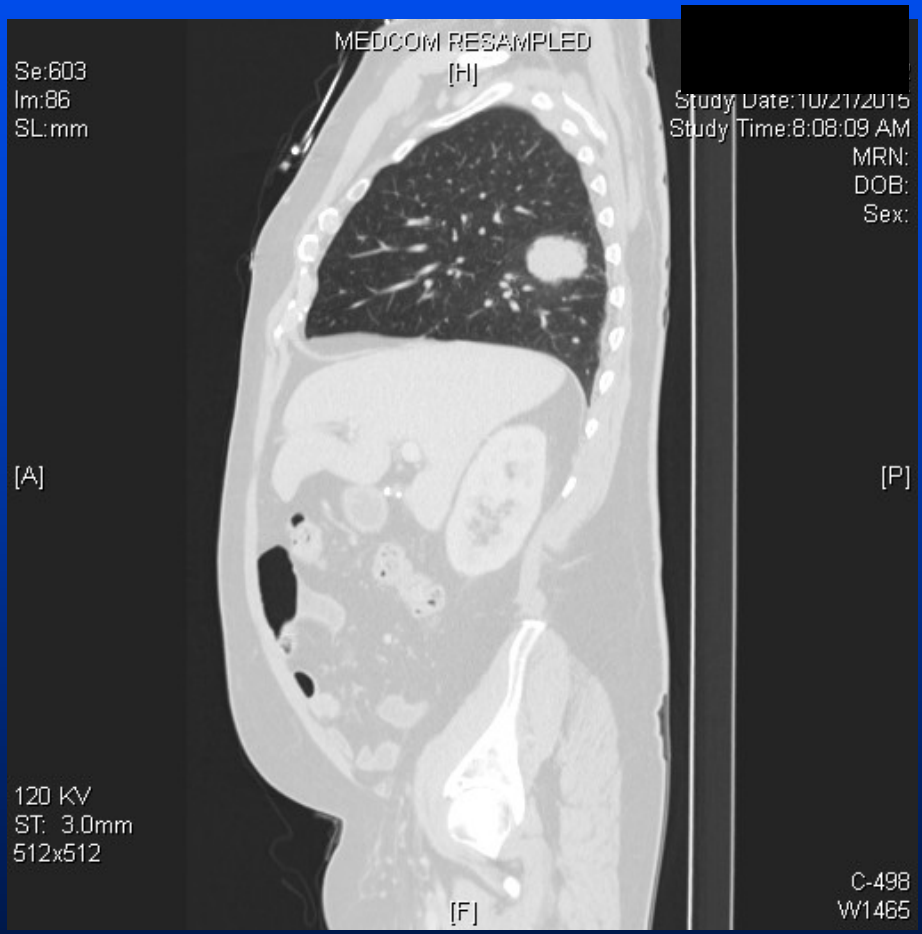
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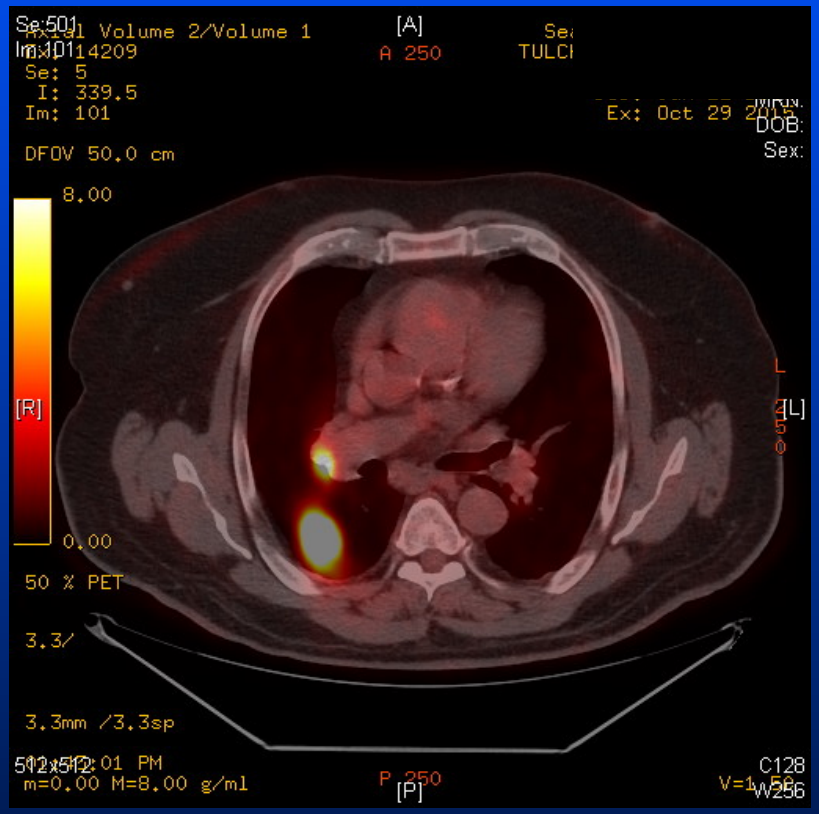
C-498
W1465

Adjuvant EGFR TKIs?



cT2aN1M0 adenocarcinoma
50 mm
Max SUV T 50 N1 9.4

Radical med/ open RLL, HD 5
pT2aN1M0R0 adenocarcinoma
50 mm, G3, 6/21 N1 LN +
Favorable EGFR mutation…

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Disclosures

Consultant for Genentech BioOncology, GlaxoSmithKline, Myriad Genetics and Spiration-Olympus Respiratory America

Prognostic molecular models in early-stage lung cancer

- Standard of care is for AC after R0 anatomical resection of Stages IB(>4 cm), II and III NSCLC
- AC being with one of 5 platinum doublets (3-4 cycles)
- As established by the results of randomized phase III trials published a decade ago

Standard of care is for AC after R0 anatomical resection of Stages IB(>4 cm), II and III NSCLC

Pignon et al. *J Clin Oncol* 26(21): 3552-3559.

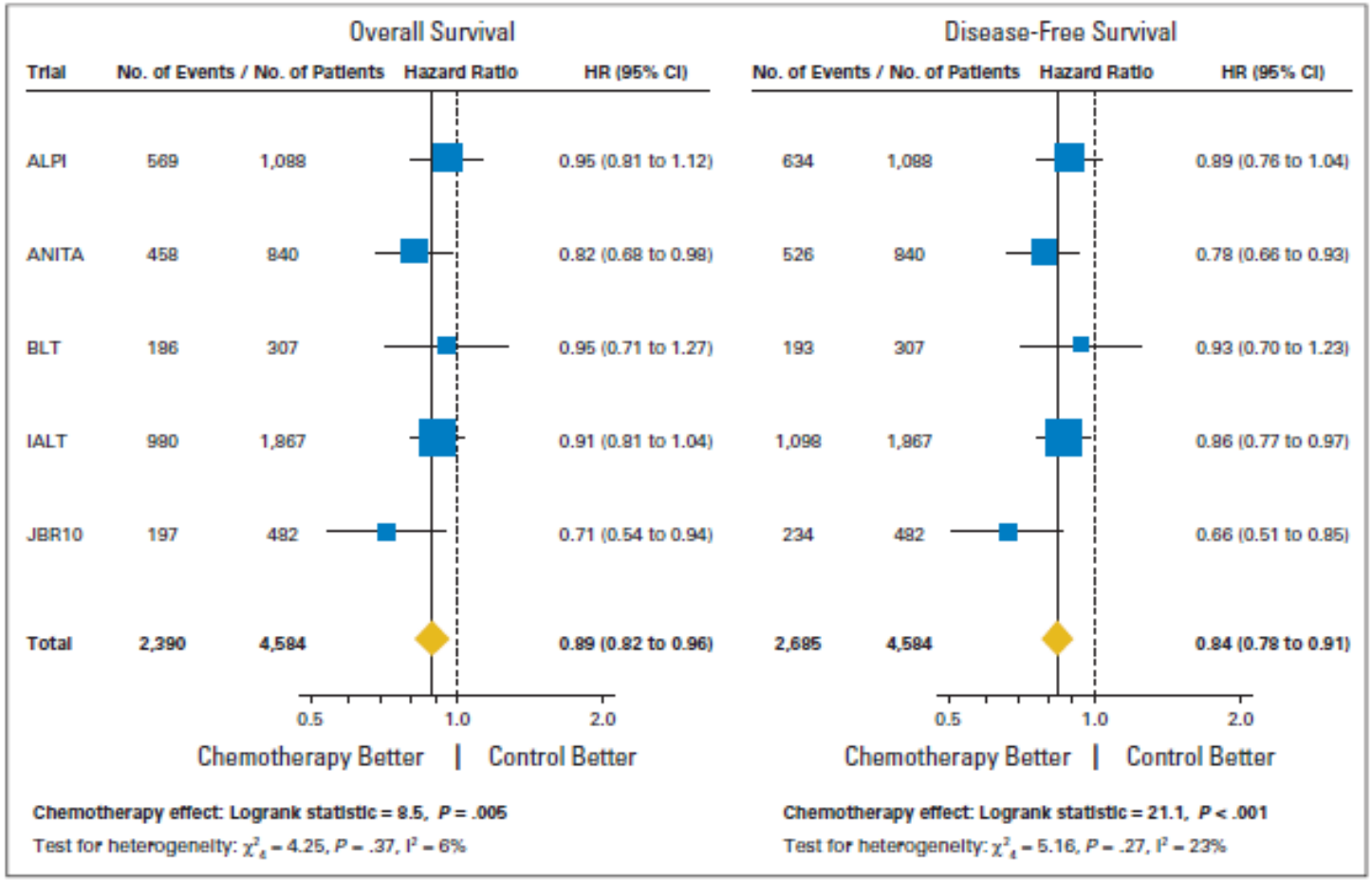
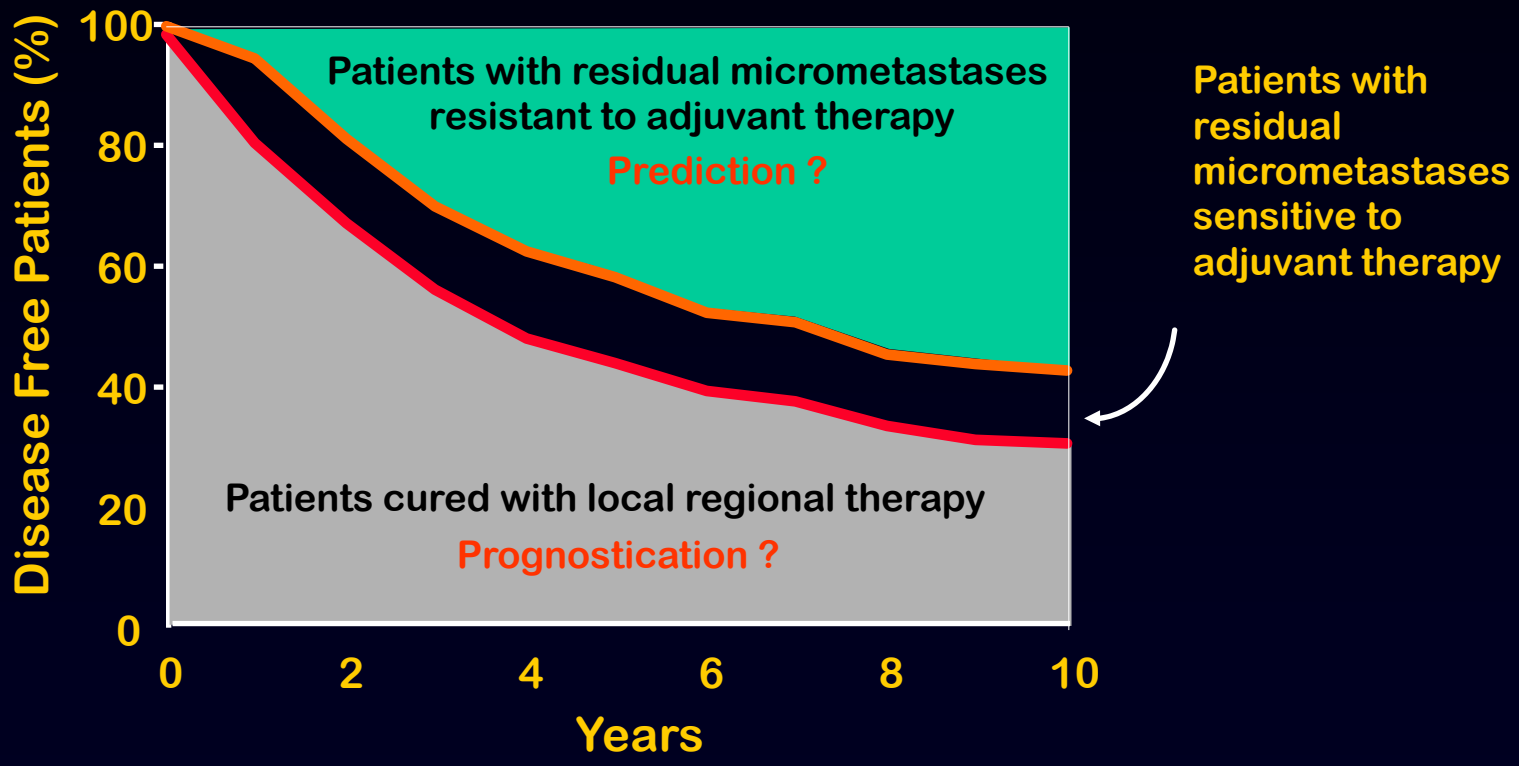


Fig 1. (A) Overall survival (OS): hazard ratio (HR) of death with chemotherapy versus control (no chemotherapy). (B) Disease-free survival (DFS): HR of recurrence or death with chemotherapy versus control. HR for individual trials and overall effect are given with 95% CIs. The horizontal scale used is a logarithmic scale. ALPI, Adjuvant Lung Cancer Project Italy; ANITA, Adjuvant Navelbine International Trialist Association 01; BLT, Big Lung Trial; IALT, International Adjuvant Lung Trial; JBR10, National Cancer Institute of Canada Clinical Trial Group trial JBR10.

Potential Benefit from Adjuvant Systemic Therapy



Courtesy of Dr Giorgio V Scagliotti

Standard of care is for AC after R0 anatomical resection of Stages IB(>4 cm), II and III NSCLC

These results are influenced by the risks of stage X disease developing systemic disease (I<II<III) and by how good AC is in controlling it.

Standard of care is for AC after R0 anatomical resection of Stages IB(>4 cm), II and III NSCLC

We could potentially improve on these results by:

- Better surgery… i.e. nodal work
- Better identification of the risk by limiting both undertreating and overtreating in the adjuvant setting
- Having better drugs (Dr Kelly to address)

Better surgery…

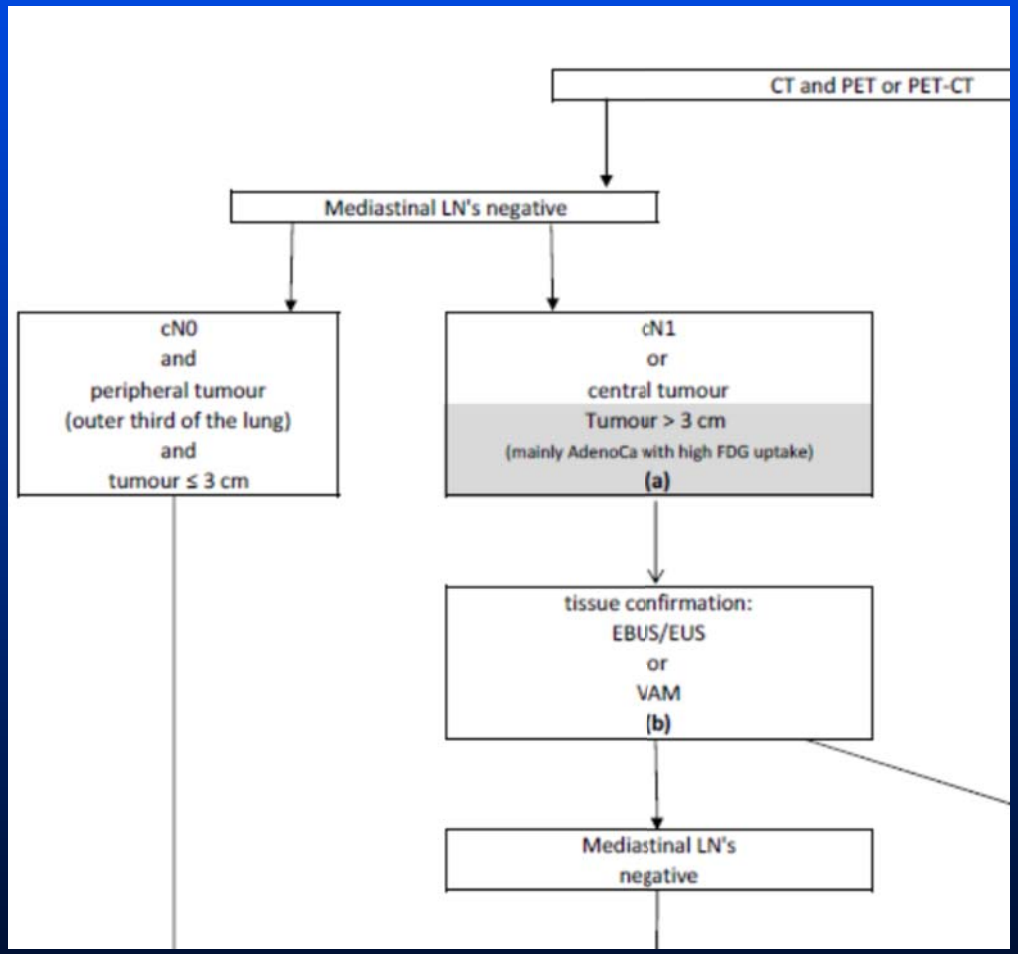
- … means better nodal work
- EBUS upfront does not mean we can skip hilar and mediastinal nodal dissection at resection
- The results of ACOSOG Z30 are misleading… by design

randomization. For tumors in the right lung, lymph node stations 2R, 4R, 7, and 10R were sampled. For tumors in the left lung, stations 5, 6, 7, and 10L were sampled. Any suspicious lymph nodes were also biopsied. The surgeon had the option of sampling by mediastinoscopy (2R/L, 4R/L, and 7), thoracotomy, or video-assisted thoracic surgery (VATS). Station 10 nodes were sampled at thoracotomy or VATS. If all sampled lymph nodes showed no evidence of cancer on frozen-section examination, patients were randomized intraoperatively via telephone by the central coordinating

Darling et al. *J Thorac Cardiovasc Surg* 141: 662-70, 2011.

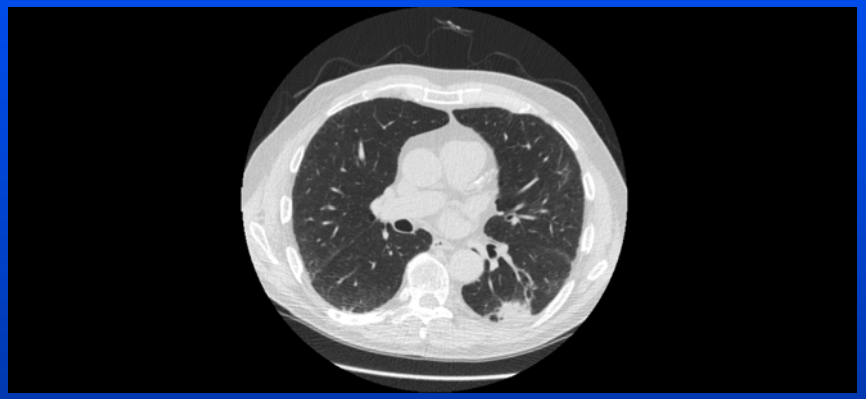
Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small cell lung cancer

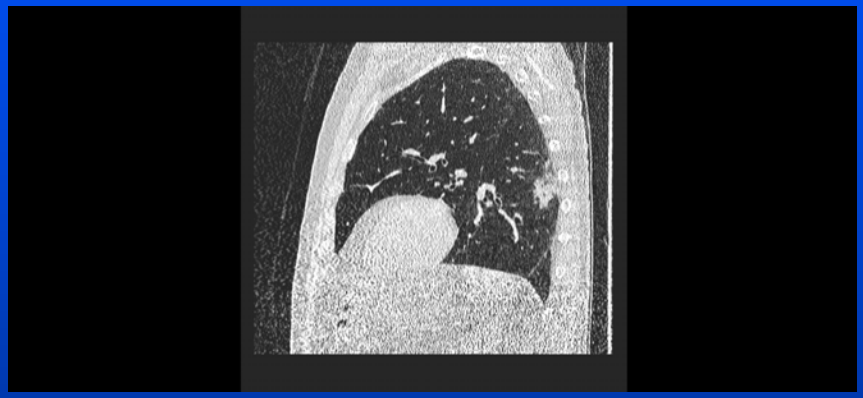
Paul De Leyn[1], Christophe Dooms[2], Jaroslaw Kuzdzal[3], Didier Lardinois[4], Bernward Passlick[5], Ramon Rami-Porta[6], Akif Turna[7], Paul Van Schil[8], Frederico Venuta[9], David Waller[10], Walter Weder[11], Marcin Zielinski[12]



Better identification of the risks?

AC or not?





73 M, VATS LLL, HD3, 37 mm G2 adenocarcinoma, 0/13 LN, LVI+

Better identification of the risks?

Wistuba et al. *Clin Cancer Res* 19, 2013.
31 prolif. genes/CCP score

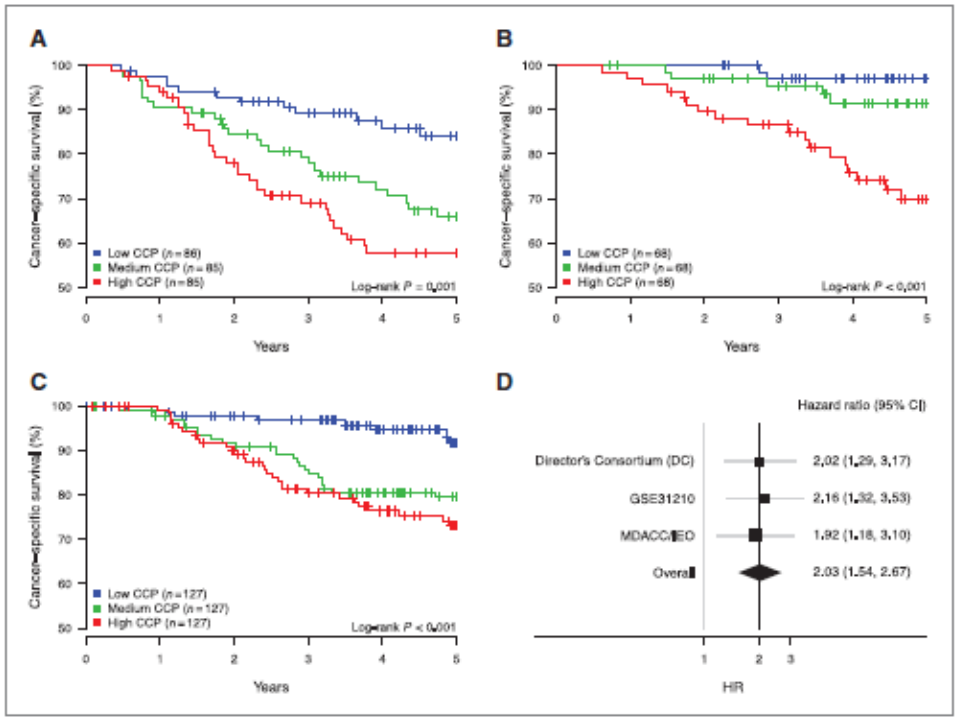


Figure 1. Association between CCP scores and lung cancer death in several cohorts: Director's Consortium (A), GSE31210 (B), and MDACC/IEO (C). Each patient set was separated into 3 equally sized groups based on CCP scores. The lowest tercile of CCP scores defines a subpopulation with higher survival. D, forest plot of HRs for the interquartile CCP range observed in the 3 study sets.

Kratz et al. *Lancet* 379, 2012.
14 gene expression (UCSF)

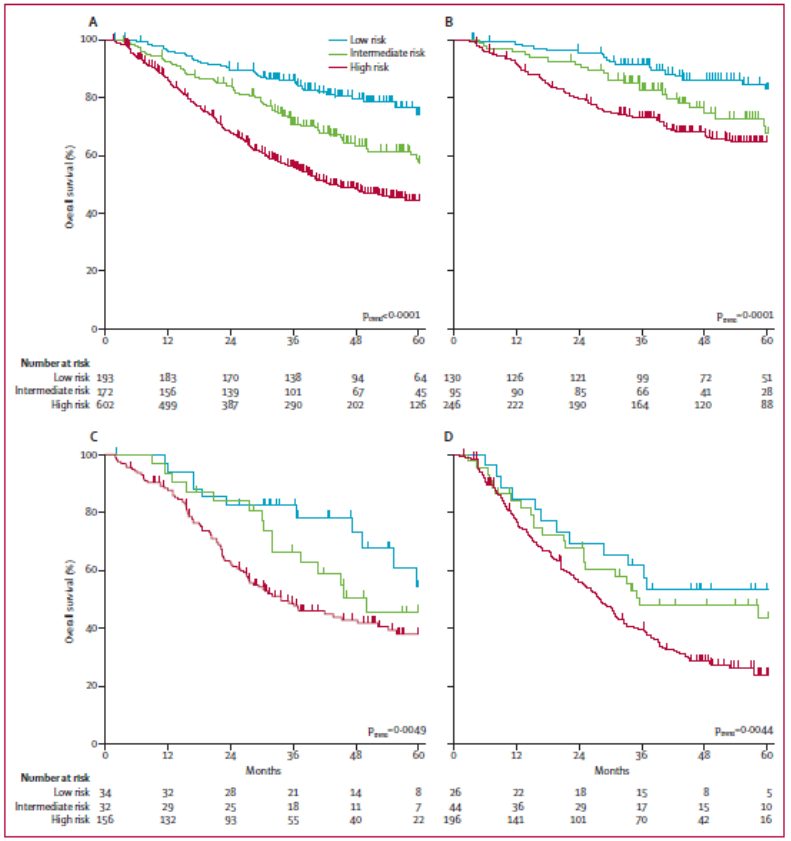


Figure 3: Survival analysis by risk category in the China Clinical Trials Consortium validation cohort
(A) Overall survival for the entire cohort. Survival in patients with stage I (B) stage II (C) and stage III (D) disease.

Cell cycle progression score is a marker for five-year lung cancer–specific mortality risk in patients with resected stage I lung adenocarcinoma

Takashi Eguchi[1,2], Kyuichi Kadota[3,4], Jamie Chaft[5], Brent Evans[6], John Kidd[6], Kay See Tan[7], Joe Dycoco[1], Kathryn Kolquist[6], Thaylon Davis[6], Stephanie A. Hamilton[6], Kraig Yager[6], Joshua T. Jones[6], William D. Travis[3], David R. Jones[1], Anne-Renee Hartman[6], Prasad S. Adusumilli[1,8]

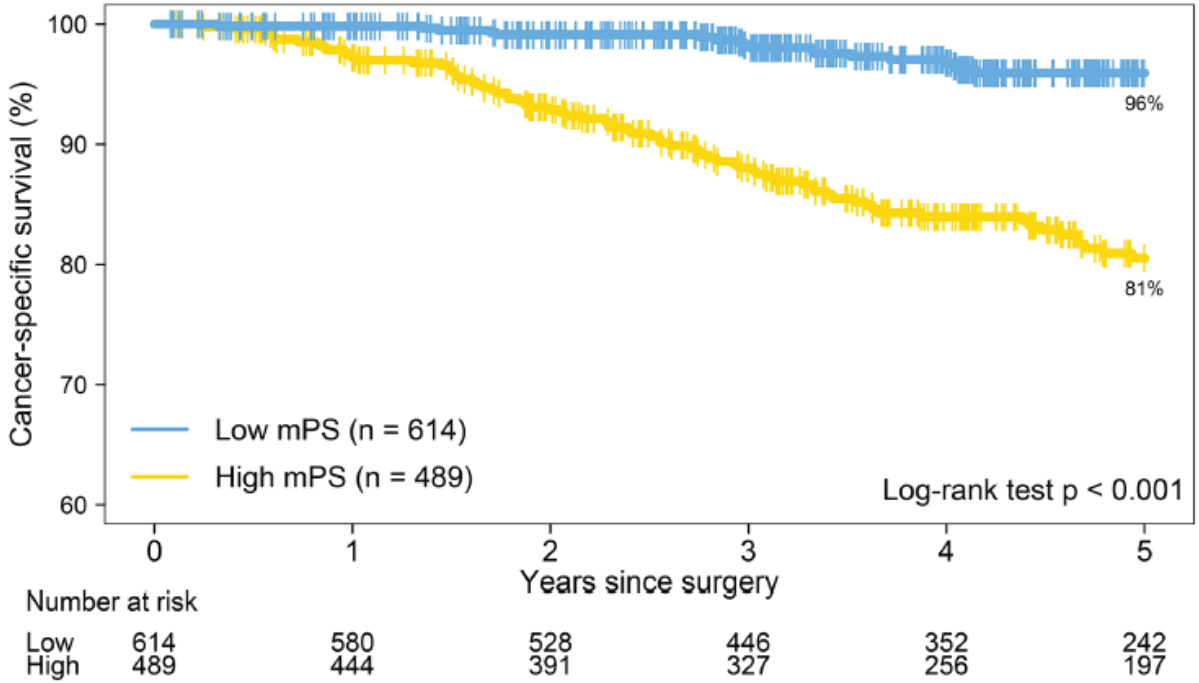


Figure 2: The Kaplan-Meier survival estimates for patients with low molecular prognostic score (mPS; N = 614) and high mPS (N = 489) show that the 5-year lung cancer–specific survival rate is 96% for patients with low mPS and 81% for patients with high mPS (*P* < 0.001).

Oncotarget, Vol. 7, No. 23 2016

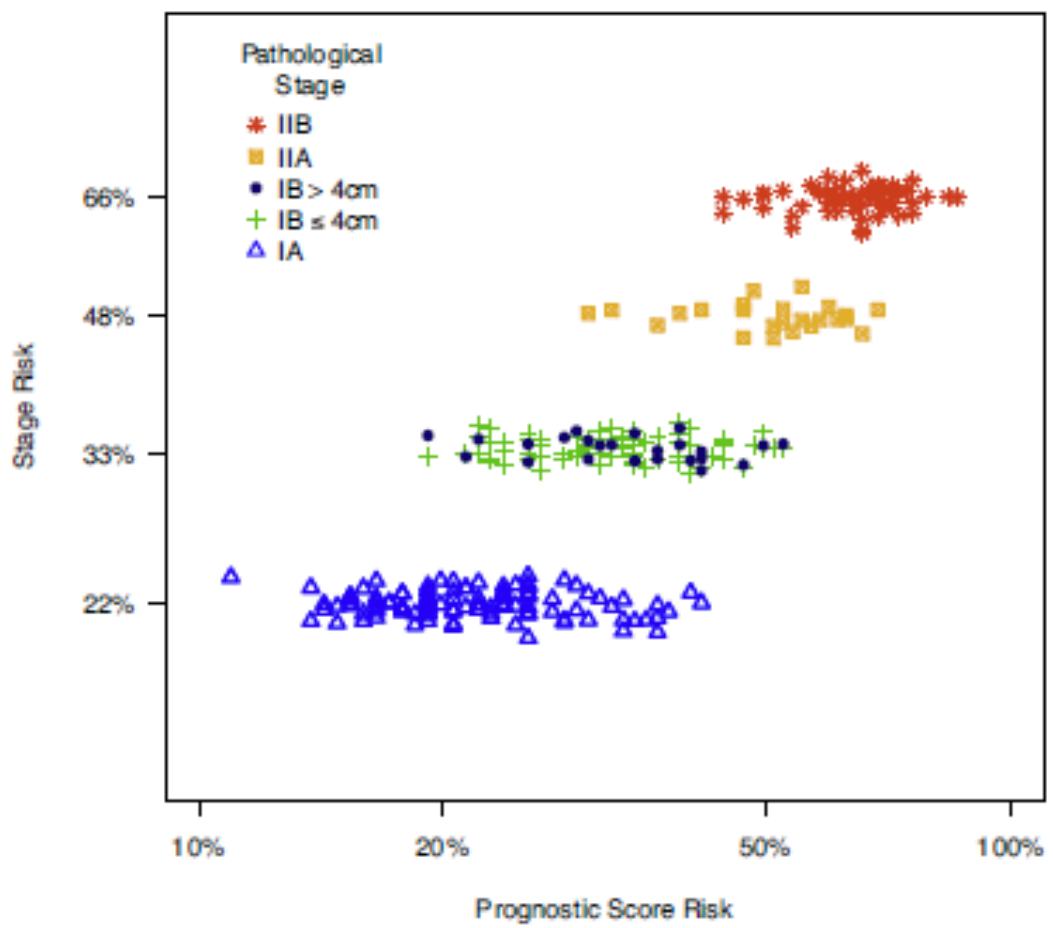


Fig. 2. Five-year distant recurrence-free survival estimated by pathological stage compared to survival estimates according to the molecular prognostic score. Risk estimates are displayed on a log scale. Each point represents one patient. Points have been jittered along the y-axis for clarity. Average risk for each pathological stage category is noted on the y-axis. Within stage IB, patients have been separated by tumor size into lesions larger than 4 cm and those with a diameter of 4 cm or less.

Early2 factor (E2F) deregulation is a prognostic and predictive biomarker in lung adenocarcinoma

Lu Chen[1,*], Courtney A. Kurtyka[1,*], Eric A. Welsh[1,*], Jason I. Rivera[1,*], Brienne E. Engel[2], Teresita Muñoz-Antonia[3], Sean J. Yoder[4], Steven A. Eschrich[1], Ben C. Creelan[5], Alberto A. Chiappori[5], Jhanelle E. Gray[5], Jose Luis Ramirez[6], Rafael Rosell[6], Matthew B. Schabath[7], Eric B. Haura[5], Dung-Tsa Chen[1] and W. Douglas Cress[2]

[1] Biostatistics and Bioinformatics, H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida, USA

deriving no benefit. Herein, deregulation of the E2F pathway was explored as a biomarker in lung adenocarcinoma patients. An E2F pathway scoring system, based on 74 E2F-regulated genes, was trained for RNA from two platforms: fresh-frozen (FF) or formalin-fixed paraffin-embedded (FFPE) tissues. The E2F score was tested

The E2F Score is a prognostic marker

Oncotarget, 2016, Vol. 7, (No. 50), pp: 82254-82265

The E2F score predicts benefit of ACT

Although the ACT treatment effect in stage I patients did not reach statistical significance, stage I patients with high E2F, 5-year survival increased from 31% without ACT to 61% with ACT. In contrast, in stage I patients with low E2F, 5-year survival was 83% in untreated patients and 77% in ACT-treated patients.

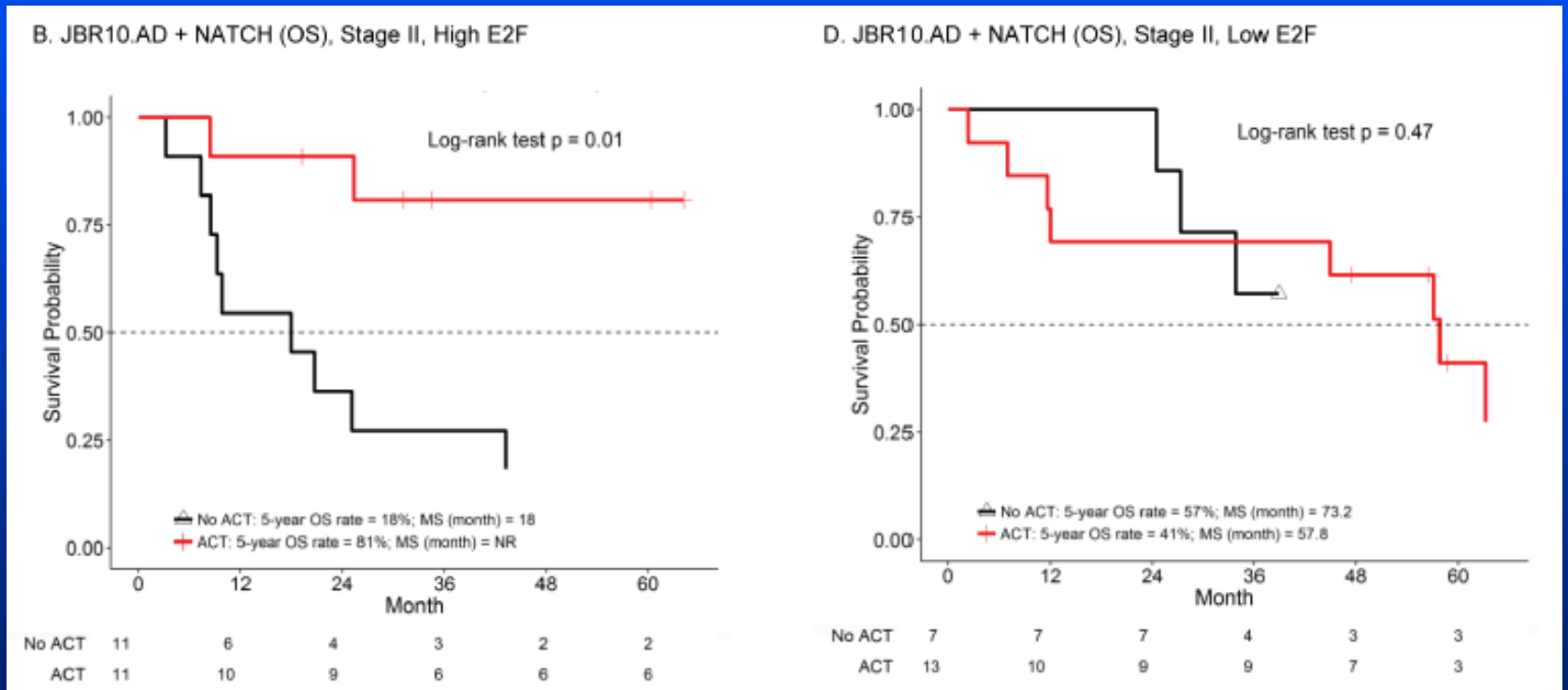


Figure 3: The E2F score predicts benefit of ACT in two randomized clinical trials. K-M analysis of OS in the indicated combined cohorts was performed comparing patients with high E2F **A.** and **B.** with ACT (red line) or without ACT (black line) or low E2F **C.** and **D.** with ACT (red line) or without ACT (black line). Results for 5-year survival and the log-rank test p value are included in each panel. Numbers at the bottom of the graph indicate the number of patients in each group at risk at 12-month intervals. MS represents median survival time and NR means the MS was never reached. Graphs are truncated at 60 months. A and C represent patients of all stages. B and D represent stage II patients only.

A 10-Gene Yin Yang Expression Ratio Signature for Stage IA and IB Non-Small Cell Lung Cancer

Wayne Xu, PhD,[a,b,c,*] Gaofeng Jia, PhD,[a] James R. Davie, PhD,[a,b]
Leigh Murphy, PhD,[a,b] Robert Kratzke, MD,[d,e] Shantanu Banerji, MD[a,f,g]

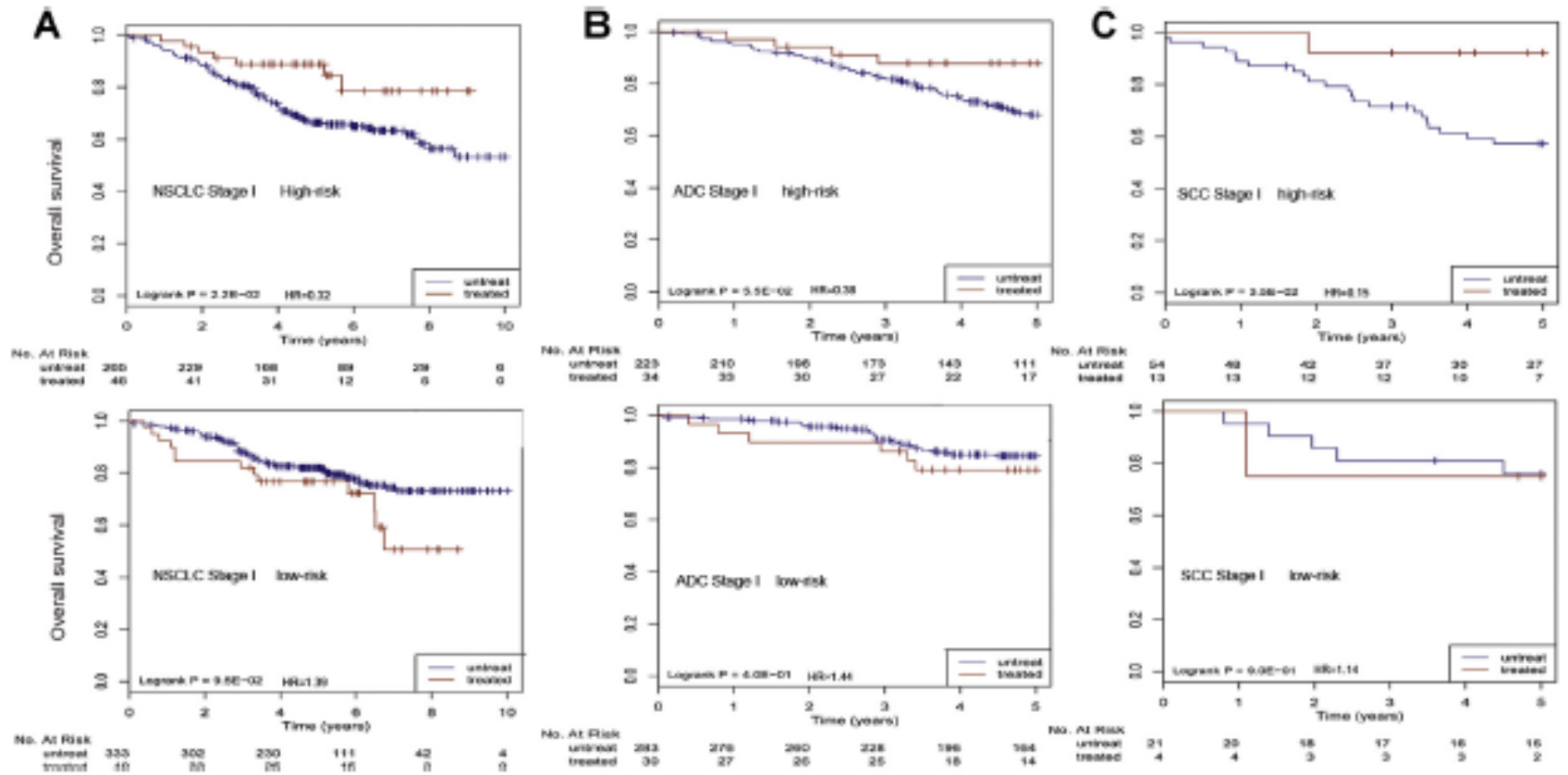
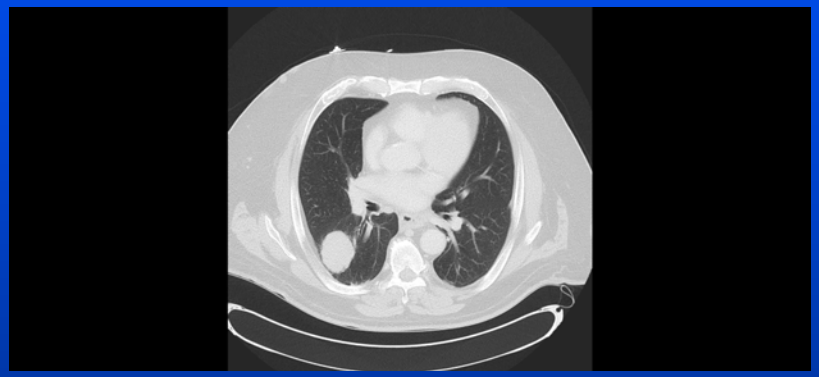
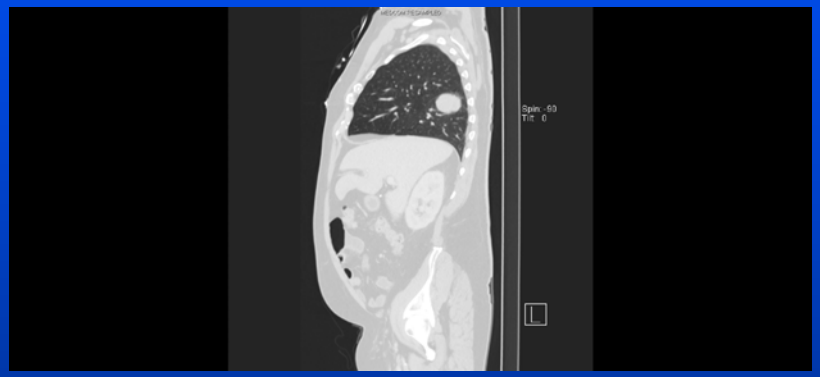


Figure 4. The 10-gene Yin and Yang mean ratio signature predicts benefit for adjuvant chemotherapy using the combined data set. The high-and low-risk groups were defined by the 10-gene Yin and Yang mean ratio signature score. (*A*) Stage I NSCLC, (*B*) stage I adenocarcinoma (ADC), and (*C*) stage I squamous cell carcinomas (SCC). HR, hazard ratio.

EFGR mutation





65 M, never smoker, radical RLL, 50 mm G2-3 adenocarcinoma, 6/21 N1+, 0/12 N2, favorable EGFR mutation (exon 19 deletion)

Prognostic molecular models in early-stage lung cancer

Conclusions:

- Standard of care remains for AC after R0 anatomical resection of Stages IB(>4 cm), II and III NSCLC, though the use of genomics in better identifying the populations at risk is probably around the corner…