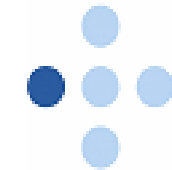


The effect of TCM herbal medicine in metastatic Non-Small Cell Lung Cancer

Jan P. A. Baak, MD, PhD, FRCPath, FIAC(Hon), FICP
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*Stavanger University Hospital and
University in Bergen, Norway*

Vrije Universiteit, Amsterdam, Netherlands

University of Siena, Siena, Italy

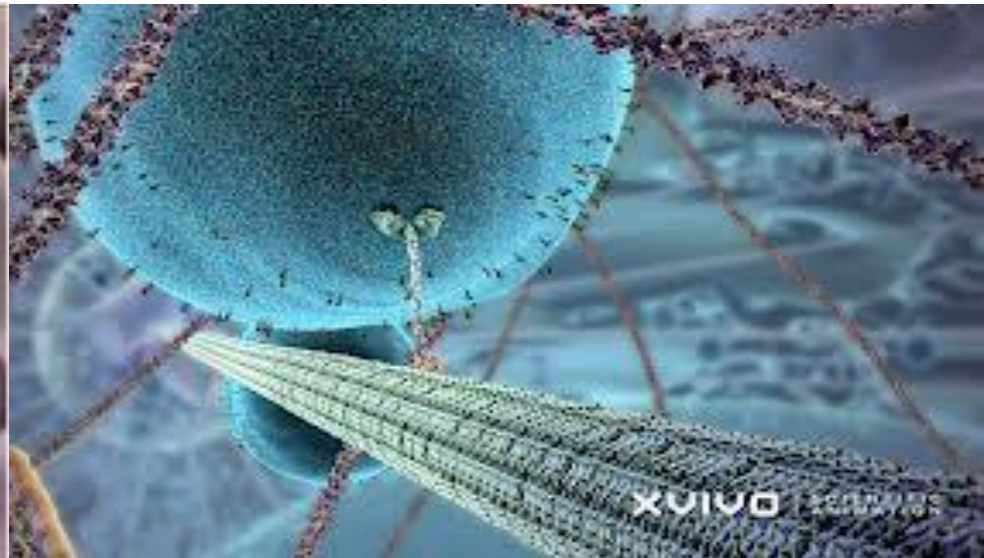
**Typical reaction of nearly all TCM doctors:
“What? Pathologist? TCM in dead people?”**

THE JOURNAL OF
Pathology
Understanding Disease

THE SCIENCE OF UNDERSTANDING DISEASE



The Crawling Leukocyte



The Inner Life of a Leukocyte

- Since 1965 personally motivated to find “the” cure for cancer
- Medical study (VU Amsterdam) 1966-1974, started research in 3rd year of medical study
- Specialist in Pathology (1980), prof. pathol. 1984
- Worked in Amsterdam, Siena, Boston, Baltimore, Toronto, Melbourne, since 2001 in Norway
- Mostly research 452 Internat’l Pubmed publications, supervised 42 PhDs
- Analytical, quantitative, molecular, genetics, proteomics, evidence-based
- Medical view 1966-2007: Human body is like a house, repair/replace malfunctioning parts
- **Against any form of alternative medicine**

Why changed?



FUDAN UNIVERSITY CANCER CENTER

Cancer research since 1969, MD 1974,

Pathologist 1980, prof. Pathology 1984

Until 2008 fanatic opponent of TCM

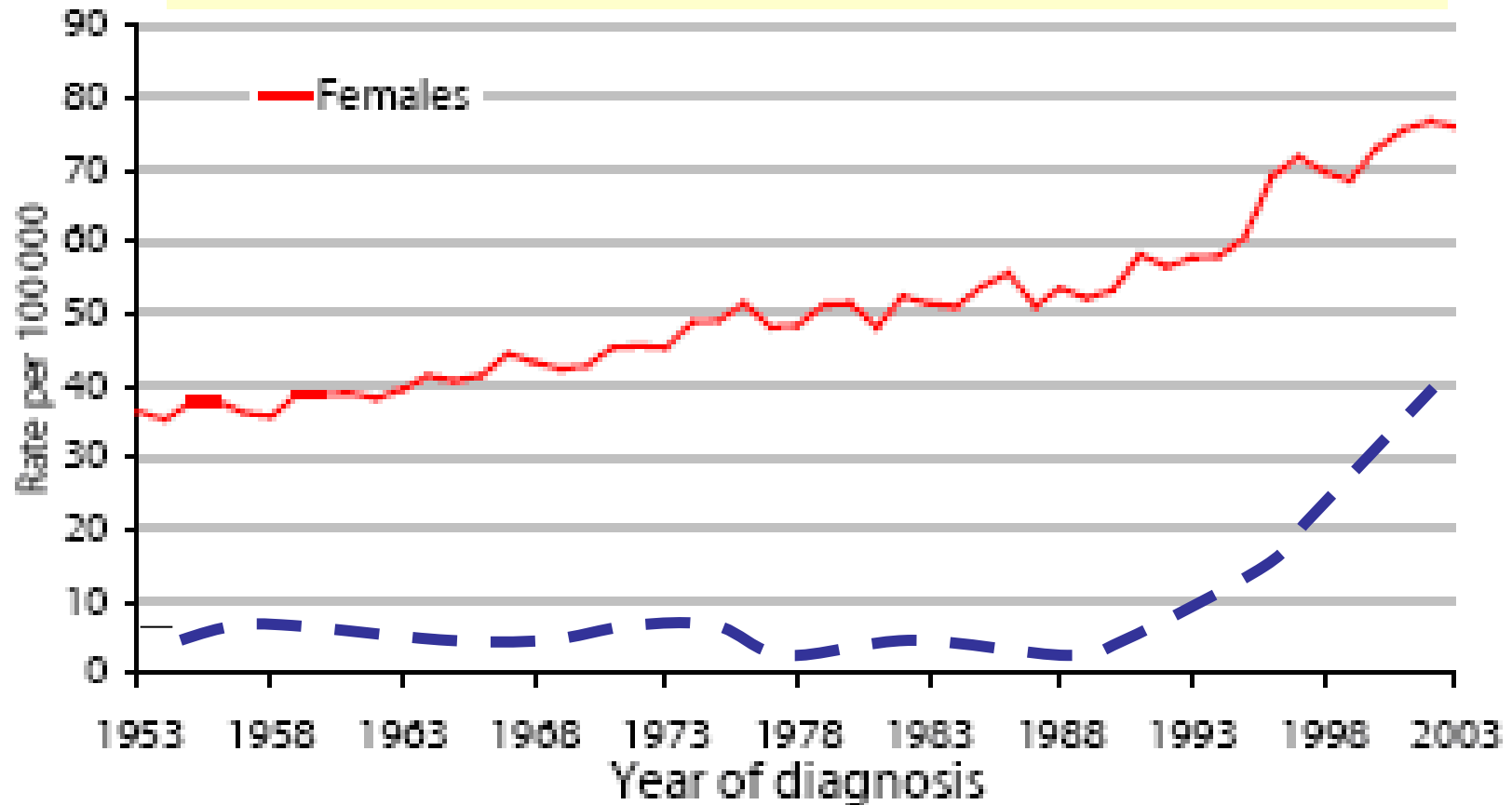
2008-2009 Breast cancer research at
Fudan University Shanghai Cancer Center

Very large and modern

2500 new breast cancers per year

Breast cancer research

Breast Cancer Incidence in Norway and China



*In China, much lower incidence,
but dramatic increase since mid-90s*

Classical Chinese Diet

- Three meals per day
- Many vegetables
- Little meat
- Fish, chicken, duck
- Meager, often cooked, not fried
- Limited carbohydrates, mostly brown rice
- No food in between meals
- Not sweet

But since 1985, high-glycemic carbohydrates have become much more popular



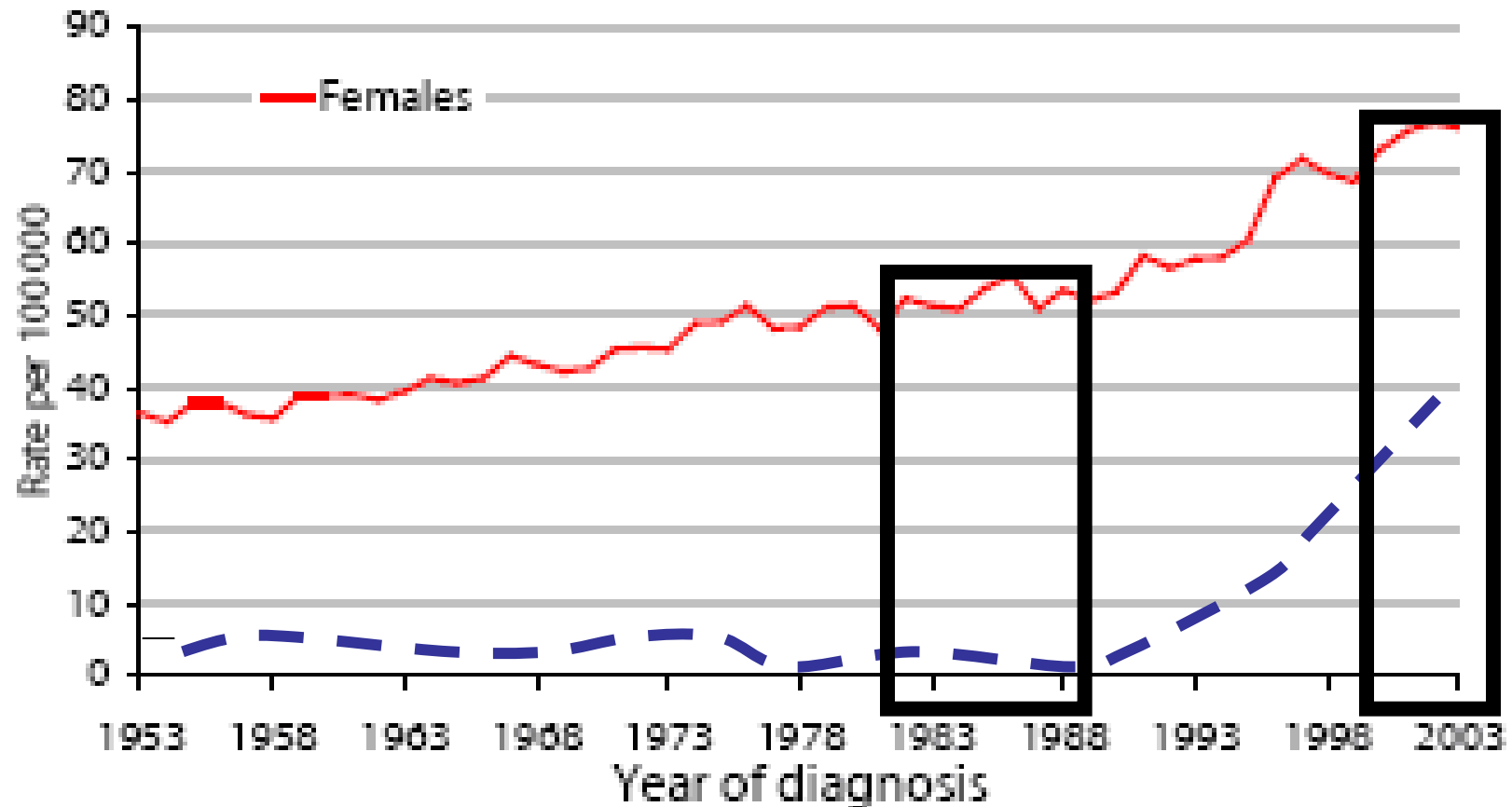


25 years ago, walking and biking was the main type of transport in China

Could it be? Here in China? A pair of pants where the waist measures the same as the length? Yes indeed --China's largest pair of pants!
Novelty? Unfortunately not!
Abdominal obesity has been a Western problem for some time and is growing into an international phenom as well.
So what do we know about the waistline and health? How do you measure up? Are you an apple or a pear?



Comparison of breast Cancers in Norway and China



If carbohydrates and less physical activity are a major cause of the increased cancers in China, one would expect

- 1. a change in invasive cancers versus In Situ carcinomas, and an increase in the proliferative activity in Chinese breast cancers;*
- 2. that the 1980s cancers from Norway would look more similar to the 2000 Chinese cancers in proliferation*

Cancer and carbohydrates

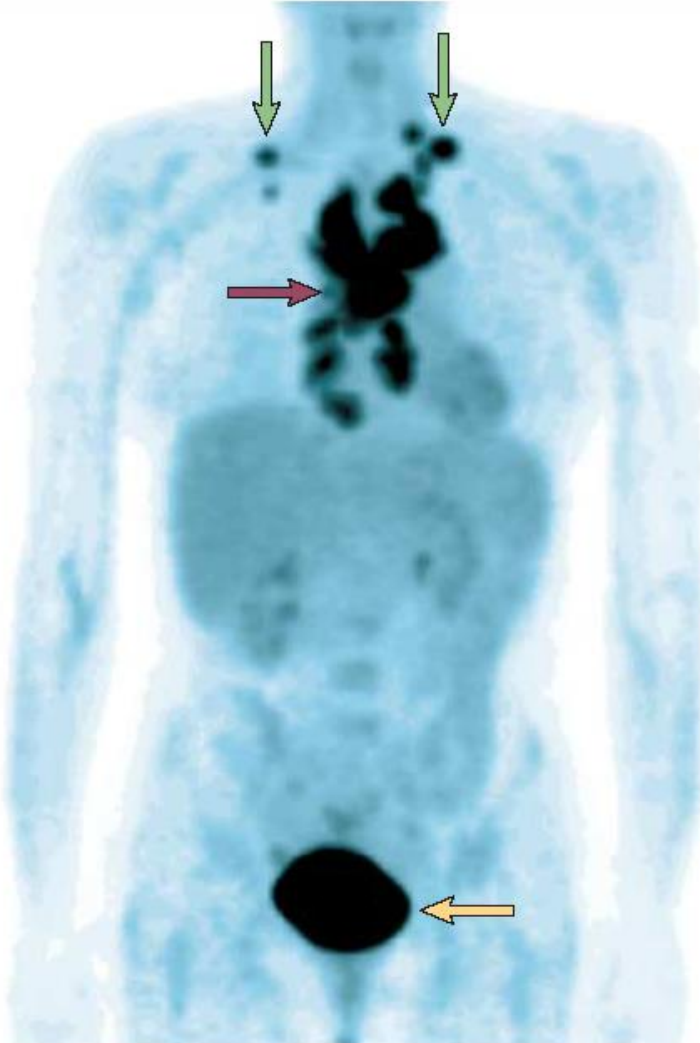


Figure 2 | Positron-emission tomography imaging with ^{18}F fluorodeoxyglucose of a patient with lymphoma. The mediastinal nodes (purple arrow) and supraclavicular nodes

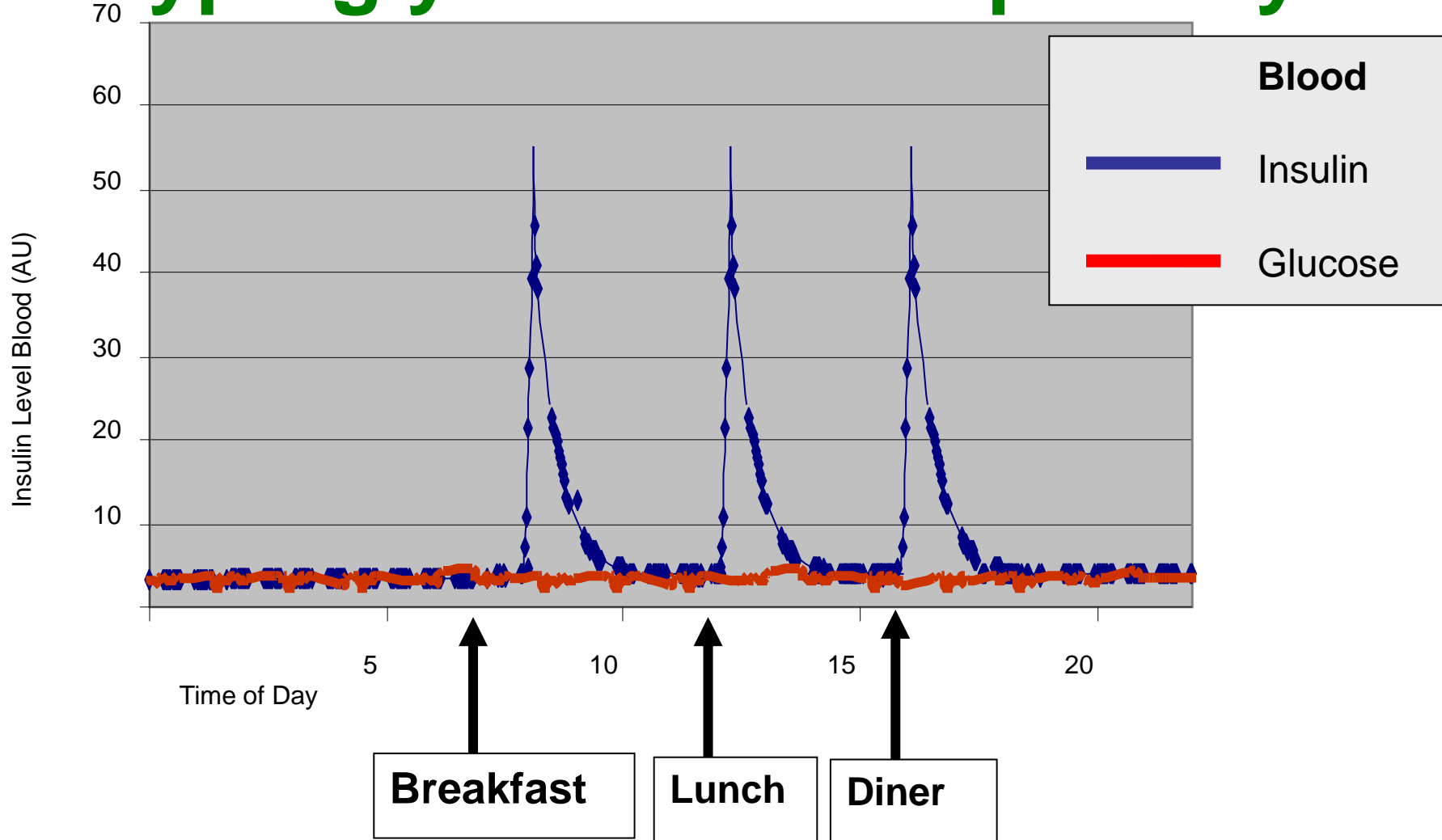
Cancers show up to 30x increased glucose uptake (Warburg 1924)

Glucose metabolism visualized by

^{18}F -Fluoro-deoxy-glycose PET scanning

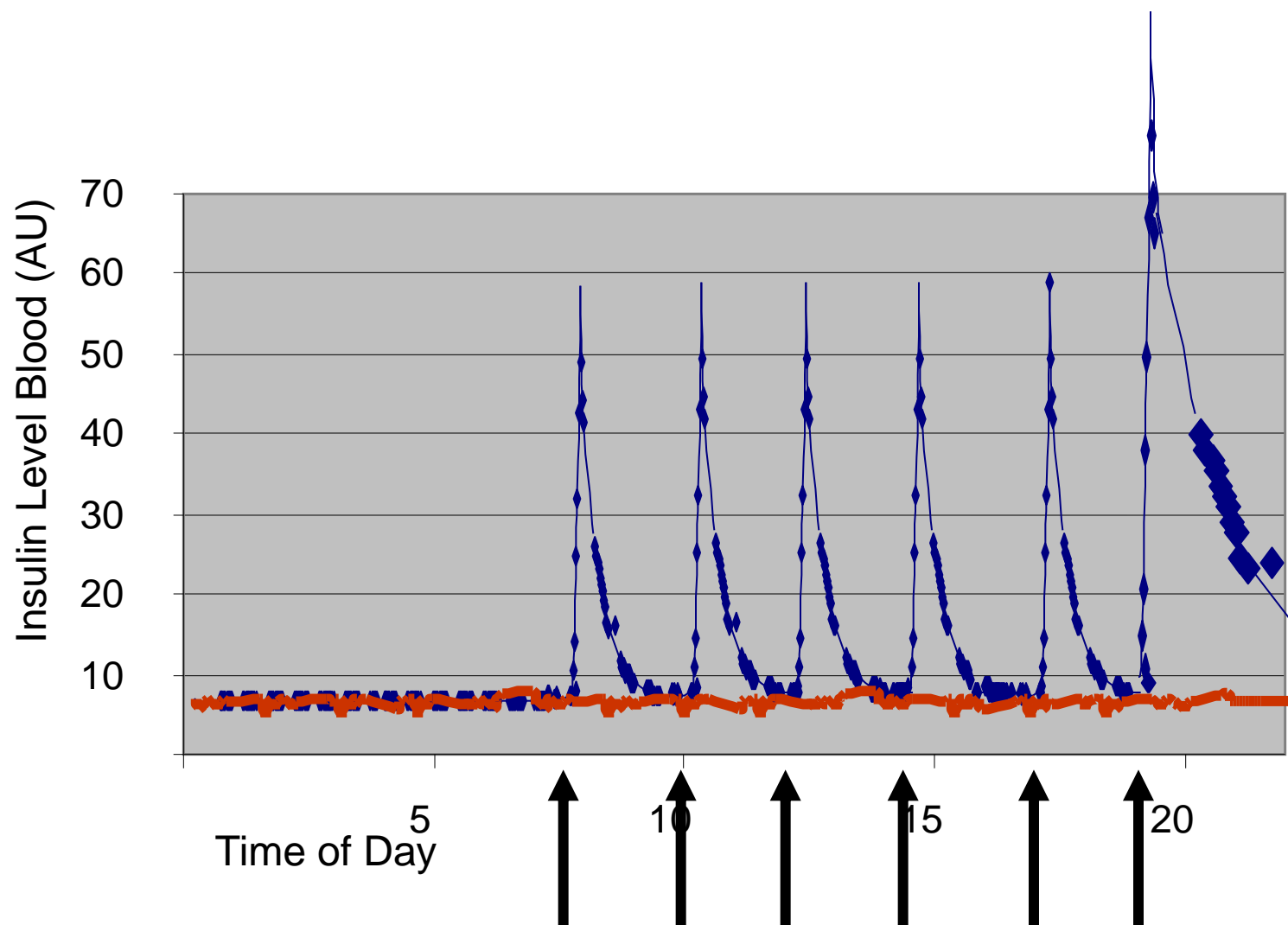
*Gatenby and Gillies,
Nature Reviews Cancer
2004*

The Effect of Three Hyperglycemic Meals per Day



Glucose stable, but Insulin shows high peaks in the blood

Uncontrolled junk food diet strategy





Fudan University Cancer Center

also has large Integrative Oncology department

- *spleen phlegm, liver heat*

??????

- decided to study TCM and acupuncture



**Basic and Advanced TCM and Acupuncture study,
Shanghai University of TCM
September 2008-July 2009**

Longhua Hospital, Shanghai

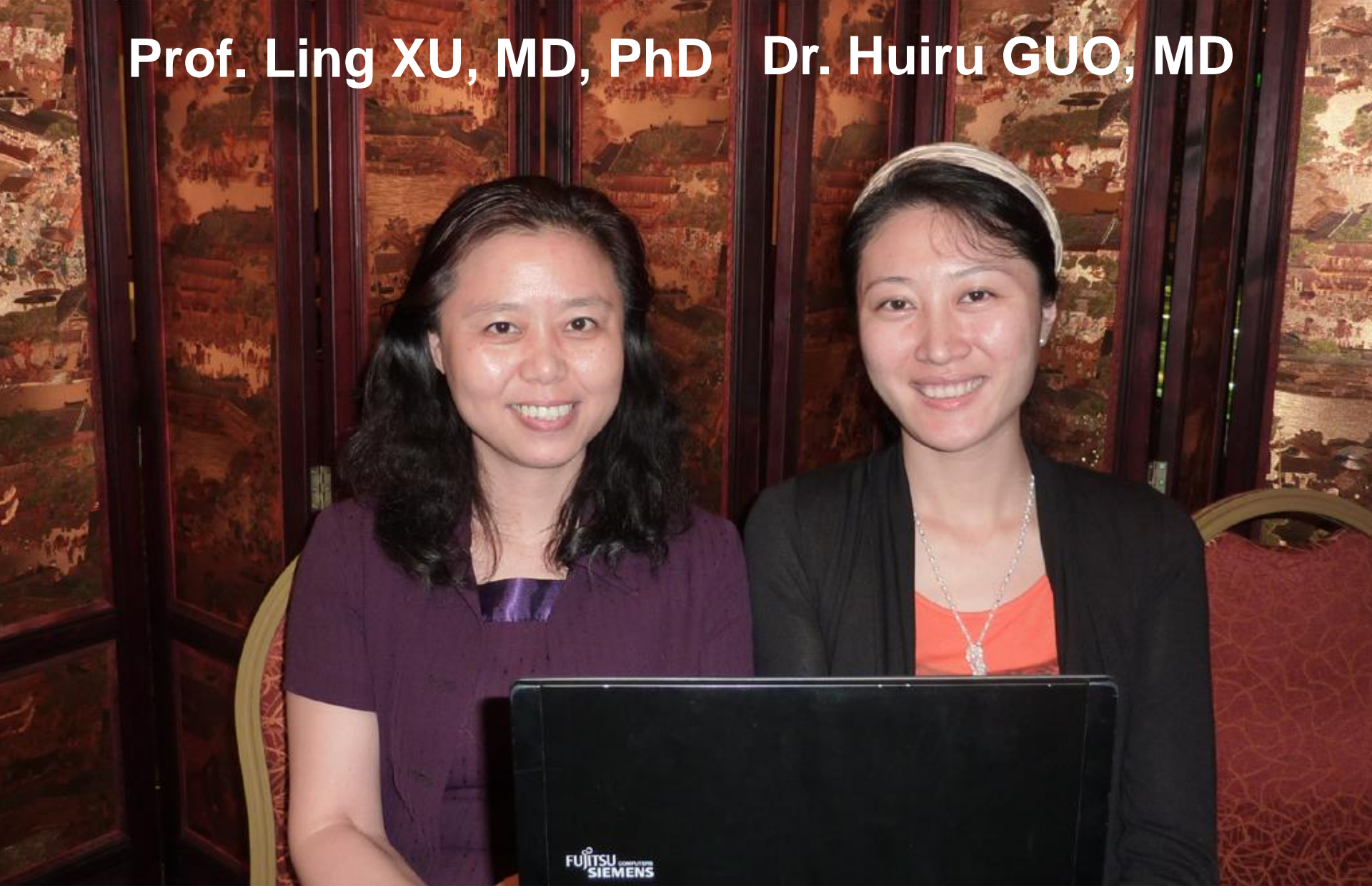
- TCM
- 1000 beds
- Massive outpatient numbers





Prof. Ling XU, MD, PhD

Dr. Huiru GUO, MD



Guo needed help with her PhD on Lung cancer

Long cancer

- Most common malignant tumors in the world, leading cancer death
- 2 million new cases/yr; 1,5 million die <5 years
- Majority of patients have metastases at diagnosis (=stage IIIB-IV)
- Survival after chemotherapy improved in past decades, but prognosis still very poor
- Targeted therapy promising but unaffordable for many patients in developing countries

Agenda

1. Prognostic proof for TCM herbal medicine in patients with metastatic lung and colorectal cancer
2. Is TCM-improved survival in cancer real?
Or due to treatment delay (Lag-time-to-treatment)?
3. Effect of TCM on Quality of Life in metastatic lung cancer patients.

TCM in stage IIIB-IV pulmonary adenocarcinoma

Study Objective

To study whether TCM improves survival in ambulant stage IIb-IV pulmonary adenocarcinoma patients treated with

- Platinum-based chemotherapy (PBCT), or
- Combined PBCT & second line Target Therapy

TCM in Stage IIIB-IV NSCLC and Prognosis

Study-Design

1. Retrospective, case-control study, n=122
2. **TCM:** All **ambulant** patients with **primary** stage **IIIB-IV Adenocarcinoma**, Longhua hospital, Shanghai, 2007-2009, n=61
 - ◆ Platinum based Chemotherapy (PBCT)
 - ◆ or combined PBCT & Targeted therapy (TT)
 - ◆ with Traditional Chinese Medicine herbs
3. **Controls:** Pulmonary Hospital Shanghai, age-, gender-, diagnosis date randomly 1:1 selected, PBCT- or +TT, no TCM herbs, N=61.

TCM in Stage IIIB-IV NSCLC and Prognosis

TCM Syndroms:

1. *Combined Qi and Yin deficiency*

2. *Yin deficiency or Internal Heat*

3. *Qi deficiency*

4. *Combined Yin und Yang deficiency*

Chinese name	Chinese name (Pinyin)	Latin name	English name	Dosage
<i>Syndrome of Deficiency of Qi and Yin</i>				
黄芪	Huangqi	Radix Astragali seu Hedysari	Membranous Milk Vetch Root / Mongolian Milk Vetch Root	30
白术	Baizhu	Rhizoma Atractylodis Macrocephale	Largehead Atractylodes Rhizome	9
北沙参	Beishashen	Radix Glehniae	Coastal Glehnia Root	15
天门冬	Tiandong	Radix Asparagi	Cochinchinese Asparagus Root	15
麦冬	Maidong	Radix Ophiopogonis	Dwarf, Lilyturf Tuber, Ophiopogon	15
杏仁	Xingren	Semen Armeniacae Amarum	Bitter Apricot Seed	9
<i>Syndrome of Deficiency of Yin and Internal Heat</i>				
北沙参	Beishashen	Radix Glehniae	Coastal Glehnia Root	30
天门冬	Tiandong	Radix Asparagi	Cochinchinese Asparagus Root	15

TCM in Stage IIIB-IV NSCLC and Prognosis

Strongest prognosis improving factor is by TCM

		P	Hazard Ratio	95% CI	
				Lower	Upper
Step 1	TCM or not	<0.0001	0.14	0.08	0.25
Step 2	TCM or not	<0.0001	0.22	0.11	0.43
	Targeted therapy	0.03	0.41	0.19	0.92

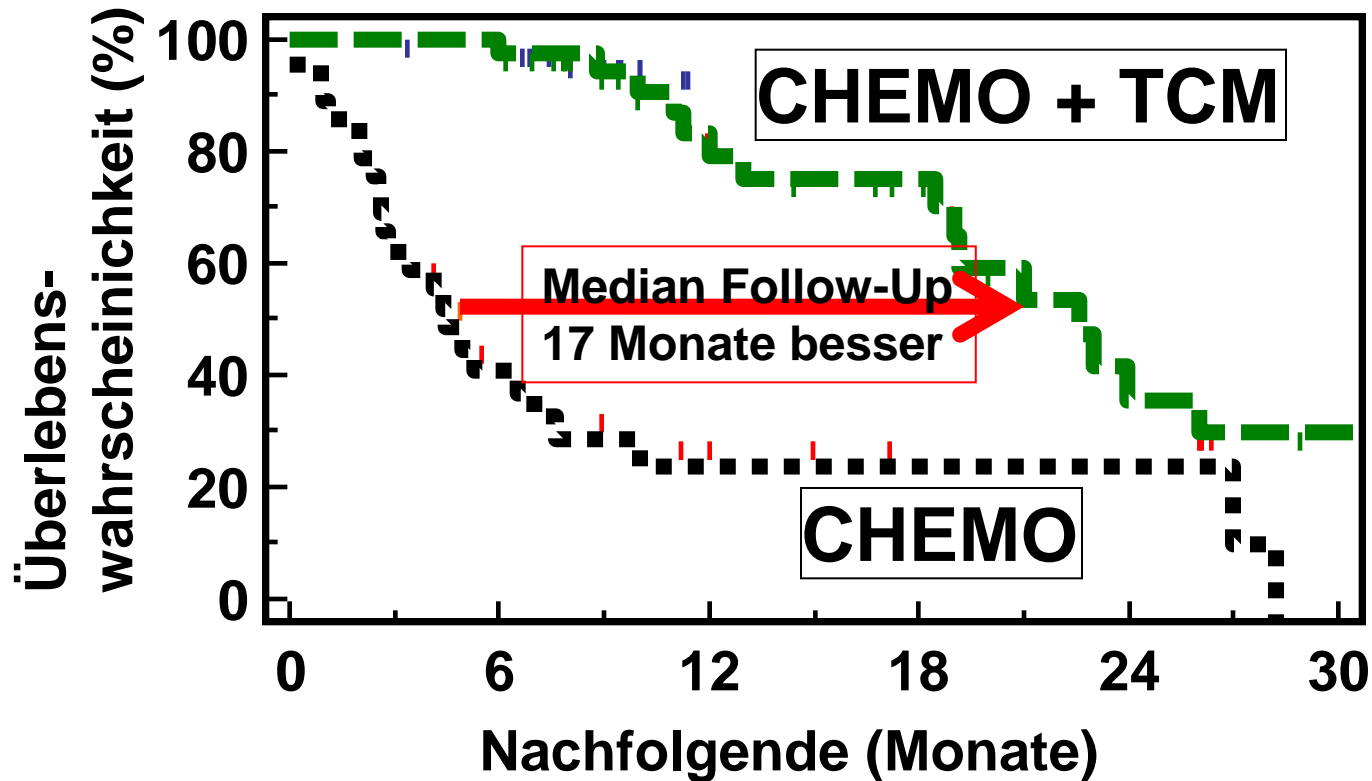
		Score	Df	Sig.
Step 2	Hospital	1.4	1	0.23
	Sex	3.2	1	0.07
	Age	4.6	3	0.20

a Residual Chi Square = 150.4 with 6 df Sig. = 0.02

b Residual Chi Square = 90.2 with 5 df Sig. = 0.10

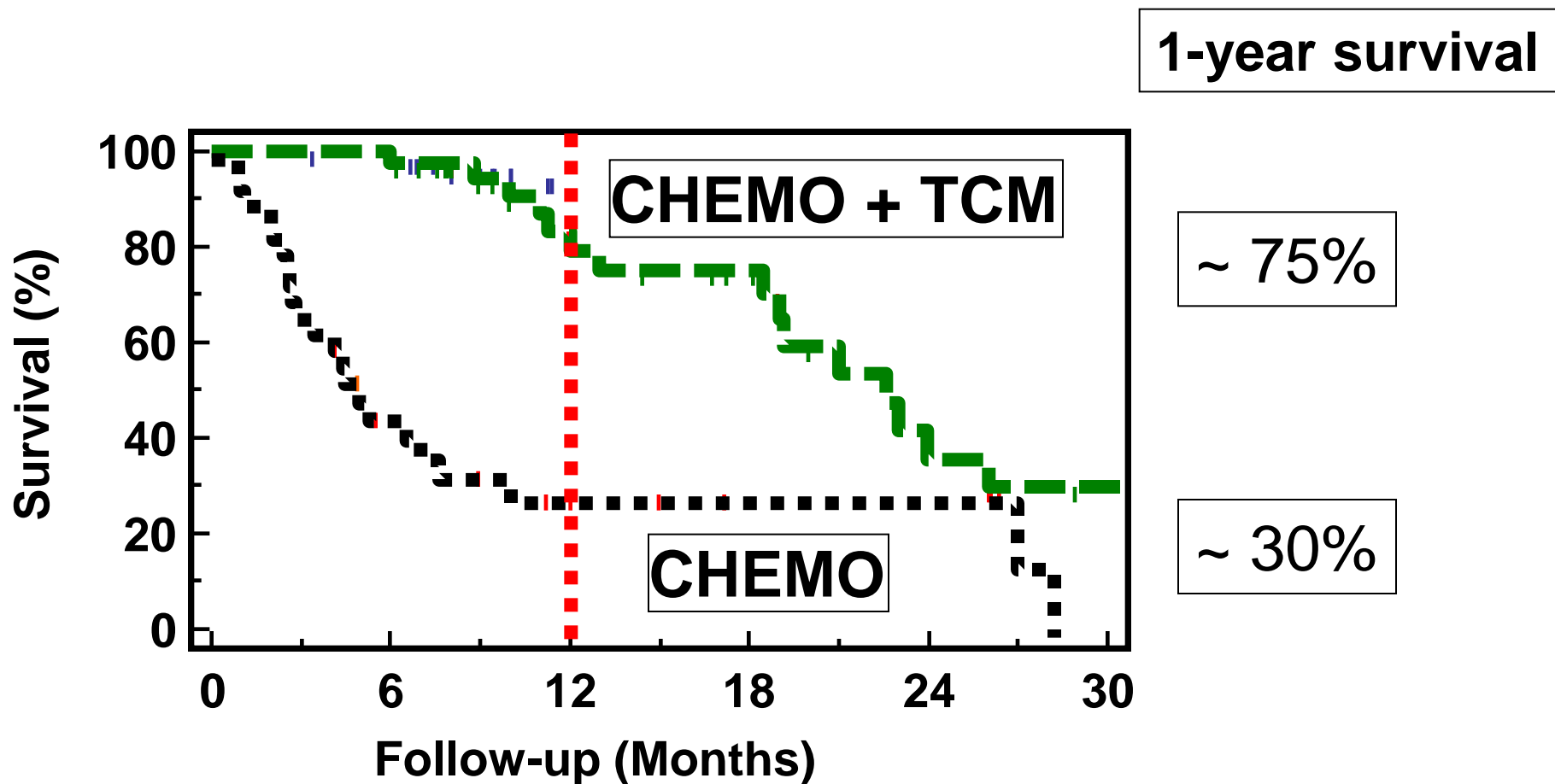
Shanghai, China study

Metastatic Lung Cancer

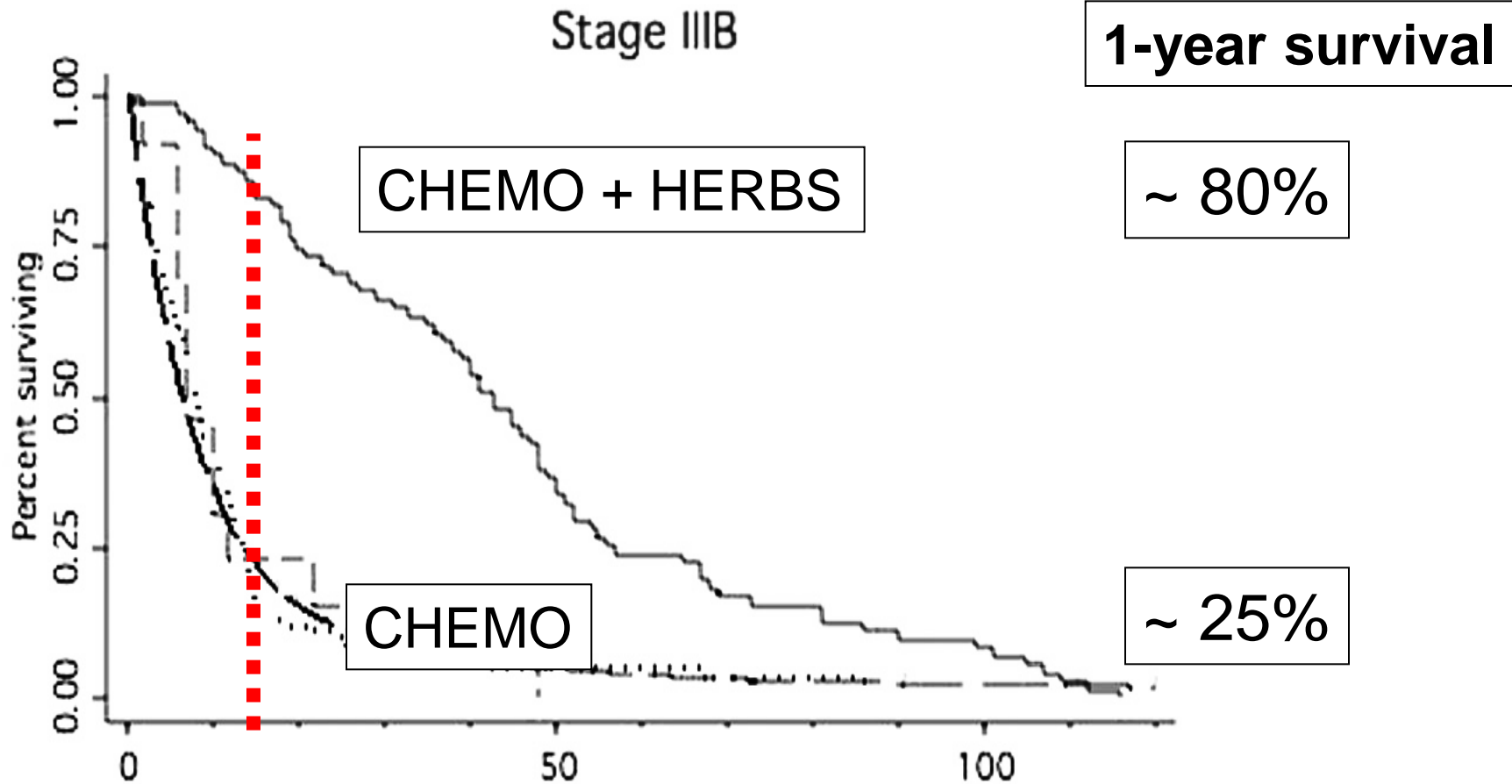


Shanghai, China study

Metastatic Lung Cancer



April 2009 discovered
Since then TCM focused

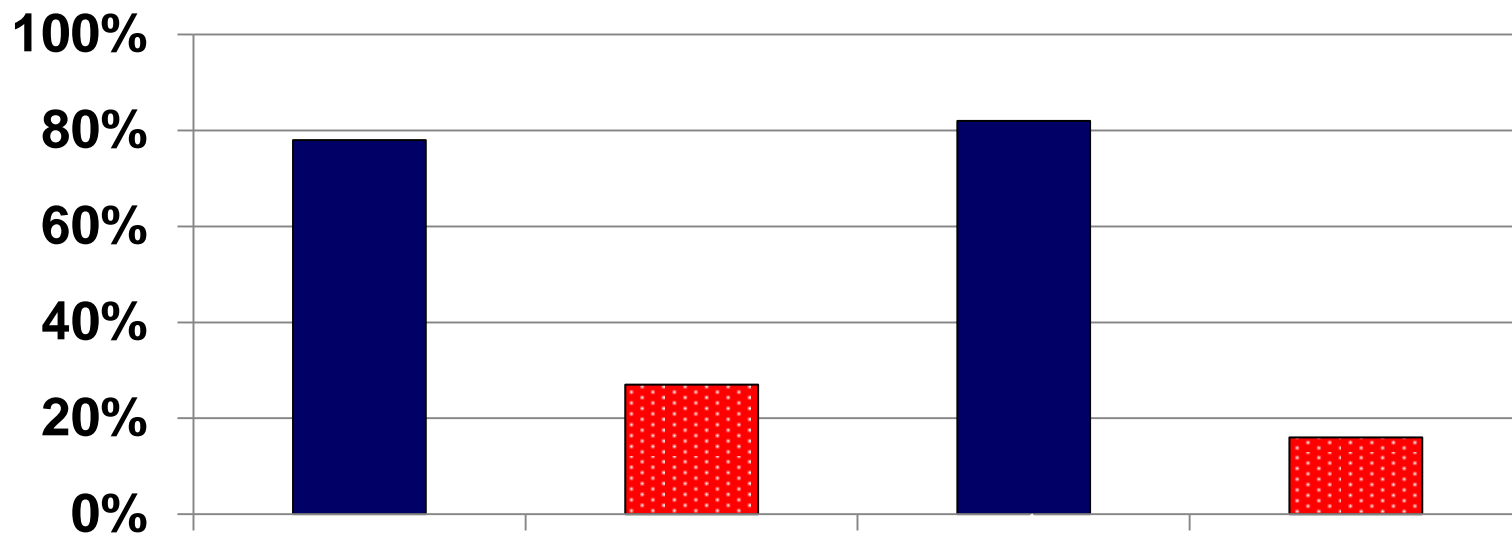


San Francisco, USA study

Metastatic Lung Cancer Only

McCullough et al Integr Cancer Ther. 2011 ;10:260-79.

1 Year Survival



Guo TCM&Chemo

Guo Chemo

McCulloch TCM+Chemo

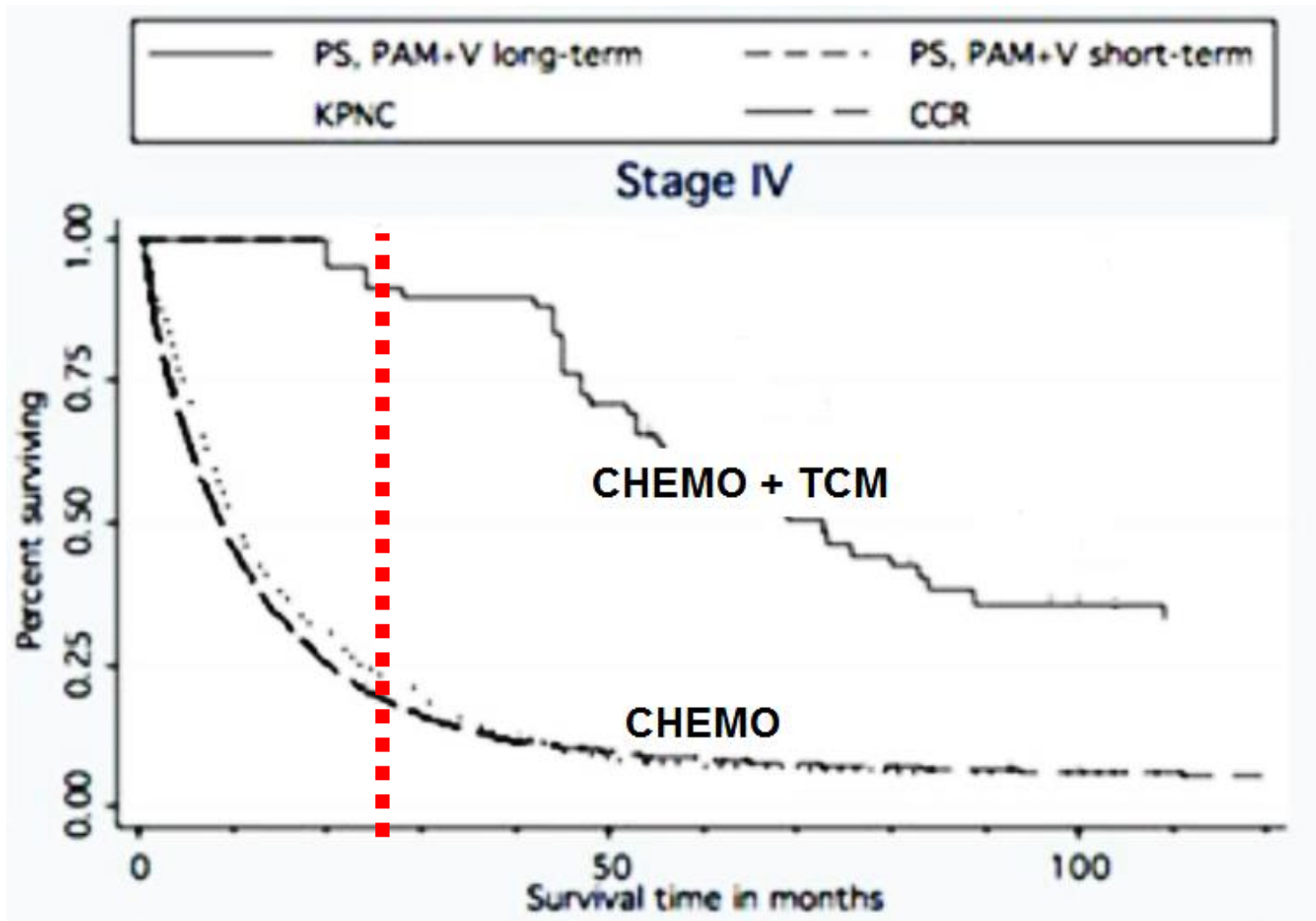
McCulloch Chemo

Metastatic Lung Ca
Shanghai, China

Metastatic Lung Ca,
San Francisco, USA

Colon Cancer , metastatic

Integr Cancer Ther. 2011 September ; 10(3): 240–259.



TCM herbal treatment in advanced lung cancer

Life gain of

CT plus TT	: 4-6 months
CT plus TCM	: 18 months

Does Traditional Chinese Medicine herbal treatment improve the prognosis of ambulant stage IIIB-IV adenocarcinoma of the lung treated with platinum-based chemotherapy

Huiru GUO, Jia Xiang LIU, Ling XU,
Tesfaye MADEBO, Jan P. A. BAAK



Longhua Hospital, Shanghai, China,
Stavanger University Hospital, Stavanger,
University of Bergen, Norway and
Free University, Amsterdam, the Netherlands



Integr Cancer Ther. 2011;10:127-137.



Agenda

1. Prognostic proof for TCM herbal medicine in patients with metastatic lung and colorectal cancer
2. Is TCM-improved survival in cancer real?
Or due to treatment delay (Lag-time-to-treatment)?

Is the improvement of prognosis of patients with metastatic pulmonary adenocarcinoma treated with TCM herbal medicine due to lag time to treatment bias?

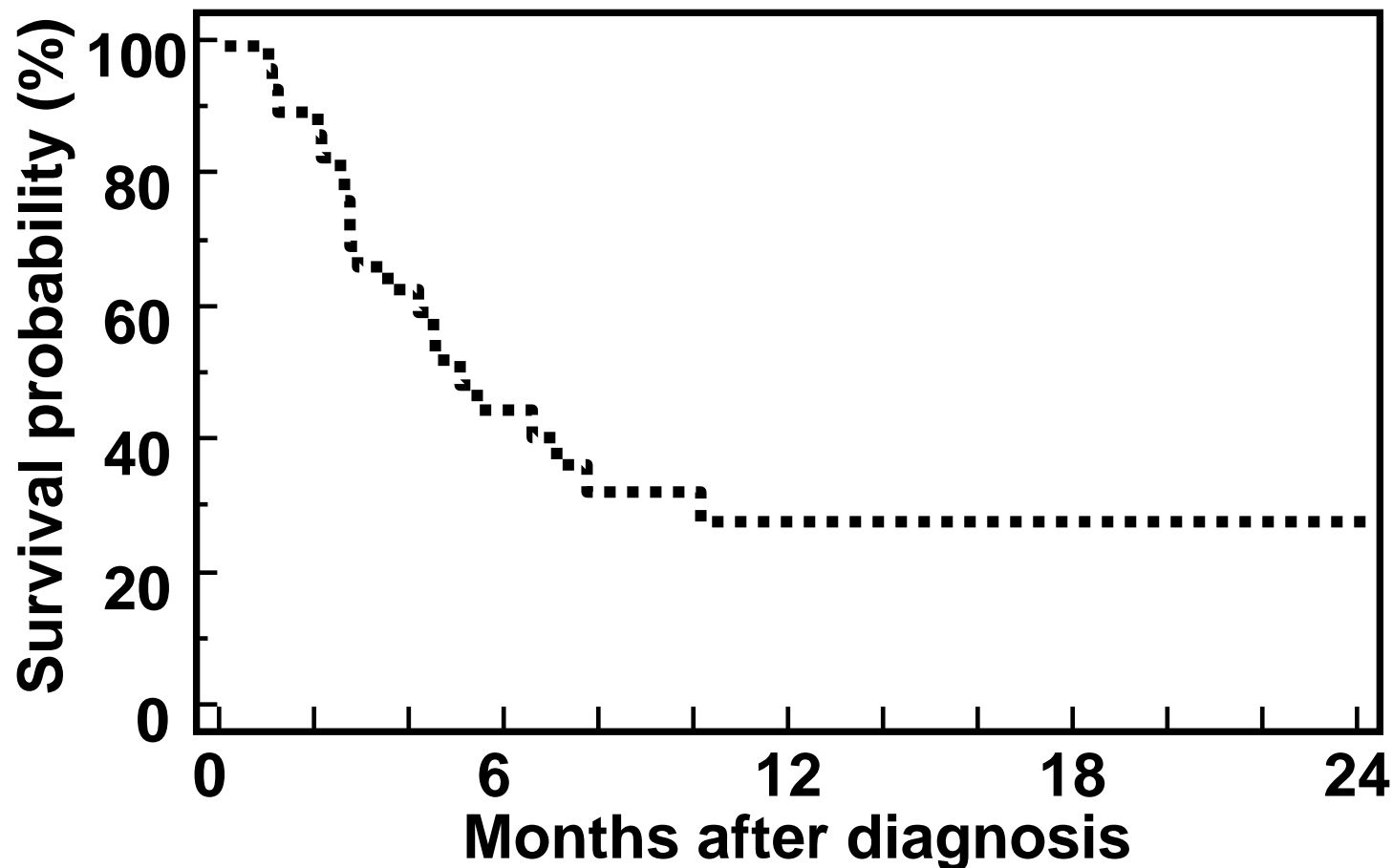
Guo HR, Liu LM, Baak J
Int Cancer Therapies, 2011

- Patients get diagnosis of metastatic lung cancer
- They understand soon that they have poor prognosis
- Receive chemo
- Some become soon very bad,
die within 1-3 months

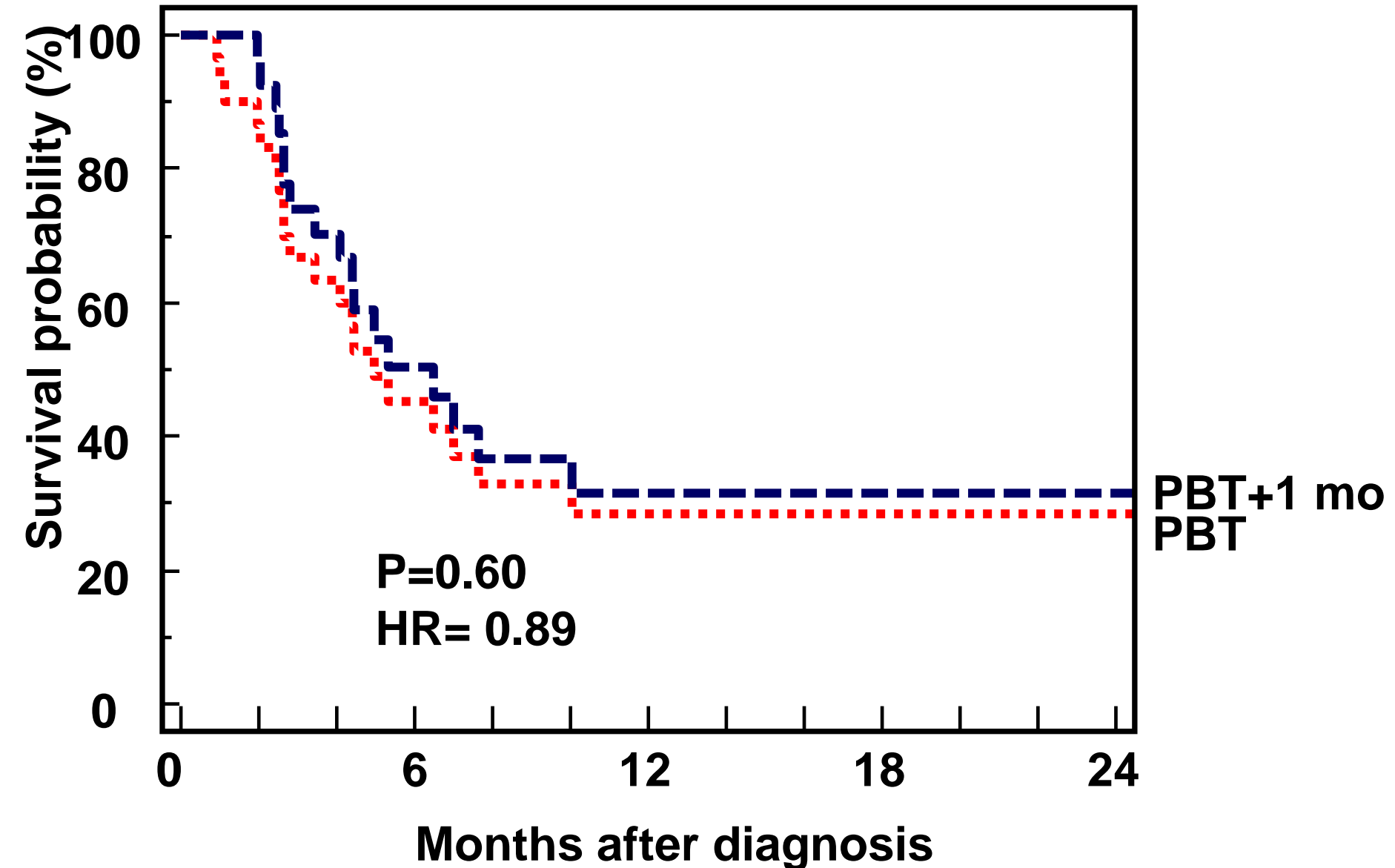
Is the improved survival of metastatic adenoca of the lung patients due to TCM herbs, or due to lag time to treatment?

- Some days/weeks after diagnosis, patients decide to visit a TCM doctor, who may have a waiting list of 1 week-3 months
- So, TCM treatment does not start at once after diagnosis of stage IIIB-IV lung cancer
- Total interval between diagnosis and TCM treatment (=lag-time to treatment): **median 1 mo**
- Consequently, patients with stage IIIB-IV who get Platinum-based chemo, but still die within 2-3 months, will never be seen by a TCM specialist

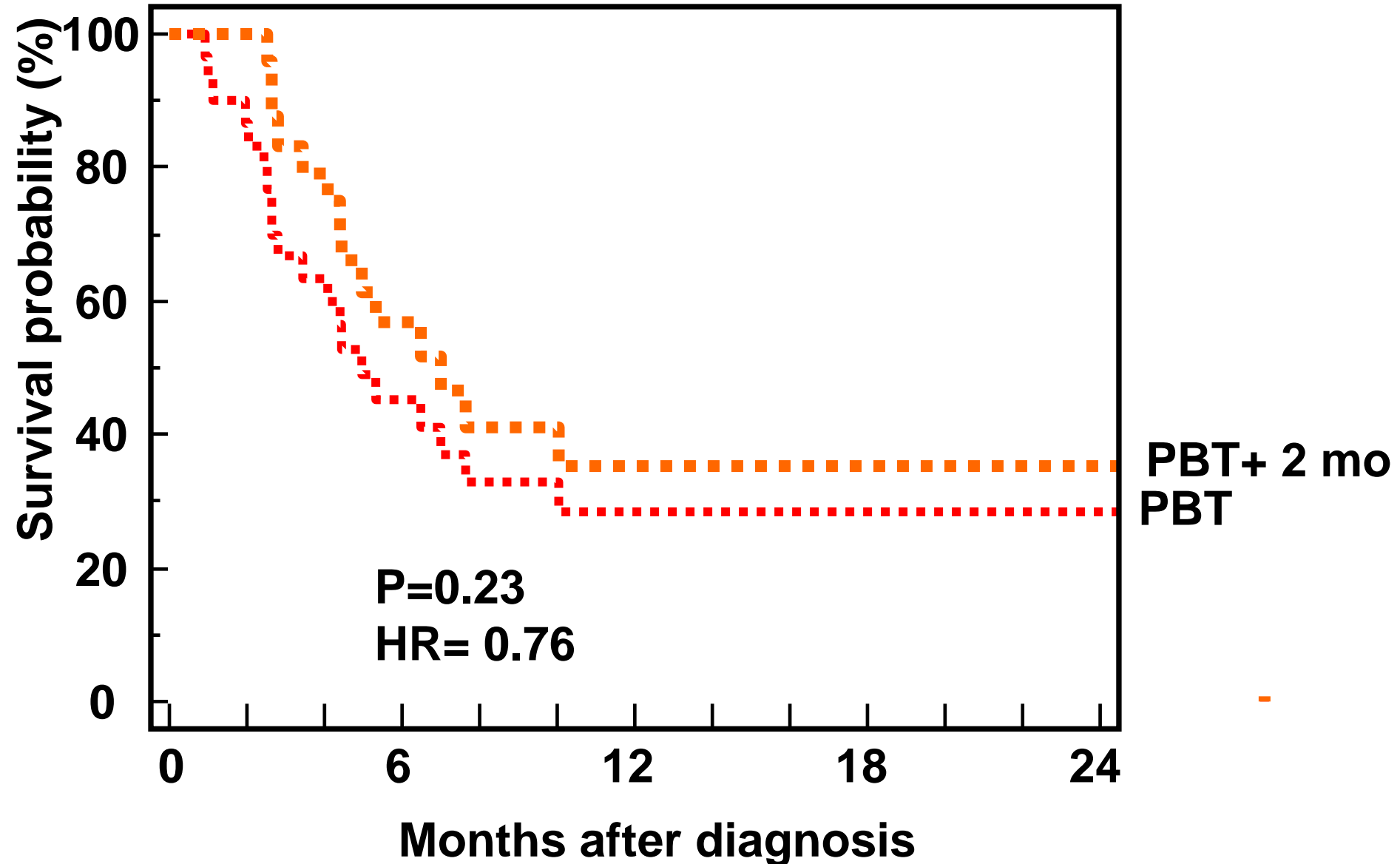
To investigate the effect of lag-time to treatment, we did a computer simulation of Stage 4 Adenocarcinoma of the lung, treated with Platinum-Based Chemotherapy



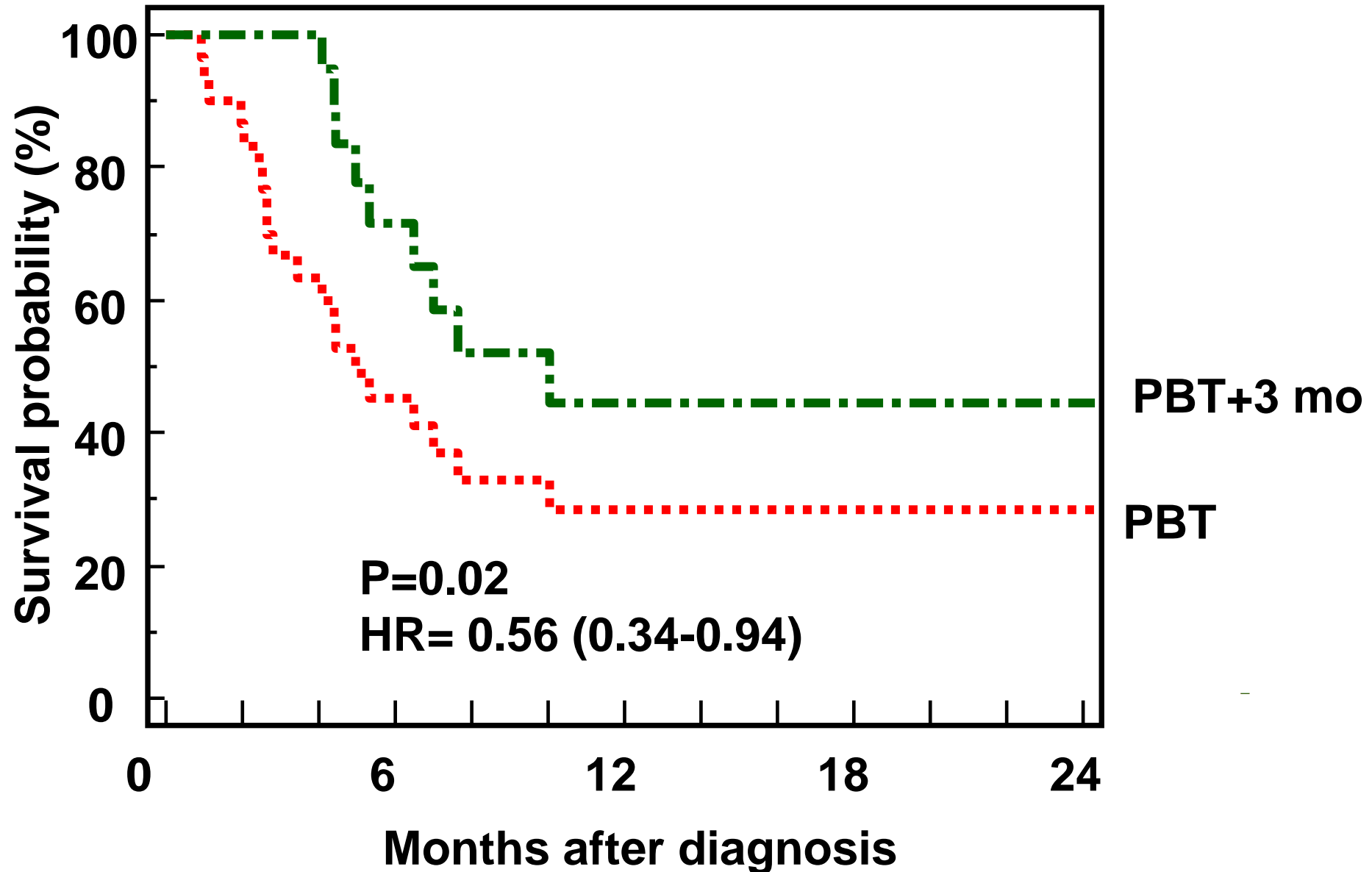
**Survival of Platinum-based chemo treated patients (red line)
and same patients, but leaving out those who die
within 1 months after the diagnosis (blue line)**



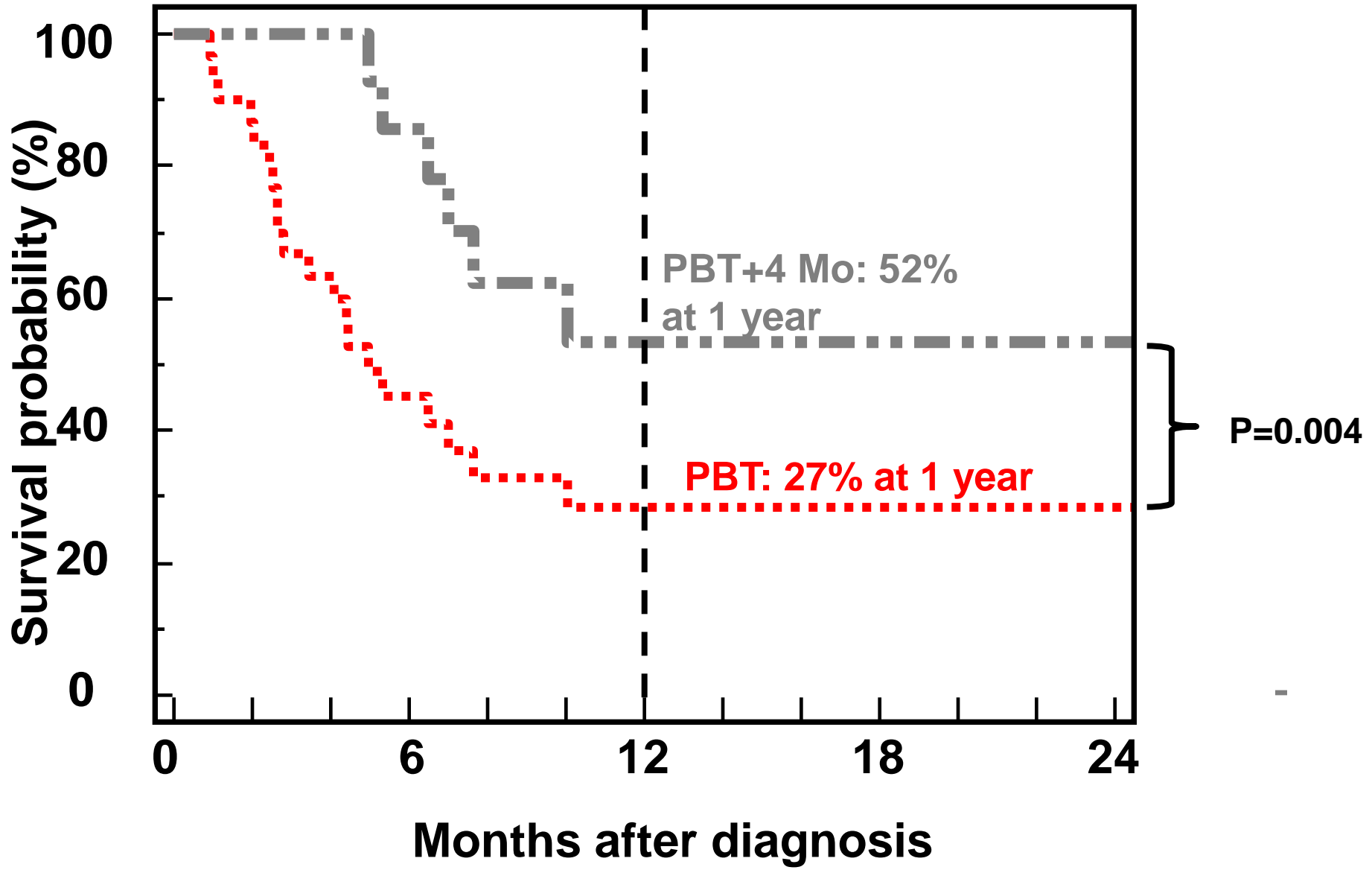
**Survival of Platinum-based chemo treated patients (red line)
and same patients, but leaving out those who die
within 2 months after the diagnosis (blue line)**



**Survival of Platinum-based chemo treated patients (red line)
and same patients, but leaving out those who die
within 3 months after the diagnosis (blue line)**



**Survival of Platinum-based chemo treated patients (red line)
and same patients, but leaving out those who die
within 4 months after the diagnosis (blue line)**

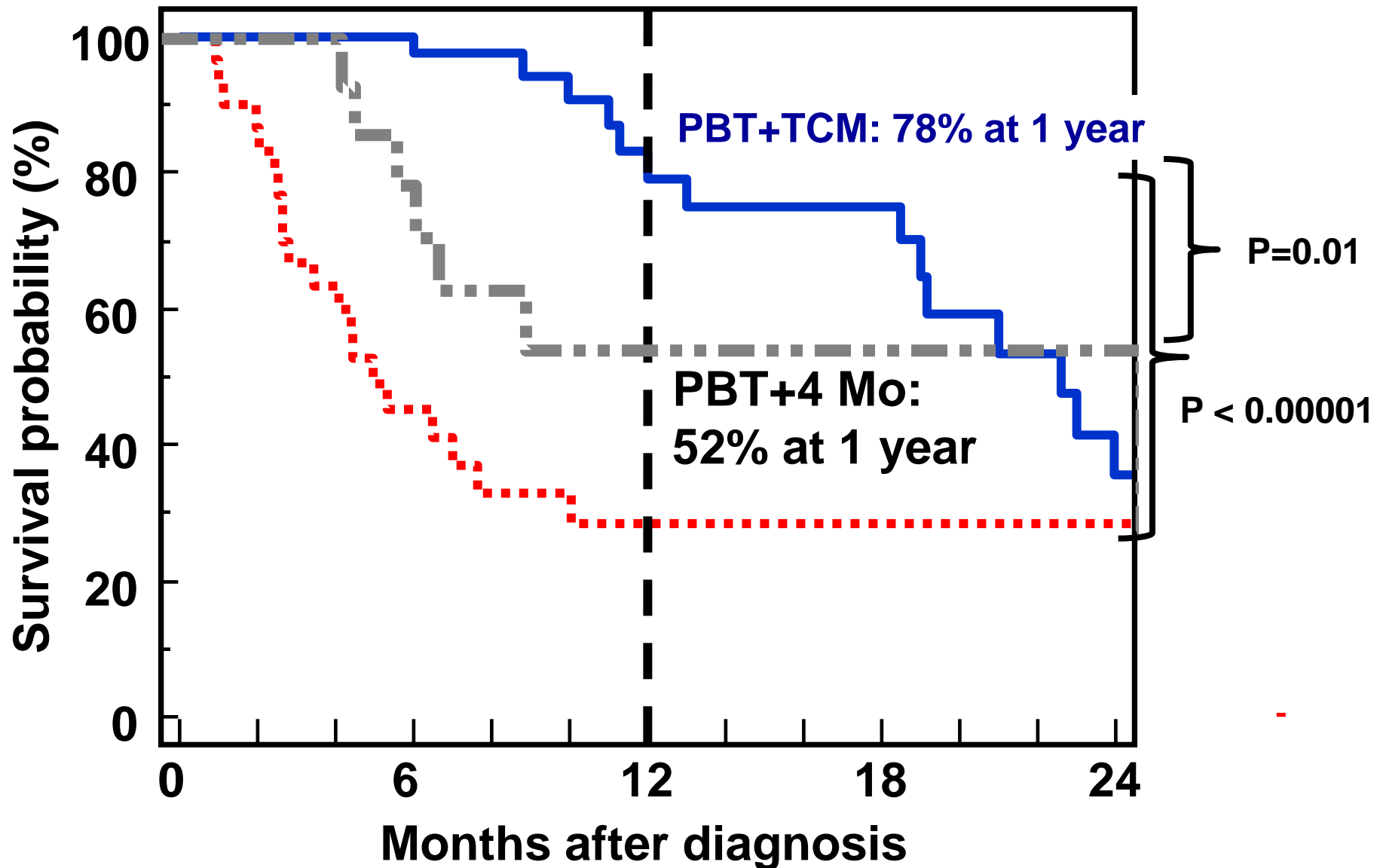


TAKE HOME MESSAGE 1:

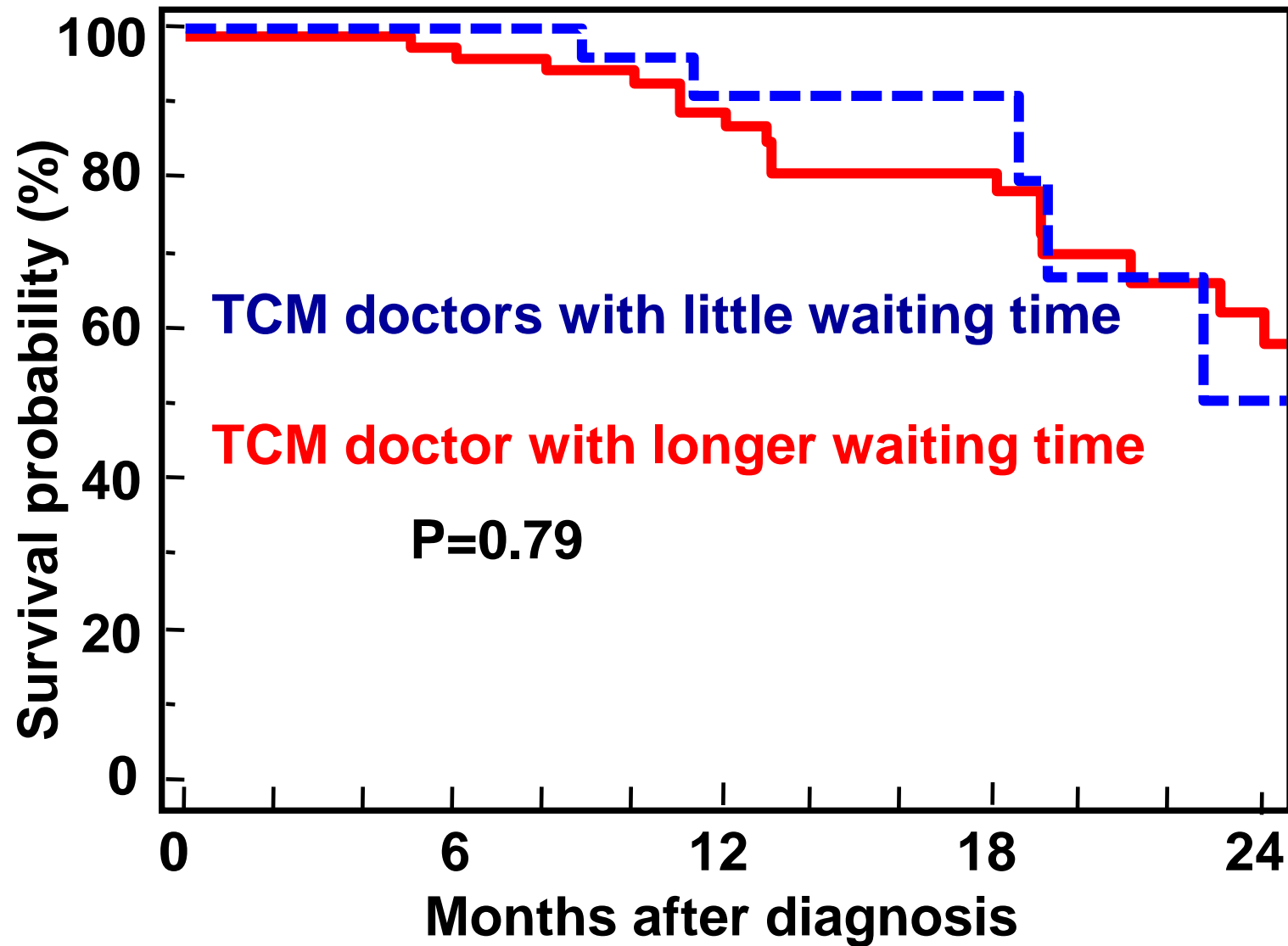
**Lag time to treatment
significantly improves the survival
and can be
serious confounder (disturbing factor)
in the evaluation of the
survival-improving effect of TCM in
patients with advanced cancer
and poor prognosis**

**Articles claiming a prognosis improving
effect without considering lag-time to
treatment must be distrusted**

Remember the survival improving effect of TCM treatment in Platinum-based chemotherapy



No difference in survival of Stage IV adenocarcinoma of the lung treated with PBT+TCM, treated by different TCM doctors



Conclusion

Lag time to treatment up to 4 months is unlikely to explain the greatly improved prognosis of adjuvant TCM treatment in patients with metastatic pulmonary Non-Small Cell Lung Cancer

TCM and Quality Of Life in NSCLC

A prospective randomized clinical study

H. Guo¹, J. X. Liu, ¹, H. Li¹, J. P. A. Baak²

¹Dept. for Medical Oncology, Longhua Hospital,
Shanghai, China

and

² Dept. for Pathologie, Stavanger
University Hospital
Stavanger, Norway

NOT YET PUBLISHED, PLEASE NO PHOTOS!

QOL and TCM in NSCLC

Problems with other studies: very heterogeneous

Therefore in this study very rigid design criteria!

- Prospective, double-blinded clinical study
- ALL consecutive patients, dec 2009-jan 2011
- Only first-time (no-pretreated) patients, with
 1. metastasized (stage IIIB-IV),
 2. Performance Score 0-1 (ambulant)
 3. Pathologically proven NSCLC lung cancer
 4. Combined Qi and Yin deficiency,
 5. Qi and Yin deficiency sharply defined

QOL and TCM in NSCLC

Study design, continued

- Patients, MDs und medical support personnel were all blinded to TCM or placebo decoctions.
- To controll TCM / Placebo intake, **all patients were hospitalized during the total study observation period of 2 months and were very closely surveilland/controlled by nurses, 24 hours per day**
- The decoctions were given to the patients by nurses who attended/controlled intake by the patients, 2x daily, 1 hour after the meals
- QOL Criteria: FACT-L were evaluated by the same very experienced MD, before and after each Chemo

QOL and TCM in NSCLC

Definition of Qi and Yin deficiency

One of the following

TWO

main symptoms and

2 or more

secondary symptoms

Main symptoms:

1. Coughing with little sputum,
2. Dyspnoea,
3. Tired/fatigue,
4. Dry mouth.

Secondary symptoms:

1. Spontaneous sweating,
2. Night sweating,
3. Red tongue with teeth indents,
4. Weak pulse

QOL and Platinum+TCM: PATIENTS

Consecutive new Longhua patients with metastasized lung cancer –diagnosis dec 09- jan 11		154 (100%)
EXCLUDED	NUMBER (%)	REMAINING
Small-cell cancer	31 (20.1%)	123 (79.9%)
No pathology	3 (1.9%)	120 (77.9%)
Performance Score >1	28 (18.2%)	92 (59.7%)
Pretreated elsewhere	7 (4.5%)	85 (55.2%)
Refused Chemotherapy	3 (1.9%)	82 (53.2%)
Other TCM Syndromes than combined Qi & Yin deficiency	21(13.6%)	61 (39.6%)

QOL and Platinum+TCM in new NSCLC

- 61 sequential patients
- Performance Score=PS 0-1
and
- Combined Qi-Yin deficiency
- Randomised
 - PBT+Placebo, N=32;
 - PBT+TCM, N=29
- QOL: FACT-L scales
- Before and after 2 Chemo therapy cycles

TCM Kräuter Behandlung

Chinese Name	Chinese Name (Pinyin)	Latin Name	English Name	Dosage
黄芪	Huangqi	Radix Astragali Mongholici	Membranous milkvetch root/ Mongolian milkvetch root	30g
白朮	Baizhu	RhizomaAtractylodis Macrocephalae	Largeheadatractylodes rhizome	9g
茯苓	Fuling	Poria	Indian bread	15g
北沙参	Beishashen	Radix Glehniae	Coastal glehnia root	30g
南沙参	Nanshashen	Radix Adenophorae	Upright Ladybell Root	30g
天冬	Tiandong	Radix Asparagi	Cochinchinese asparagus root	15g
麦冬	Maidong	Radix Ophiopogonis	Dwarf lilyturf tuber, ophiopogon	15g
石上柏	Shishangbai	Selaginella Doederleini	SelaginellaDoederleinii	30g
石见穿	Shijianchuan	Salvia Chinensis	Chinese Sage Herb	30g

Abhängig von den spezifischen Symptomen, eine oder mehrere der folgenden zusätzlichen Kräuter hinzugeben:

- **Bei Husten:** hinzufügen von Radix Platycodi 6g, Semen Armeniacae Vulgaris 9g, Herba Houttuyniae 30g, Radix Asteris 9g und Flos Farfarae 9g;
- **Bei Schleim,** hinzufügen von Bulbus Fritillariae Thunbergii 9g und Rhizoma Pinelliae Ternatae 9g;
- **Bei blutigem Auswurf,** hinzufügen von Herba Agrimoniae Pilosae 15g und Radix Sanguisorbae 15g;
- **Bei gelblichem Auswurf:** hinzufügen von Radix Scutellariae Baicalensis 9g und Semen Benincasae 15g;
- **Bei Übelkeit und/ oder Erbrechen:** hinzufügen von Pericarpium Citri Reticulatae 9g, Caulis Bambusae in Taeniam 9g und Fructus Citri Sarcodactylis 9g;
- **Bei trockenem Stuhl:** hinzufügen von Fructus Citri Aurantii Immaturus 9g und Semen Trichosanthis Kirilowii 15g;
- **Bei weichem Stuhl und kalten Gliedmaßen:** hinzufügen von Semen Trigonellae 9g und Semen Cuscutae Chinensis 15g, Fructus Psoraleae 12g;
- **Bei Schlaflosigkeit:** hinzufügen von Semen Ziziphi Spinosae 15g, Cortex Albiziae 15g, Caulis Polygoni Multiflori 30g und Concha Margaritifera Usta 30g;
- **Bei spontanem Schwitzen, und/oder Nachtschweiß:** hinzufügen von Fructus Triticis Levis 30g und Radix Oryzae Glutinosae 30g.

QOL and TCM in NSCLC

Results

- 1. Before the first Chemo**, no differences in clinical, pathological and QOL features in PBT+Placebo und PBT+TCM ($P > 0.10$).
- 2. Side effects of TCM herbs and Placebos:**
 - rare (17% uand 13% of all Patients, $P > 0.10$),
 - light stomach/abdominal complaints, heavy feeling, only in the first 2 weeks

QOL and TCM in NSCLC - Results

3. In Chemo+Placebo patients:

most QOL features **WORSE** after treatment

4. In Chemo+TCM Patients:

most QOL features **BETTER** after treatment

5. **After the second chemo treatment, QOL of FACT-L features:** in the Chemo+TCM group all better than in the Chemo+Placebo group

6. **Frequency of nausea and vomiting** were 56% in the PBT+Placebo but only 14% in PBT+TCM ($P=0.002$).

Ambulant PS 0-1 patients with metastatic NSCLC, Platinum-based Chemotherapy

Overall conclusions

1. TCM herbs most likely improve prognosis
2. QOL criteria in Patients with Qi-Yin deficiency, treated with Platinum-based chemo after 2 months (2 treatment cycles):
 - without TCM: worse
 - with TCM: better

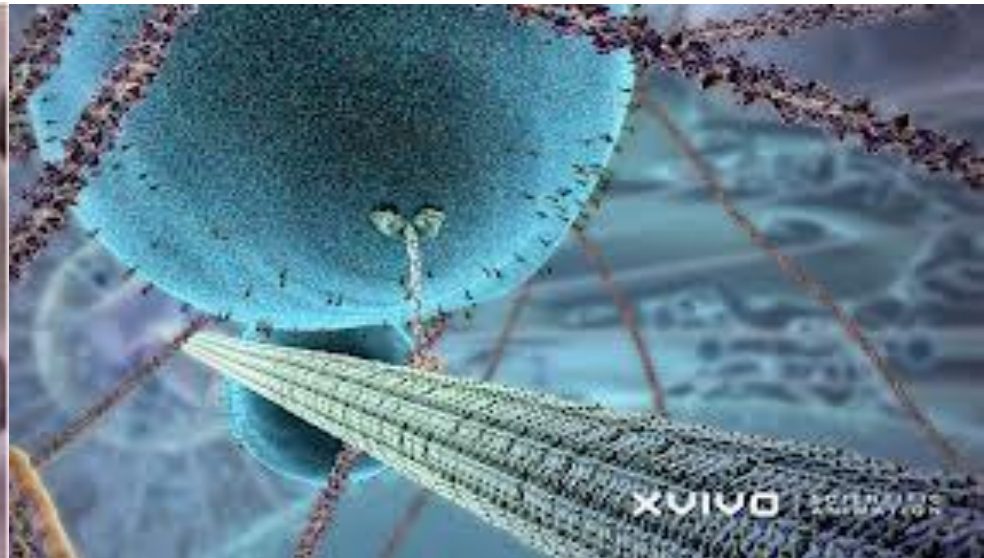
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“What? Pathologist? TCM in dead people?”**

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THE SCIENCE OF UNDERSTANDING DISEASE



The Crawling Leukocyte



The Inner Life of a Leukocyte

Ambulant PS 0-1 patients with metastatic NSCLC, Platinum-based Chemotherapy

Questions

1. Prognostic QOL effect of TCM in cancers of other organs
2. Effect in independent validation studies?
3. Relationship cancer, diet and lifestyle, carbohydrates, overweight, inflammations, cancer

Future research plans

1. Mice experiments to validate the prognostic effect of TCM in NSCLC and large intestine cancer
1. Unraveling the molecular cellular working mechanisms of TCM on QOL and prognosis in cancer patients
3. Validation in an international prospective randomized prognosis study in PS 0-1 patients with metastatic NSCLC, treated with Platinum-based chemotherapy