uPA: From Pilot Studies to Recommendation for Clinical Use

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Most Important Questions After a Diagnosis of Breast Cancer

- How “bad” or aggressive is the tumor
- Will the tumor recur
- Is adjuvant chemotherapy necessary?

Node Negative Breast Cancer

- With screening, 2/3 of newly-diagnosed breast cancer patients are node-negative
- 70% of node-negative patients cured by surgery + radiotherapy
- 30% develop recurrent disease by 10 yr

Problem: How to differentiate those with aggressive from those with indolent ca

Node-Negative Breast Cancer: Treatment Dilemma

- **Circumventing the Dilemma: Treat almost all node-negative patients with adjuvant chemotherapy**

- **Problem: Only a minority of patients will benefit but most will suffer toxic side-effects**

CHEMOTHERAPY FOR BREAST CANCER: OVERVIEW OF RANDOMISED TRIALS

- **18,000 women**
- **47 trials of chemotherapy vs no chemo**

Change in 10-yr survival (node-negative patients)

- **<50 yr: 71%→78%**
- **50-69 yr: 67%→69%**

Lancet 1998;352:930

ADJUVANT CHEMOTHERAPY FOR BREAST CANCER: OVERVIEW OF RANDOMISED TRIALS

- 145,000 women
- 194 trials of chemotherapy vs no chemo

Absolute Improvement in Mortality (%)

	5 yr	10 yr	15 yr
Women <50 yr	4.7	7.9	10
Women 50-69 yr	2.6	2.9	3.0

Lancet 2005;365:1687

Side Effects of Chemotherapy (CMF)

Side effect	% affected
• Nausea	43
• Vomiting	42
• Alopecia	40
• Ovarian failure	70
• Weight gain	12
• Diarrhea	4.5

Shapiro & Recht, N Eng J Med 2001;344:1997

QUESTION

Should most node-negative breast cancer patients be treated with chemotherapy so that a small minority benefit while a large proportion suffer from adverse toxic effects ?

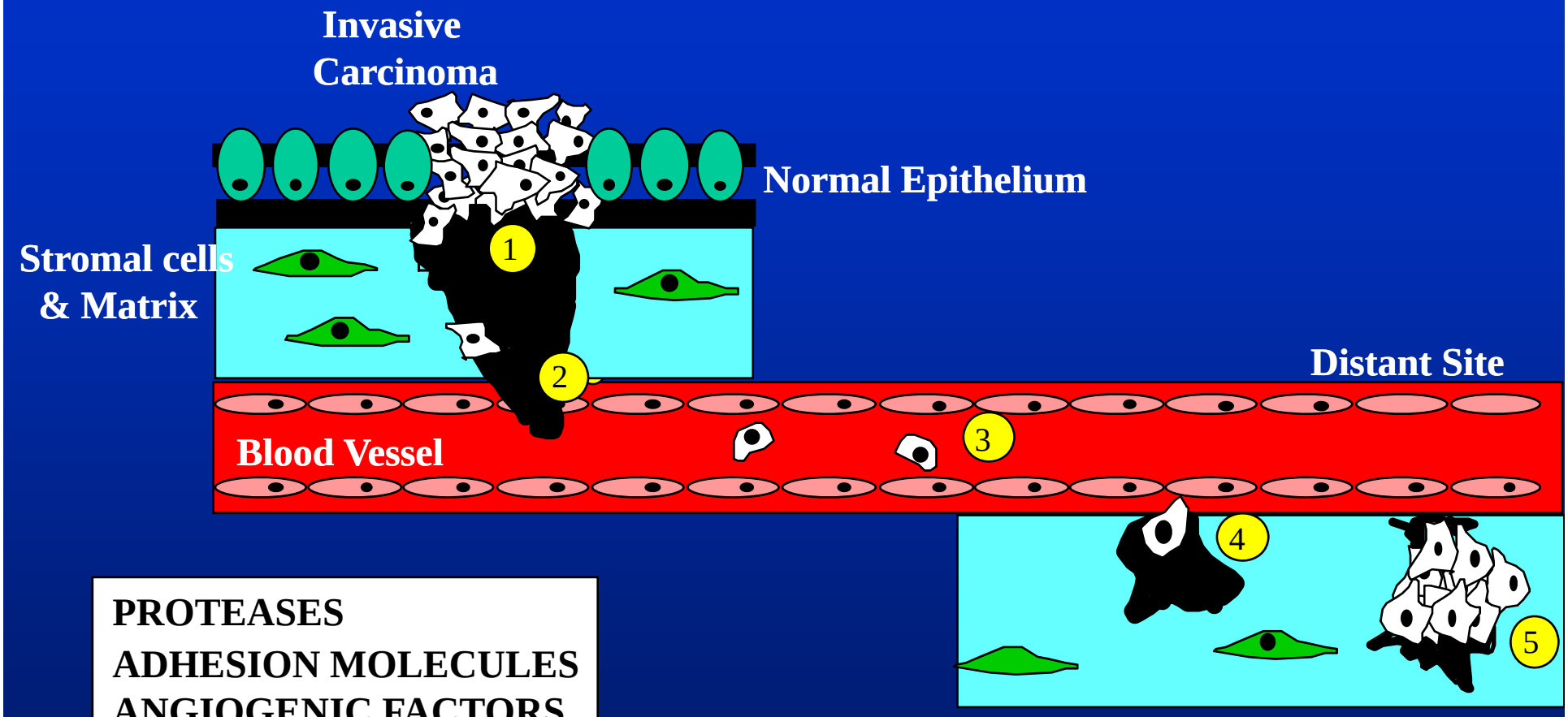
Rational Way Forward

- Develop and validate markers that will reliably differentiate between patients with aggressive and indolent disease
- Metastasis is the main causes of mortality in cancer. Since uPA is causally involved in this processes, it should be a strong marker of metastatic potential and thus of prognosis

uPA

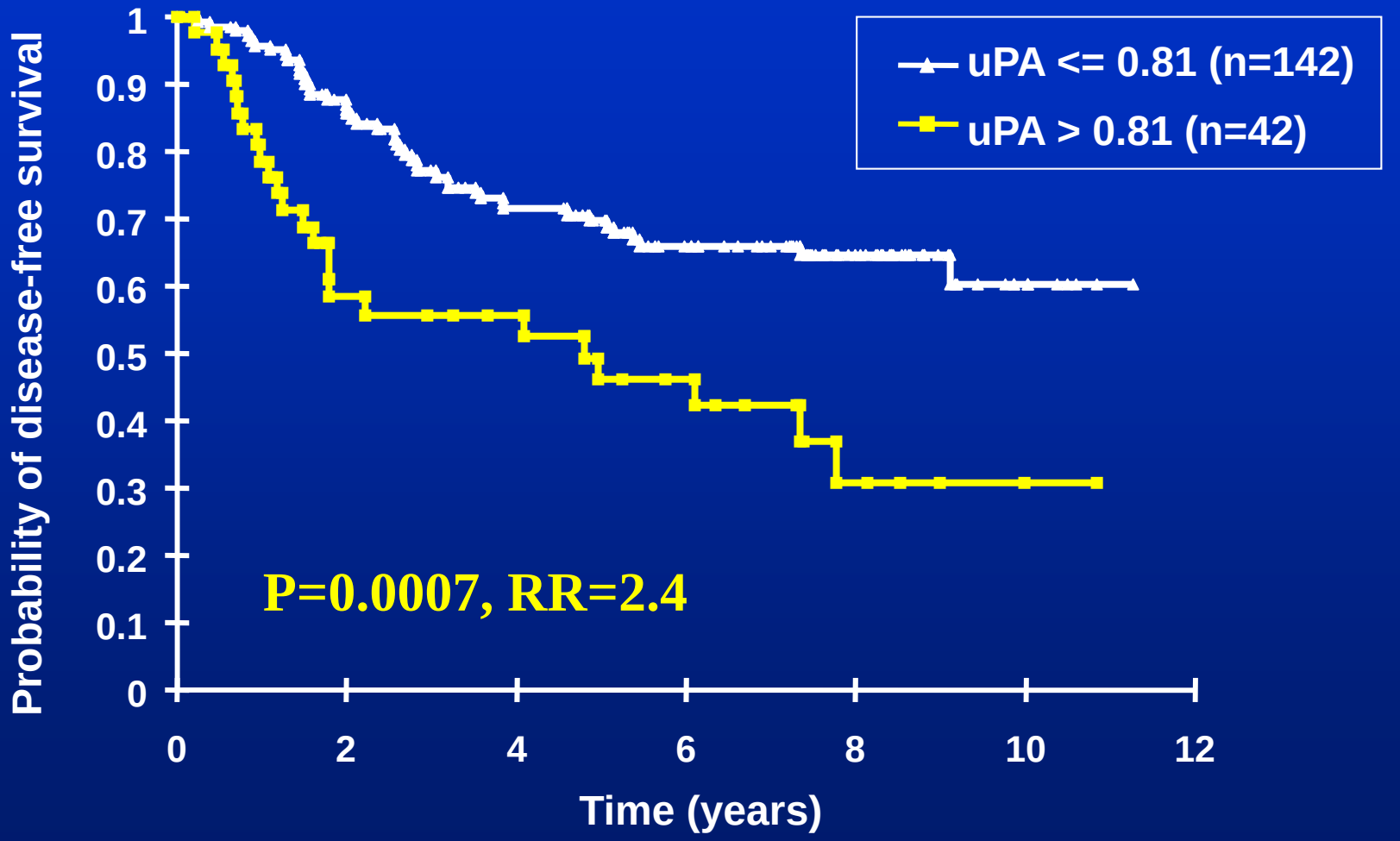
- A 53 kDa serine protease
- It degrades basement membranes and ECM
- Multiple studies with animal models suggest that uPA is causally involved in metastasis

Invasion & Metastasis

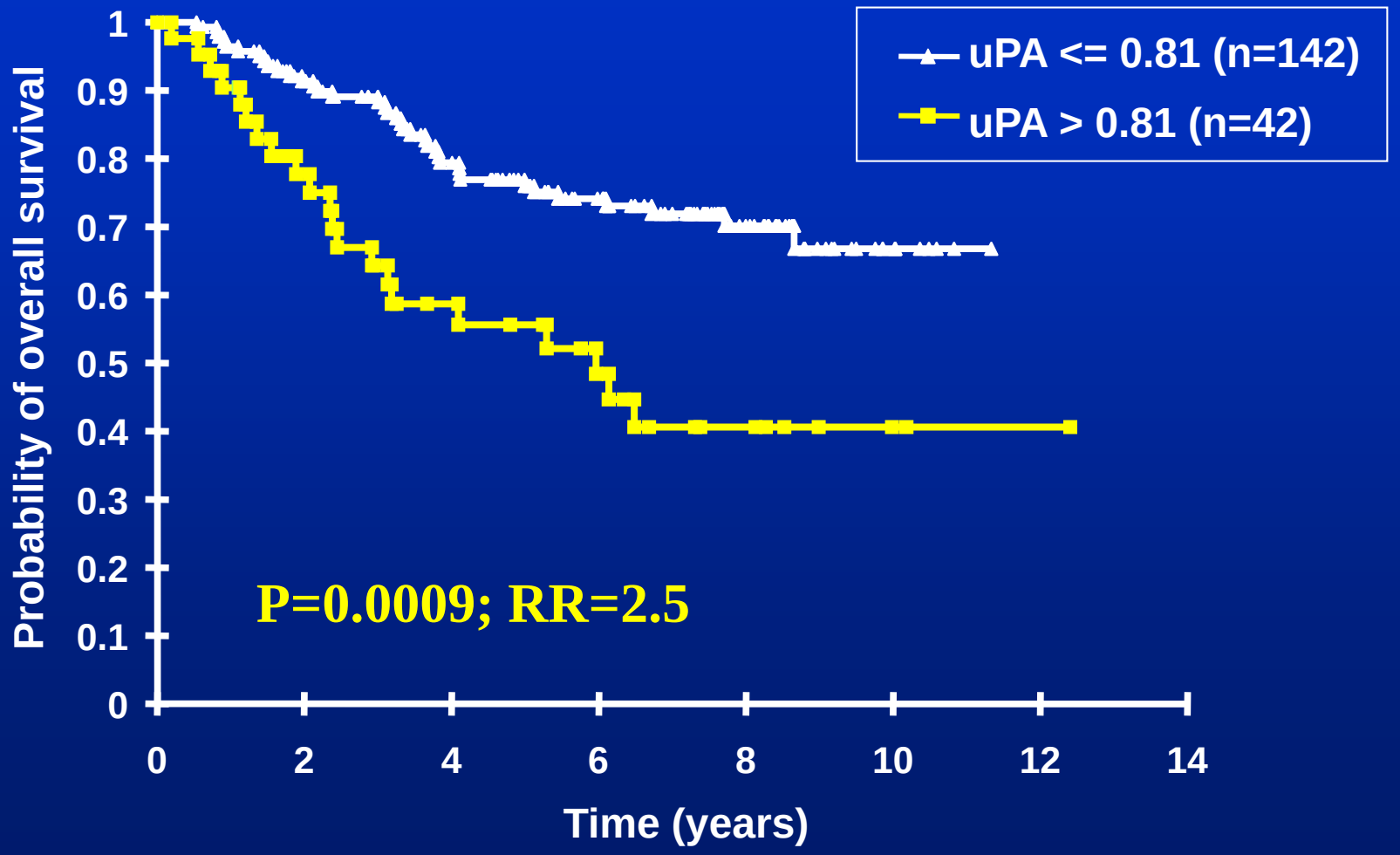


PROTEASES
ADHESION MOLECULES
ANGIOGENIC FACTORS
MOTILITY FACTORS

uPA vs DFI


Probability of disease-free survival
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
Time (years)
uPA <= 0.81 (n=142)
uPA > 0.81 (n=42)
P=0.0007, RR=2.4

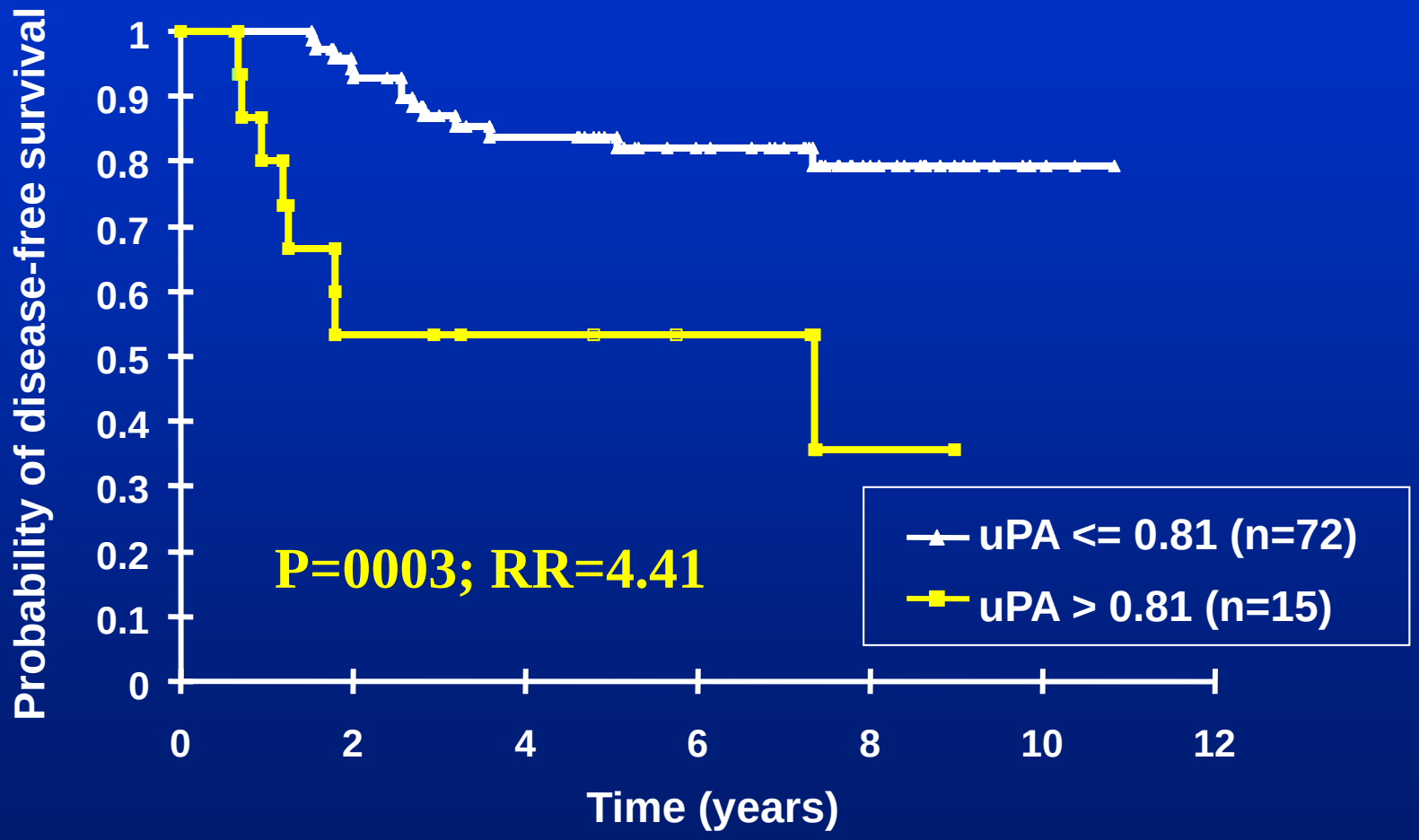
uPA vs overall survival



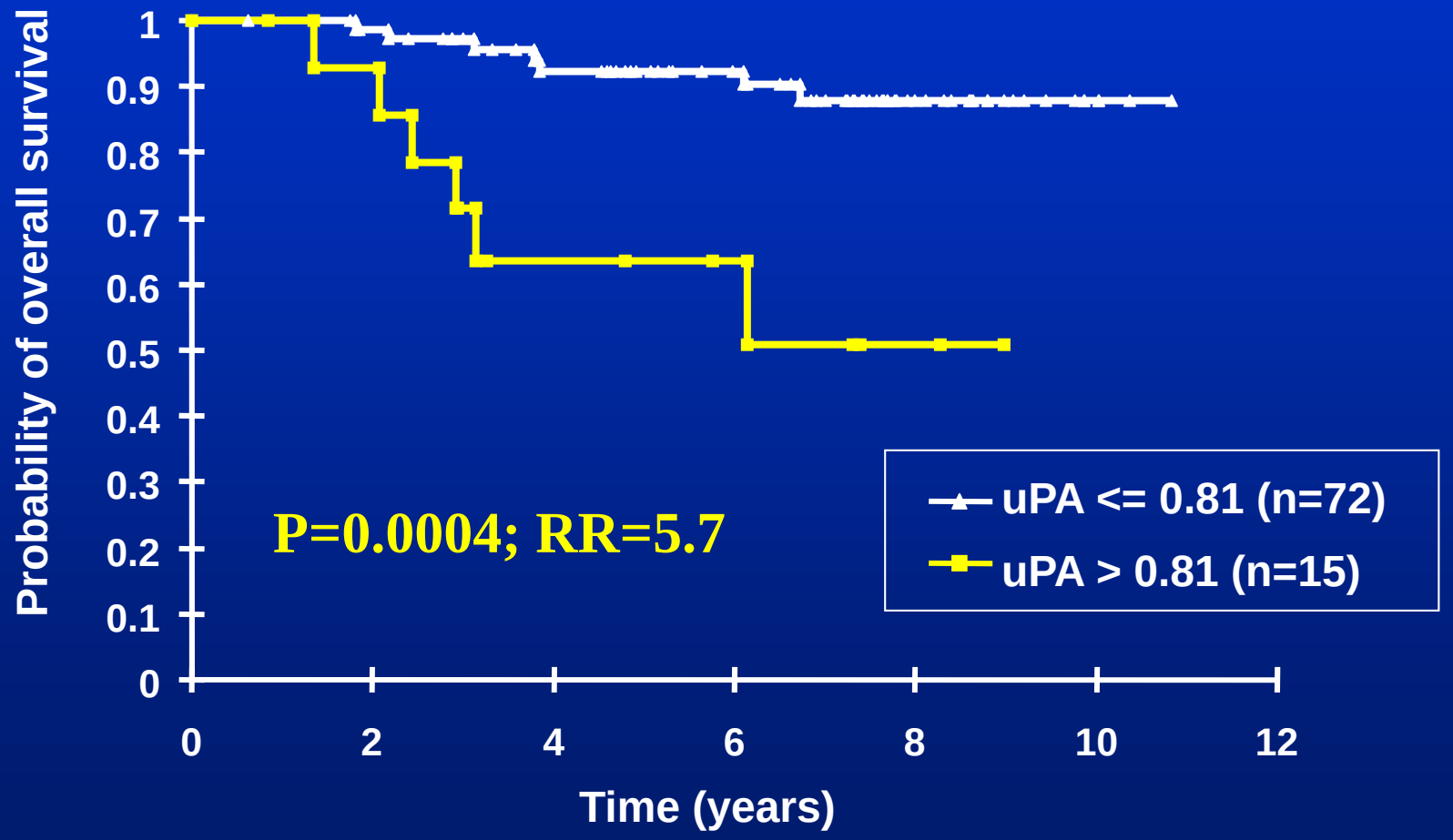
uPA vs OS

	Univariate	Multivariate
	p	p
LN	<0.0001	<0.0001
uPA	0.0004	0.0003
Size	0.003	0.006
ER	0.020	NS

uPA vs DFI; NODE-NEGATIVE PATIENTS



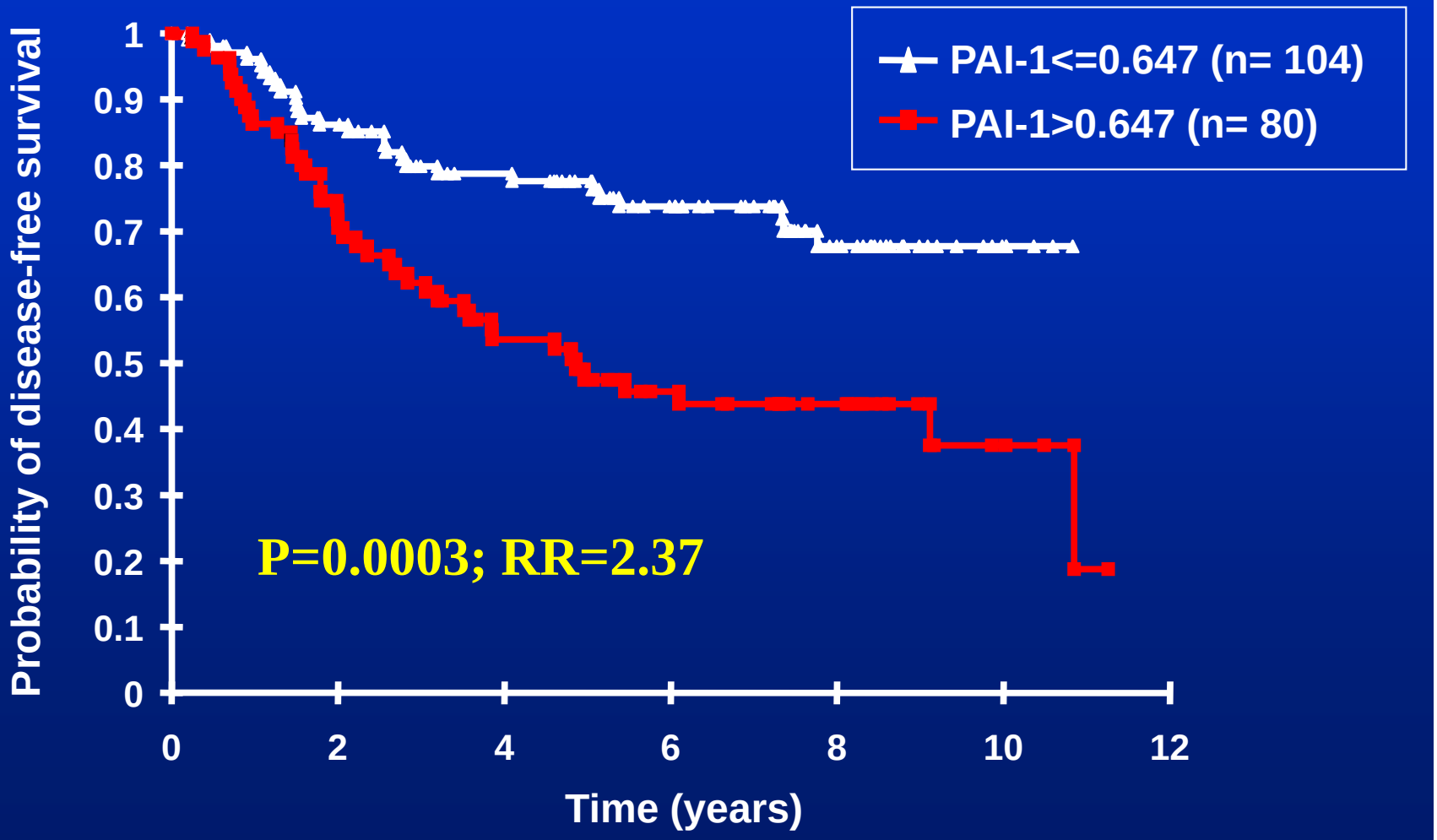
uPA vs overall survival; NODE NEGATIVE PATIENTS



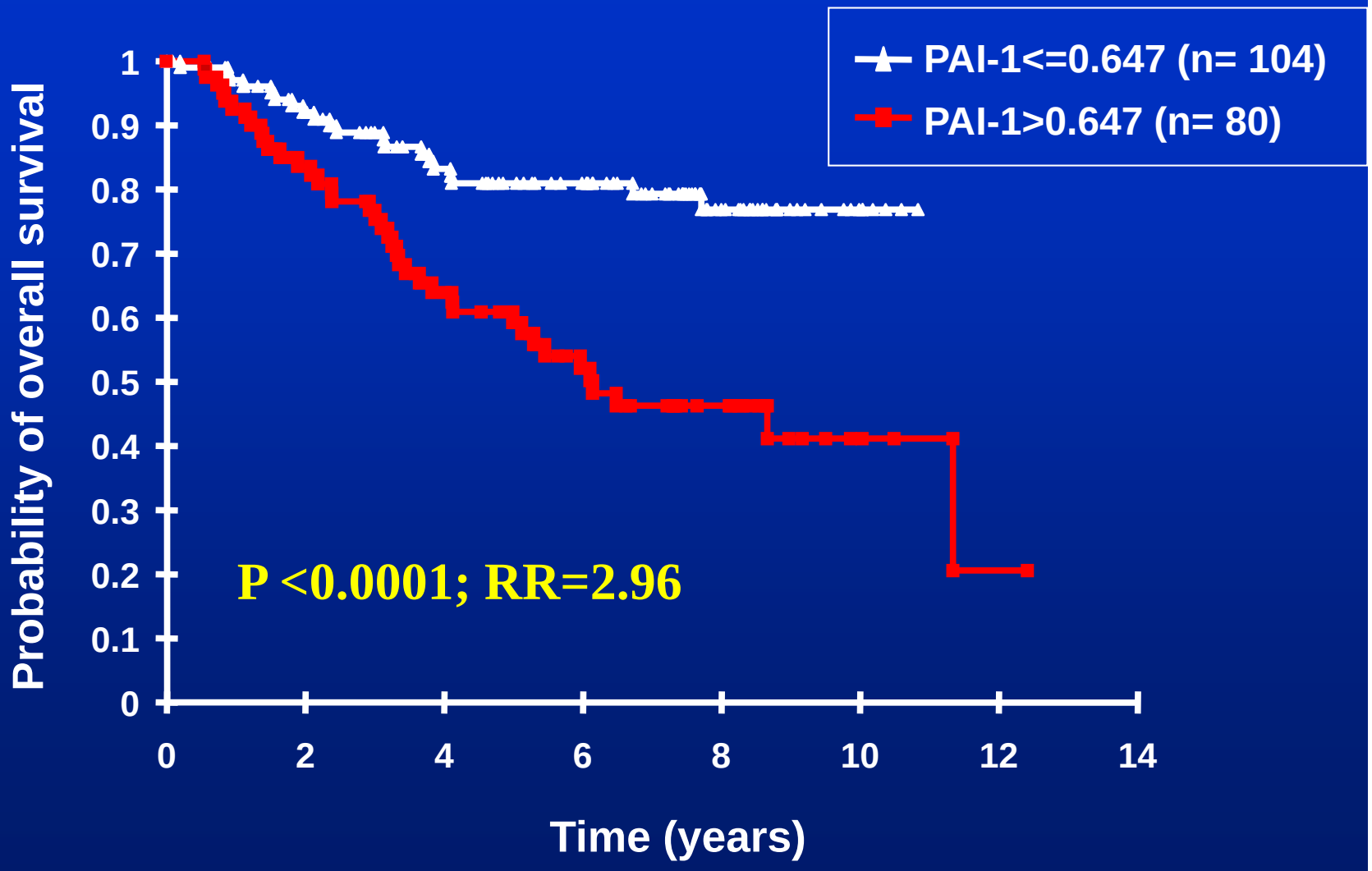
PAI-1: Inhibitors of uPA

- If uPA is involved in metastasis and predicts poor patient outcome, high levels of PAI-1 might be expected to block metastasis and thus predict good outcome

PAI-1 vs DFI


PAI-1<=0.647 (n= 104)
PAI-1>0.647 (n= 80)
Probability of disease-free survival
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
Time (years)
P=0.0003; RR=2.37

PAI-1 vs overall survival



uPA and PAI-1 as Prognostic Markers in Breast Cancer

- Prognostic impact of both confirmed by > 20 independent groups
- Prognostic value independent of traditional factors
- Prognostic value stronger than HER2, EGFR, CB, CD, p53
- Prognostic in patients with both N+ and N- disease

uPA and PAI-1: Transfer to Clinic

- Clinical value must be validated in a gold-standard or level I evidence study

LOE for Grading Clinical utility of Tumor Markers

- I. High powered randomized prospective trial or meta/pooled analysis
- II. Therapeutic trial to test therapeutic hypothesis but not marker utility
- III. Large retrospective study
- IV. Small retrospective study
- V. Pilot study

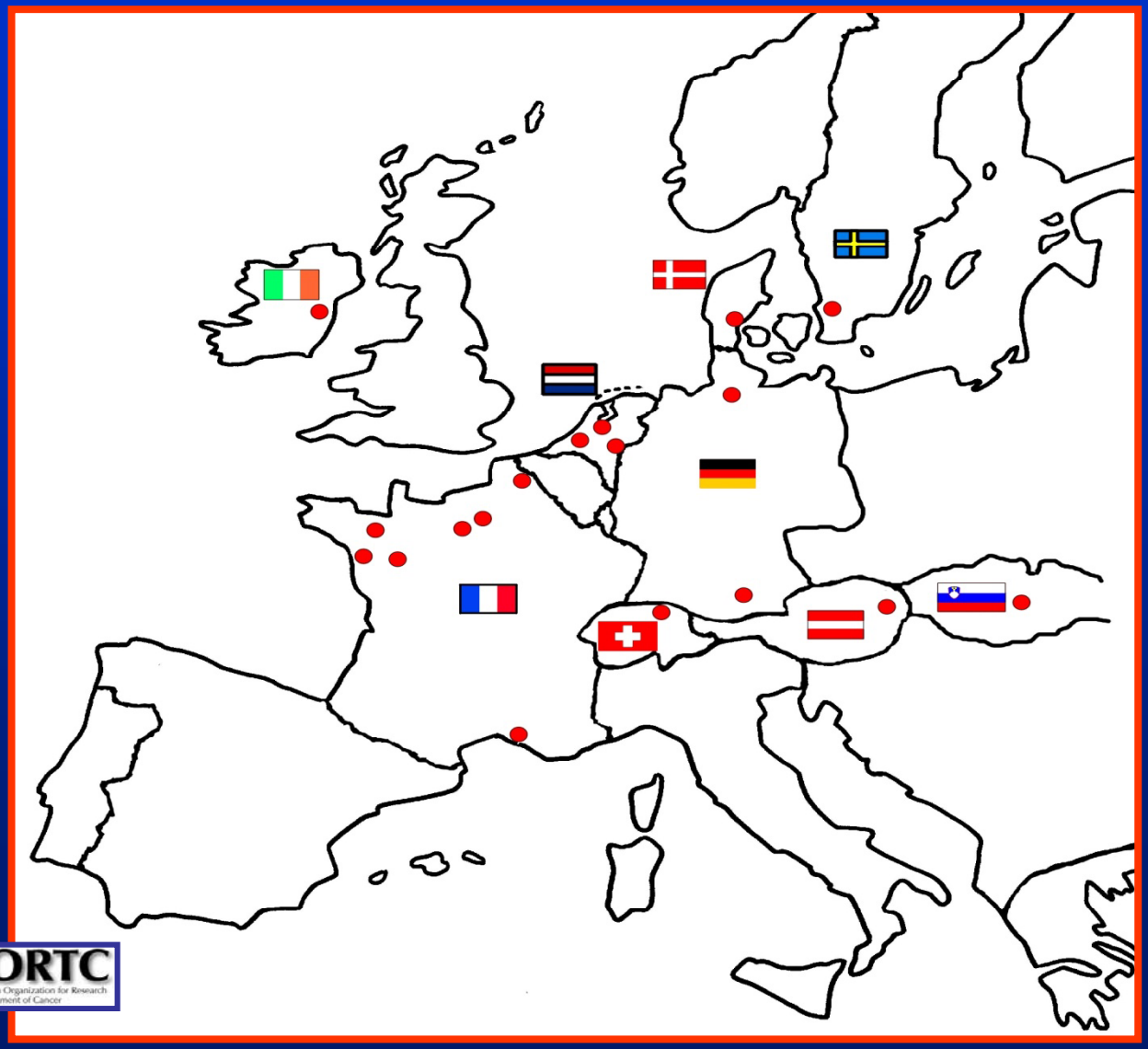
Hayes et al JNCI 1996;88:1456

Pooled Analysis of uPA/PAI-1: EORTC Study

- Raw data: 18 data sets, 8377 patients
- Published, 11; unpublished 7
- Median follow-up: 79 months
- 35% of patients relapsed
- 27% had died

Look et al. JNCI 2002;94:116

Participating laboratories (9 countries)



EORTC
European Organization for Research and Treatment of Cancer

uPA/PAI-1 Pooled Analysis

PI

M Look, Rotterdam

STEERING COMMITTEE

N Harbeck, Munich,

K Ulm, Munich,

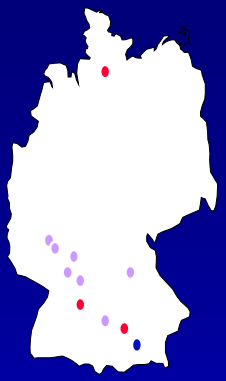
MJ Duffy, Dublin (Chairman)

Pooled Analysis: Summary

- **Both uPA and PAI-1 were independent prognostic factors**
- **uPA/PAI-1 ranked second to nodal status but stronger than size, grade, HR, age**
- **uPA/PAI-1 prognostic in N- and N+ patients**
- **uPA/PAI-1 prognostic in untreated N- patients**
- **uPA/PAI-1 together better than either alone**

Look et al. JNCI 2002;94:116

Prospective Randomized German Multicenter Therapy Trial in Node-negative Breast Cancer



Node-negative Breast Cancer

T ≥ 1 cm and ≤ 5 cm
10 LN analyzed
pre- / postmenopausal

STRATIFICATION

uPA and PAI-1 low

Observation

uPA and / or PAI-1 high

RANDOMISATION

Adjuvant Chemo (6 x CMF)

Observation

uPA/PAI-1: Prognostic Value in Breast Cancer

Prognostic value for N- patients confirmed in 2 different LOE1 studies

- **Randomised prospective trial (556)**
- **Pooled analysis (n=8377)**

Janicke et al. JNCI 2001;93:913

Look et al JNCI 2002;94:116

uPA and PAI-1: ASCO Recommendation for Clinical Use

- **uPA and PAI-1 may be used for the determination of prognosis in patients with newly diagnosed, node negative breast cancer.**
- **Low levels of both markers are associated with a sufficiently low risk of recurrence, especially in HR–positive women who will receive adjuvant endocrine therapy, that chemotherapy will only contribute minimal additional benefit.**

ASCO Recommendations: 2007

- ER/PR
- HER-2
- uPA/PAI-1
- Oncotype DX

Harris et al. J Clin Oncol 2007;25:5287

Other Expert Panels Recommending uPA/PAI-1 for Clinical Use

- American Society of Clinical Oncology
- National Academy of Clinical Biochemistry (US)
- European Group on Tumor Markers (EGTM)
- German Gynecological Society

uPA and PAI-I for Determining Prognosis in Breast Cancer: NACB Recommendation

The NACB Panel states that testing for uPA and PAI-1 may be carried out to identify lymph node-negative breast cancer patients that do not need or are unlikely to benefit from adjuvant chemotherapy. Measurement of both proteins should be performed as the information provided by the combination is superior to that from either alone.

Sturgeon et al, Clin Chem 2008;54:e11-e79

uPA and PAI-I for Determining Prognosis in Breast Cancer: NACB Recommendation

Lymph node-negative breast cancer patients with low levels of both uPA and PAI-1 have a low risk of disease relapse and thus may be spared from the toxic side effects and costs of adjuvant chemotherapy. Lymph node-negative women with high levels of either uPA or PAI-1 should be treated with adjuvant chemotherapy.

Sturgeon et al, Clin Chem 2008;54:e11-e79

Acknowledgements

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