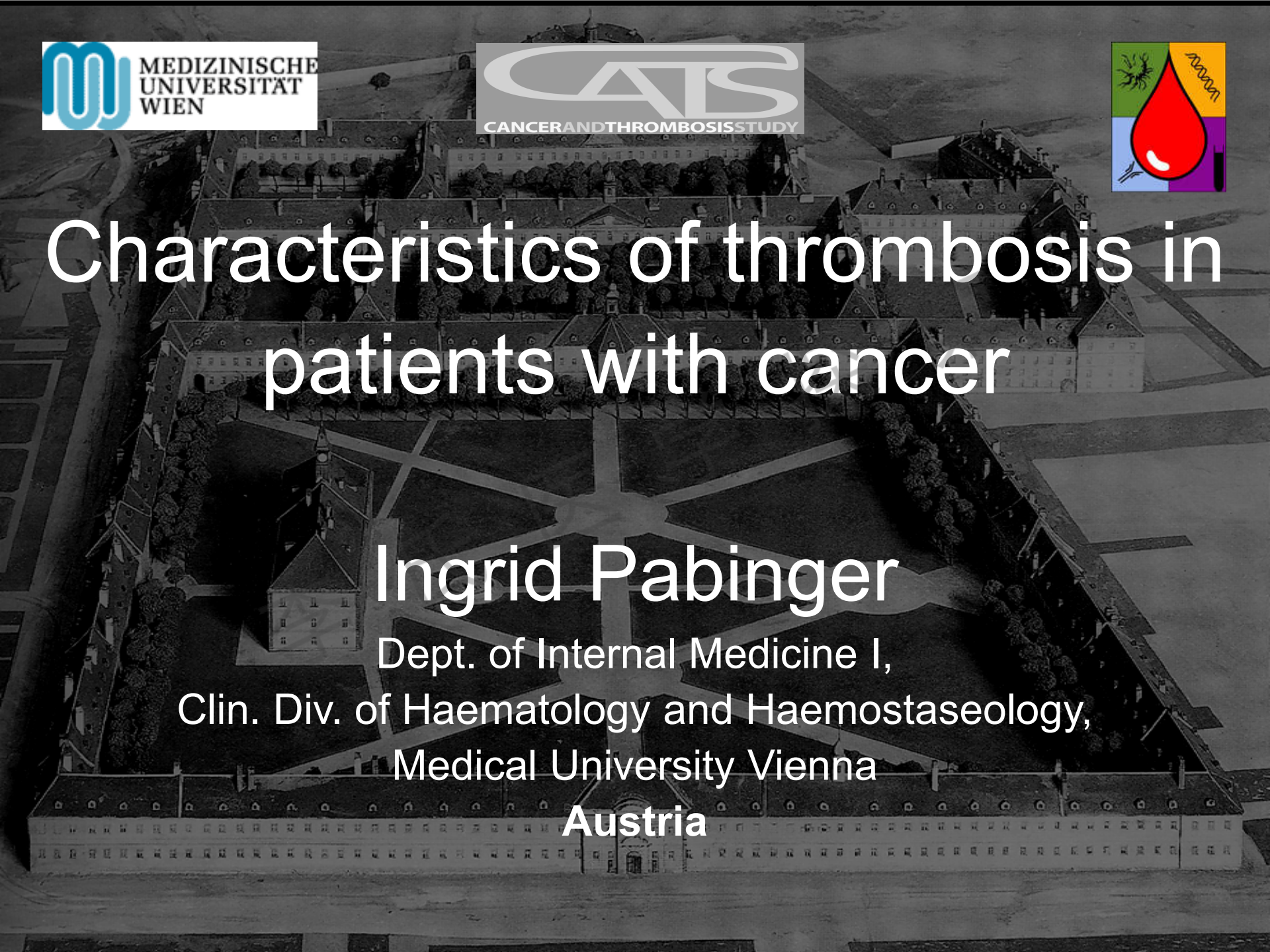

Characteristics of thrombosis in patients with cancer

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Introduction

- A higher proportion of patients with venous thromboembolism (VTE) have underlying cancer compared to individuals without (VTE)
- Cancer patients have an increased risk of venous thromboembolism

Venous thrombosis or pulmonary embolism in a cancer patient

Proven or conclusion by analogy

Is potentially fatal

Increases the disease burden (pain, swelling, dyspnea)

May lead to a postthrombotic syndrome

Increases the number of drugs administered to the patient

May lead to medication associated side effects (local side effects, bleeding)

Increases costs

May be prevented

Established risk factors for thrombosis in cancer patients

- Cancer related
  - Site
  - Stage
  - Histological Grading
- Treatment related
  - Surgical procedure
  - Chemotherapy
    - Thalidomide + Chemotherapy + Dexamethasone
    - -platins
    - Tamoxifen (+ Chemotherapy)

CATS – Cancer and Thrombosis Study

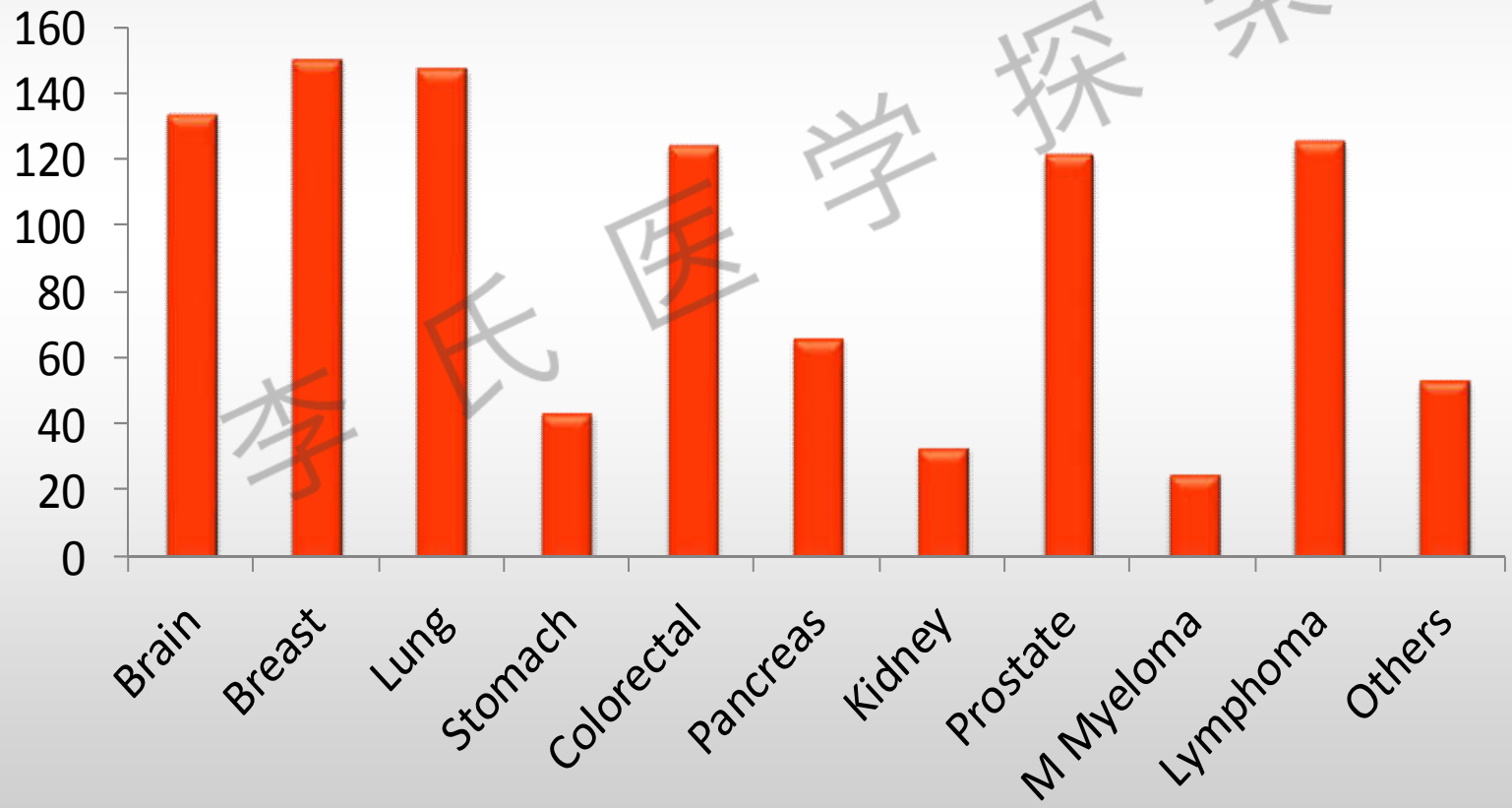
- **Aim**: To identify predictive parameters for occurrence of VTE in cancer patients
- **Design**: Prospective, observational and single center cohort study
- **Inclusion criteria:** Newly diagnosed cancer or progression of disease after complete or partial remission and written informed consent
- **Outcome measure**: Occurrence of VTE, either symptomatic or fatal and objectively confirmed

Study Participants

- Characteristics in 1033 patients
  - 458 (43%) female
  - Median age [IQR]: 62 [53-68] years
  - Median observation time: 517 days

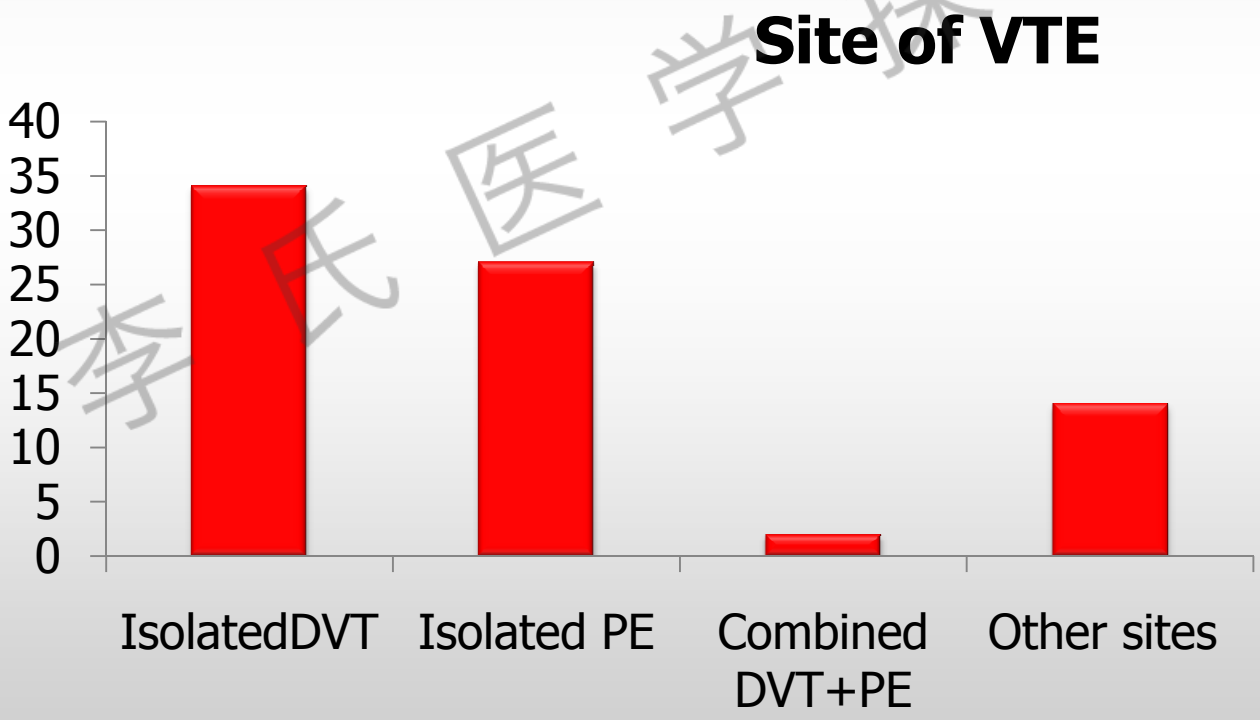
CANCERANDTHROMBOSISSTUDY

Site of Cancer

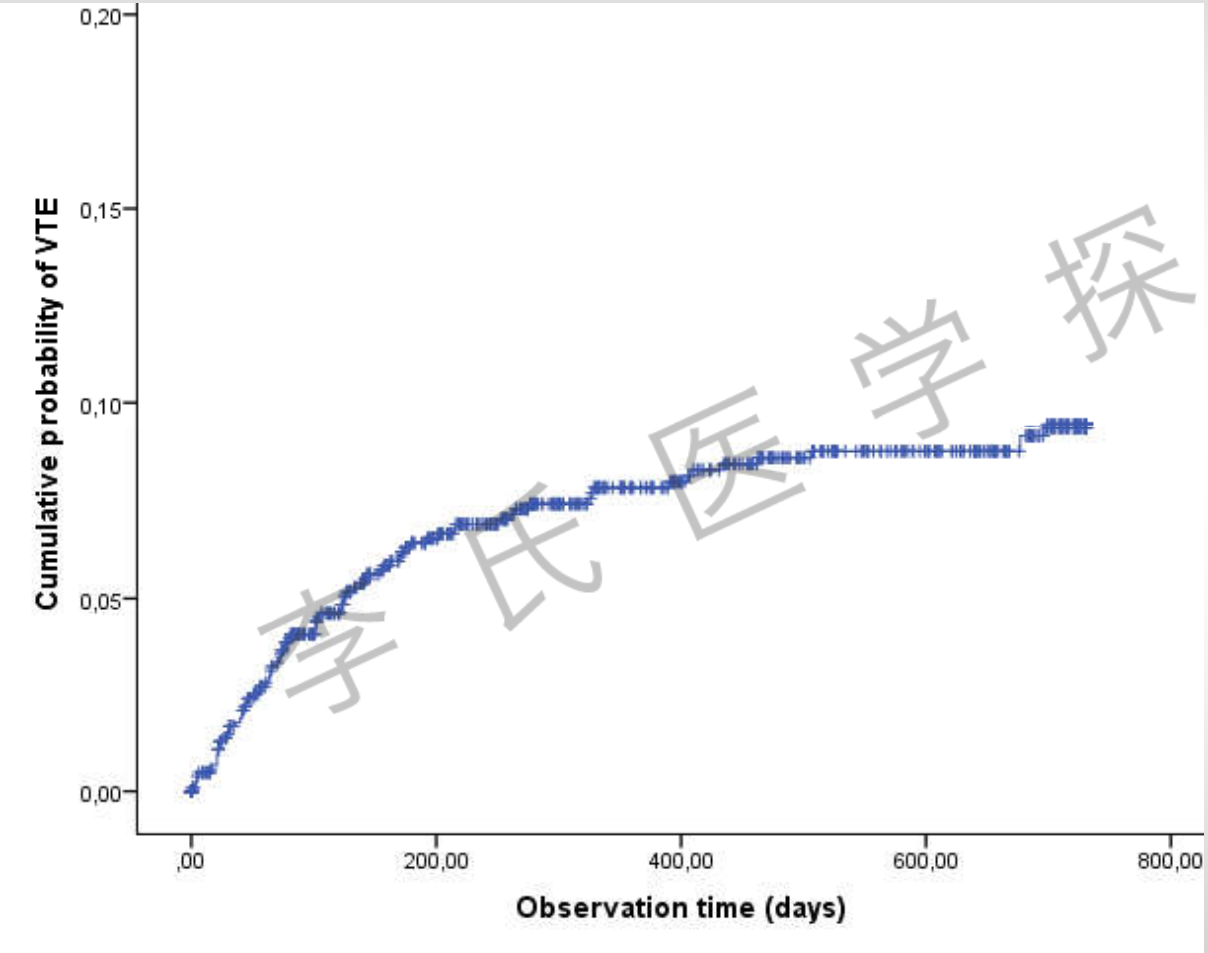


Occurrence of VTE

- 77 (7.5%) patients developed symptomatic VTE, *4 of the events were fatal*



When do thrombotic events occur in patients with cancer?



Cumulative probability of VTE

3 months: 4.2%

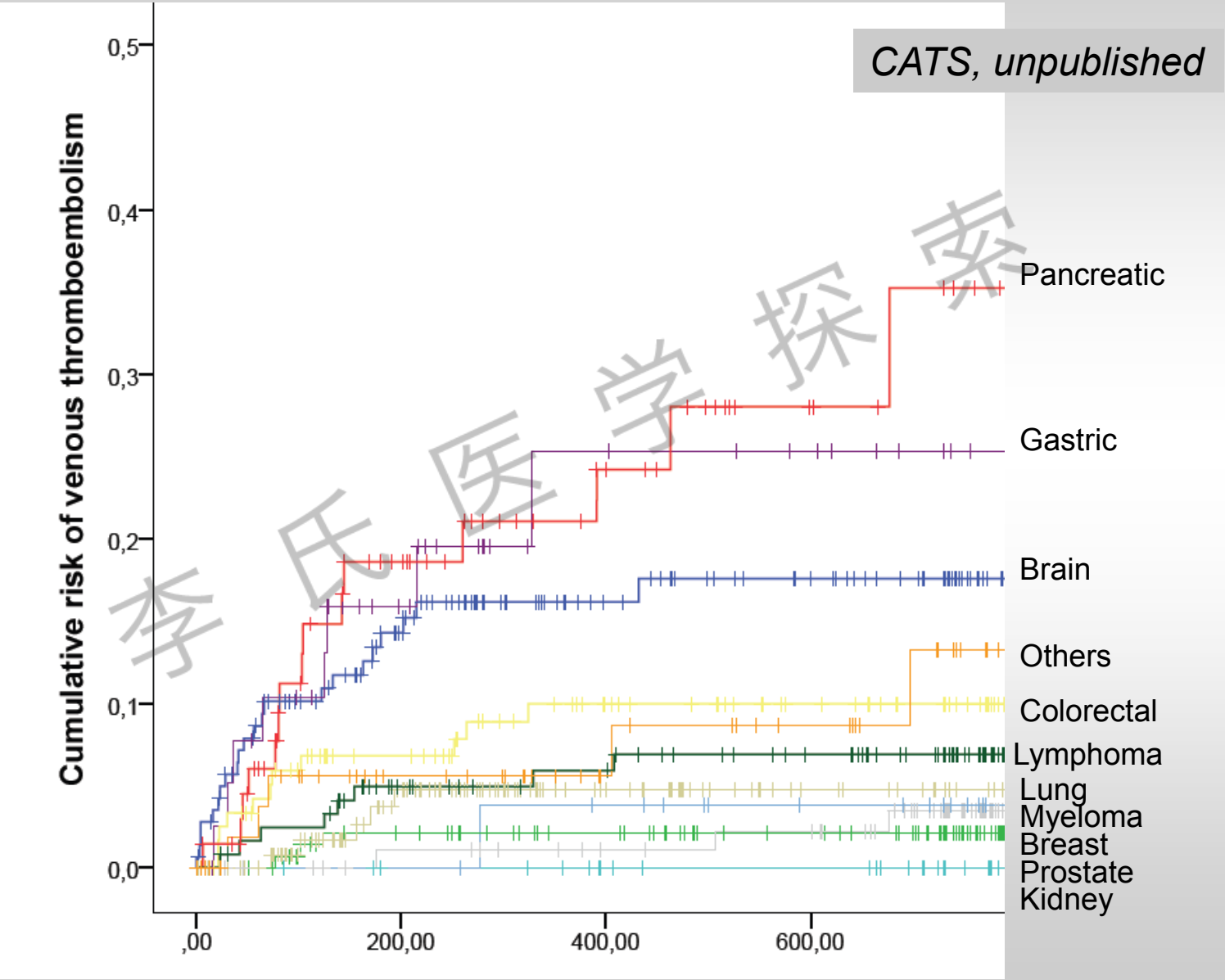
6 months : 6.1%

12 months : 8.1%

2 years: 9.4%

CATS (unpublished)

Cumulative VTE risk according to cancer type



Venous thrombosis or pulmonary embolism in a cancer patient

- Risk factors for thrombosis in cancer
  - Tumour site
  - Tumour stage
  - Biomarkers

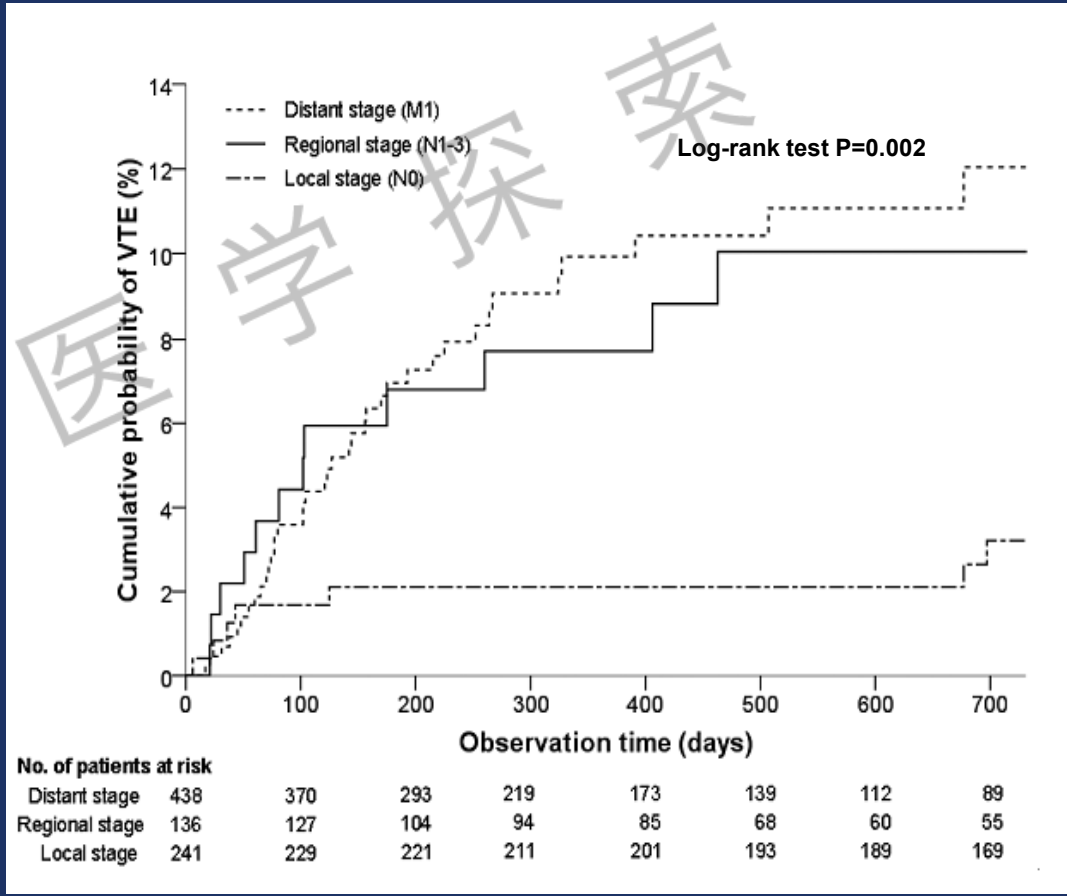
Tumour site as risk factor for VTE

- High risk (up to 15% of patients):
  Carcinoma of the pancreas, stomach, brain
- Intermediate risk (up to 8% of patients):
  Carcinoma of the lung, colon, ovar, uterus, sarcoma, lymphoma
- Low risk (up to 3-5% of patients):
  Carcinoma of the kidney, breast, prostate

Association with stage

Cumulative probability after 6 months:

2% local
7% regional LN
7% distant metastasis



Dickmann et al, in revision

Biomarkers investigated to identify patients at high/low risk of VTE

Biomarkers and laboratory tests investigated for prediction of cancer-associated VTE in CATS		
Platelet count	Simanek et al, JTH 2009	+
soluble P-selectin	Ay et al, Blood 2008	+
D-Dimer		+
Prothrombinfragment 1+2	Ay et al, J Clin Oncol 2009	+
C-reaktive Protein	Kanz et al, JTH 2011	(+)
Factor VIII activity	Vormittag et al, ATVB 2009	+
Thrombin Generation Assay	Ay et al, J Clin Oncol 2011	+
Microparticles/Tissue factor bearing microparticles	Thaler et al, JTH 2012	-/+ ?
Fibrinogen	Tiedje et al, Thromb Haemost 2011	--

Reviewed in: Pabinger, Thaler and Ay, Blood 2013

Diagnosis of venous thrombosis or pulmonary embolism in cancer patients

- May be symptomatic or found incidentally (e.g. during staging investigation)
- Symptoms might be overlooked or attributed to the cancer (e.g. swelling of the leg or dyspnea)

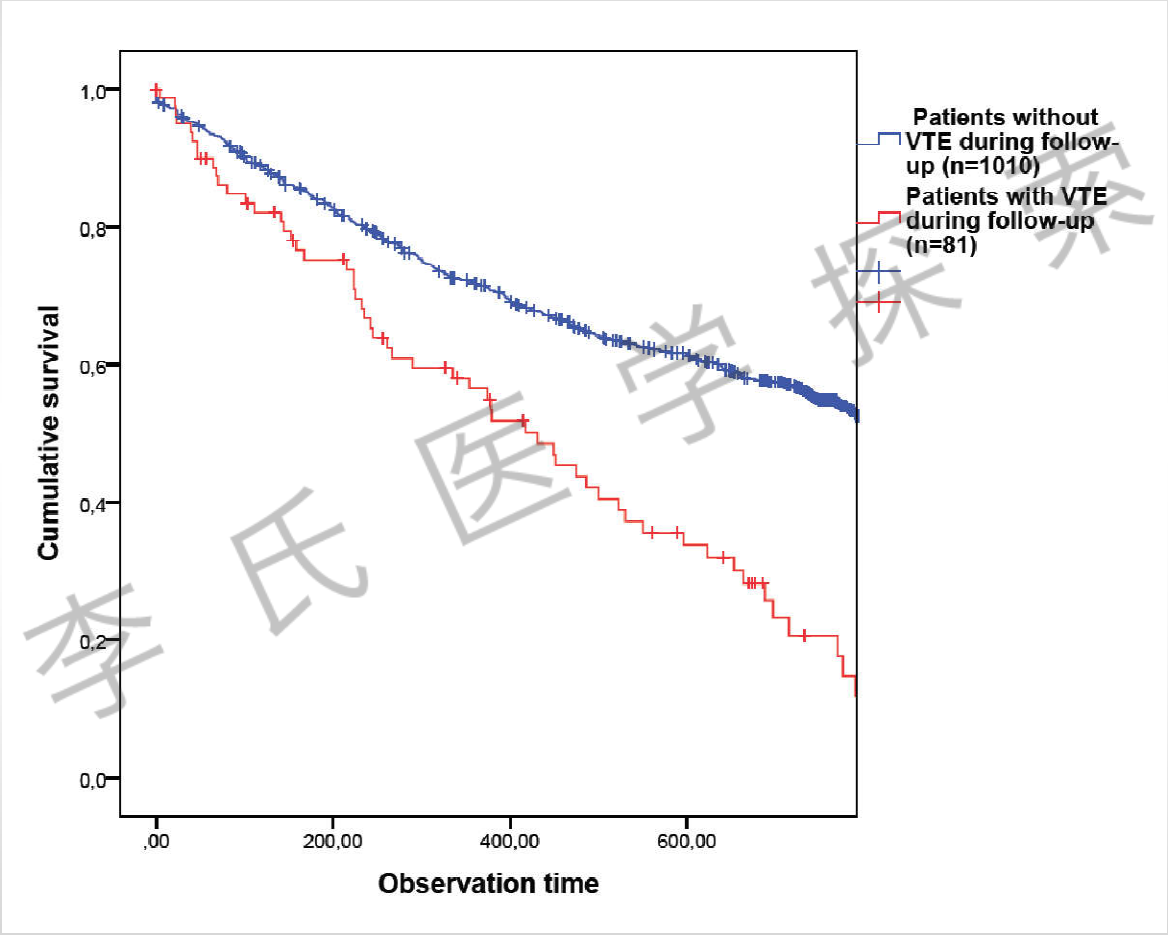
Diagnosis of venous thrombosis or pulmonary embolism in cancer patients

- D-Dimer: High sensitivity, low specificity
  - Many cancer patients have an elevation of D-Dimer, even when they do not have thrombosis
- Diagnostic procedures:Doppler or Duplex ultrasound, phlebography, computerized tomography or ventilation/perfusion lung Scan

Venous thrombosis or pulmonary embolism in a cancer patient

- Influence of cancer associated thrombosis on survival

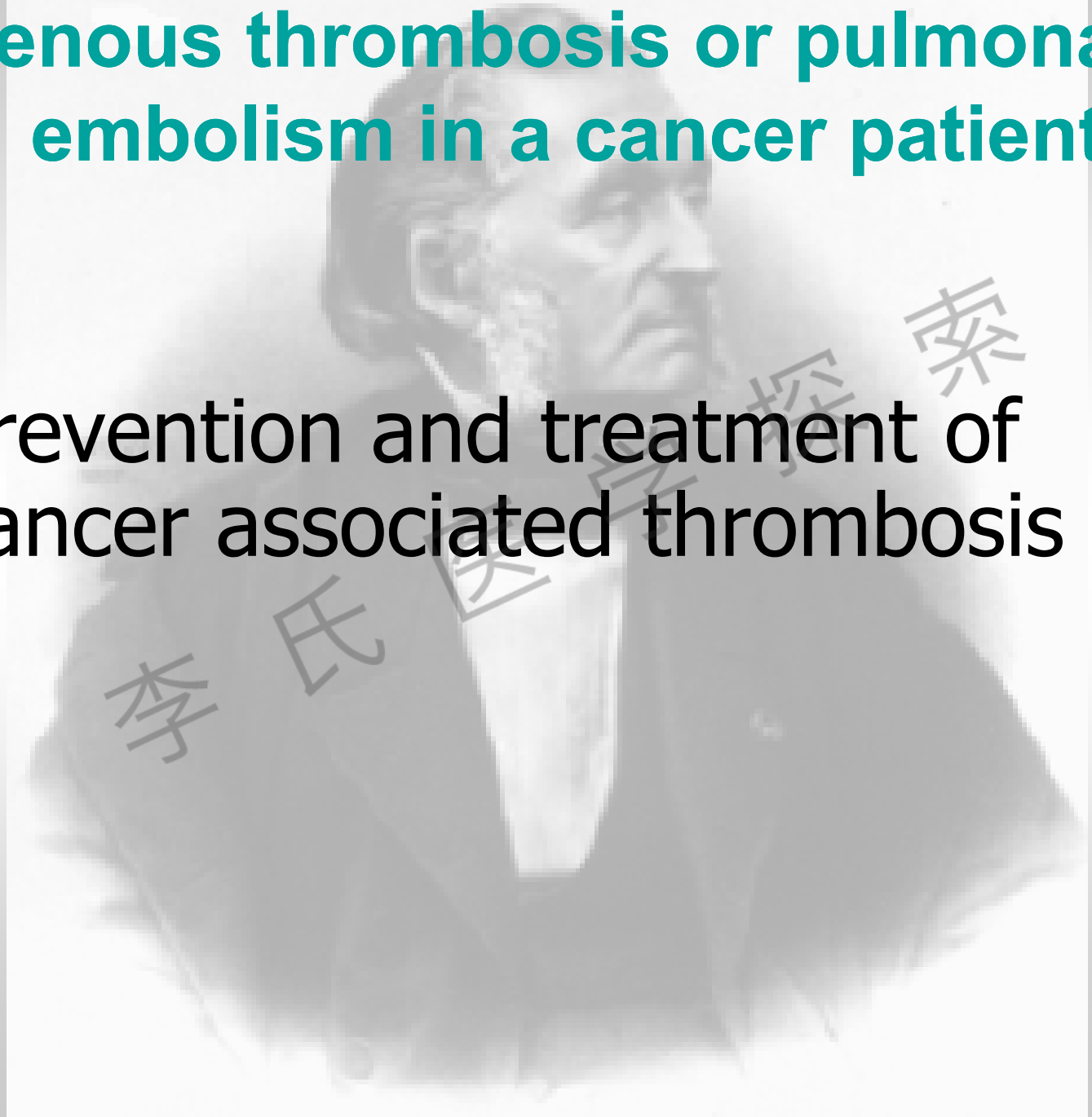
Probability of survival in cancer patients without and with VTE during follow up



Multivariable HR (including stage) in patients with VTE
HR: 2.2 (95% CI: 1.7-2.8; p<0.001)

CATS, unpublished

Venous thrombosis or pulmonary embolism in a cancer patient



- Prevention and treatment of cancer associated thrombosis

International guidelines
JTH 2013

Journal of Thrombosis and Haemostasis, **11**: 56–70 DOI: 10.1111/jth.12070

ORIGINAL ARTICLE

International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer

D. FARGE,*†[1] P. DEBOURDEAU,‡ M. BECKERS,§ C. BAGLIN,¶ R. M. BAUERSACHS,** B. BRENNER,†† D. BRILHANTE,‡‡ A. FALANGA,§§ G. T. GEROTZAFIAS,¶¶ N. HAIM,*** A. K. KAKKAR,††† A. A. KHORANA,‡‡‡ R. LECUMBERRI,§§§ M. MANDALA,¶¶¶ M. MARTY,**** M. MONREAL,†††† S. A. MOUSA,‡‡‡‡§§§§ S. NOBLE,¶¶¶¶ I. PABINGER,***** P. PRANDONI,††††† M. H. PRINS,‡‡‡‡‡ M. H. QARI,§§§§§ M. B. STREIFF,¶¶¶¶¶ K. SYRIGOS,****** H. BOUNAMEAUX††††††* and H. R. BÜLLER‡‡‡‡‡‡[1]

Treatment
Perioperative prophylaxis
Prophylaxis in medical patients

International Good Clinical Practice Guidelines (GCPG) for Antithrombotics in cancer Patients

Treatment

Low molecular weight heparin (LMWH) for initial treatment and for at least 3 months (1A) – after 3-6 months "case based" treatment

If LMWH is not tolerated, Vitamin K antagonists or novel (direct) oral anticoagulants (Rivaroxaban, Dabigatran, Apixaban or Edoxaban)

Farge et al, JTH 2013

International Good Clinical Practice Guidelines (GCPG) for Antithrombotics in cancer Patients

Perioperative prophylaxis

Use of LMWH once a day or a low dose of UFH three times a day is recommended to prevent postoperative VTE in cancer patients; pharmacological prophylaxis should be started 12–2 h preoperatively and continued for at least 7–10 days; there are no data allowing conclusions regarding the superiority of one type of LMWH over another [Grade 1A].

Use of the highest prophylactic dose of LMWH to prevent postoperative VTE in cancer patients is recommended [Grade 1A].

Extended prophylaxis (4 weeks) to prevent postoperative VTE after major laparotomy in cancer patients may be indicated in patients with a high VTE risk and low bleeding risk [Grade 2B].

Farge et al, JTH 2013

International Good Clinical Practice Guidelines (GCPG) for Antithrombotics in cancer Patients

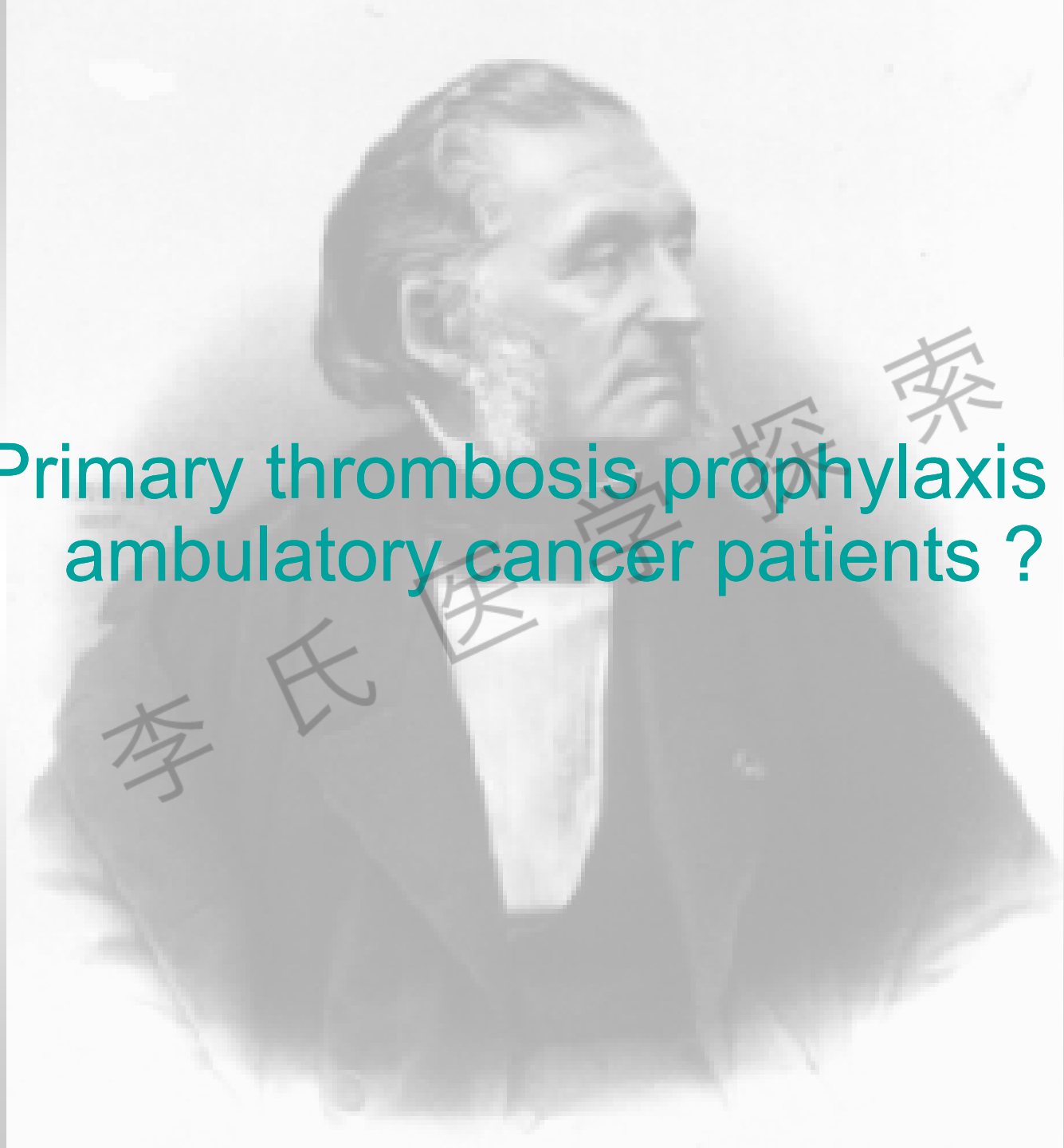
Prophylaxis in medical patients

We recommend prophylaxis with LMWH, UFH or fondaparinux in hospitalized medical patients with cancer and reduced mobility [Grade 1B].

In patients receiving chemotherapy, prophylaxis is not recommended routinely [Grade 1B].

Primary pharmacological prophylaxis of VTE may be indicated in patients with locally advanced or metastatic pancreatic cancer treated with chemotherapy and having a low bleeding risk [Grade 1B].

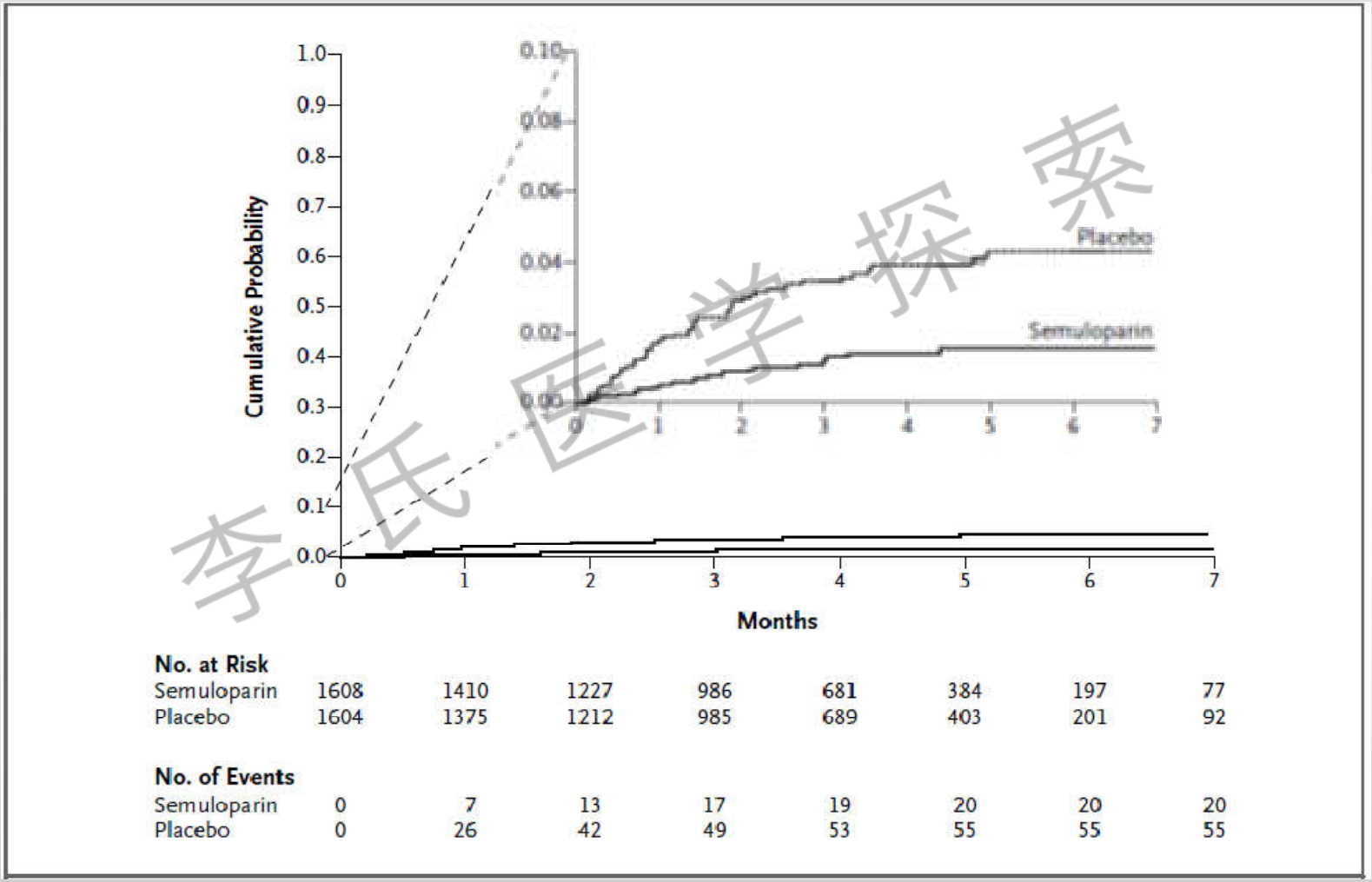
Farge et al, JTH 2013



Primary thrombosis prophylaxis in ambulatory cancer patients ?

Semuloparin vs Placebo (Save-Onco)

in metastatic/locally advanced pts on chemotherapy



No. at Risk								
Semuloparin	1608	1410	1227	986	681	384	197	77
Placebo	1604	1375	1212	985	689	403	201	92

No. of Events								
Semuloparin	0	7	13	17	19	20	20	20
Placebo	0	26	42	49	53	55	55	55

Agnelli et al, NEJM 2012, 366:601

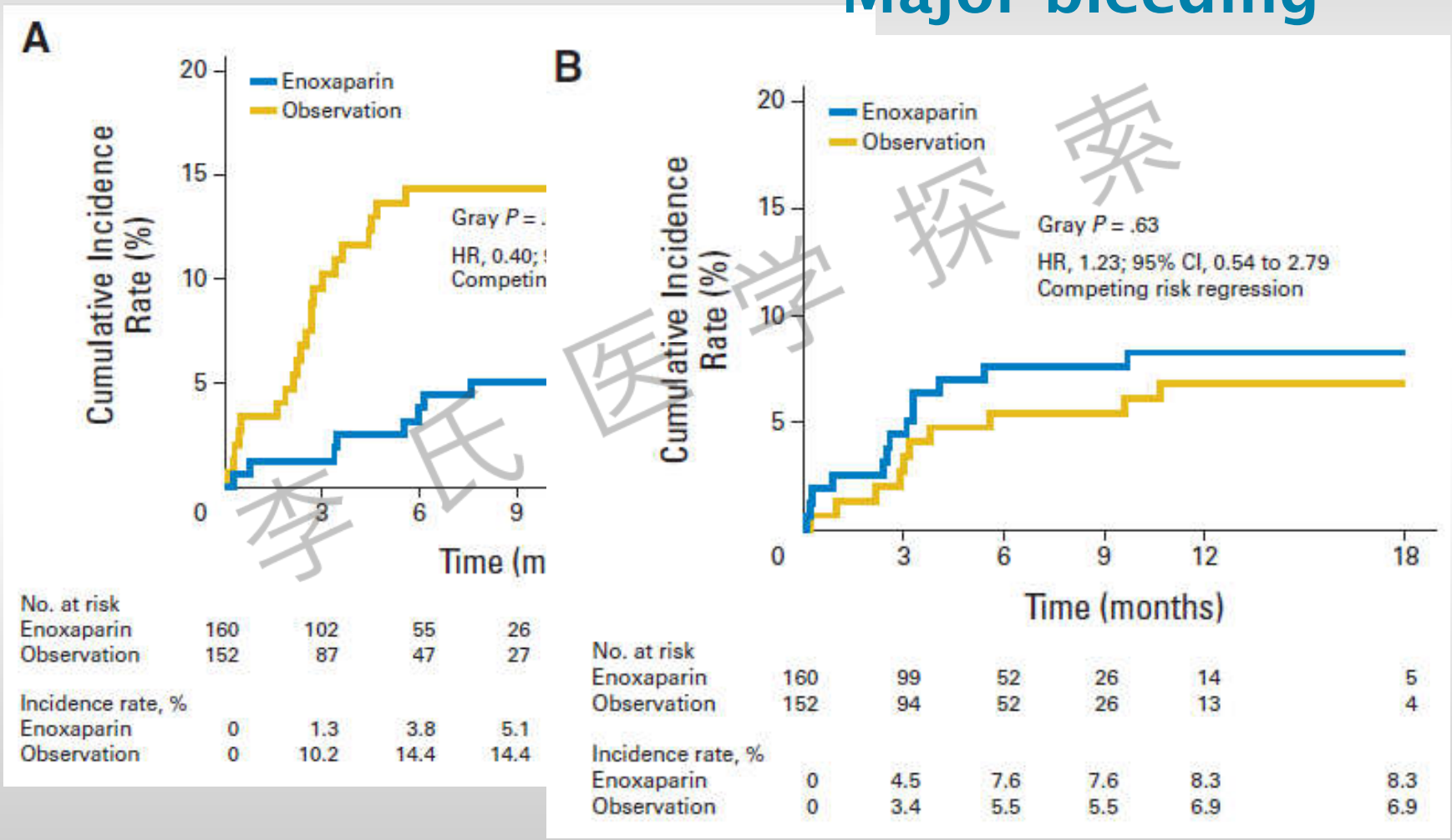
Prophylactic LMWH vs controls in advanced pancreatic cancer (CONKO-004)

- Histologically proven advanced pancreatic carcinoma
- 160 patients with LMWH, 152 observational arm
- Treatment (12 months)
  - Chemotherapy plus LMWH 80-100IU/kg/day for 3 months (primary endpoint), then 5000IU/day until progression of disease
  - Observational arm: only chemotherapy

Pelzer et al, J. Clin Oncol. 2015, 33: 2028

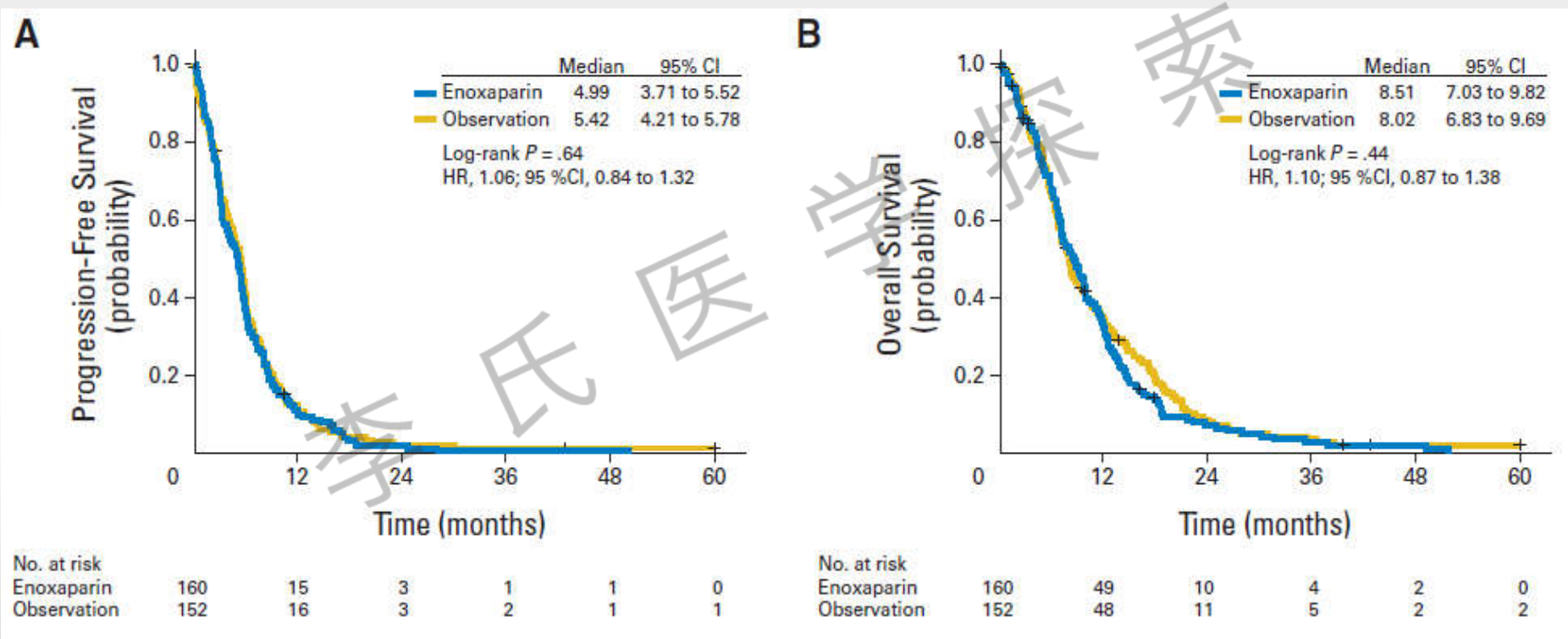
Symptomatic VTE

Major bleeding



Pelzer et al, J. Clin Oncol. 2015, 33: 2028

Progression free and overall survival



Pelzer et al, J. Clin Oncol. 2015, 33: 2028

Summary/Conclusion

- VTE is frequent in subgroups of cancer patients
- It is possible to identify high risk patients by clinical and laboratory parameters
- Patients with VTE have a decreased survival
- Diagnosis and adequate treatment of VTE are crucial for the survival and well-being of a cancer patient with venous thrombosis or pulmonary embolism
- Primary prophylaxis use in surgical or bedridden patients

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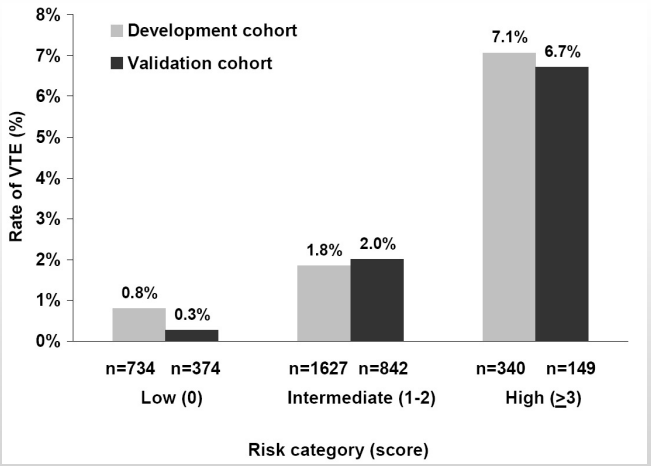
CANCERANDTHROMBOSISSTUDY
Thank you
for your attention

Risk score model to predict VTE in a cohort of 2 701 cancer patients

Patient Characteristic	β	Odds Ratio* (95% CI)
Site of Cancer		
Very high risk (stomach, pancreas)	1.46	4.3 (1.2-15.6)
High risk (lung, lymphoma, gynecologic, genitourinary excluding prostate)	0.43	1.5 (0.9-2.7)
Low risk (breast, colorectal, head and neck)	0.0	1.0 (reference)
Pre-chemotherapy platelet count ≥ 350,000/ mm^3	0.60	1.8 (1.1-3.2)
Hemoglobin < 10g/dL or use of red cell growth factors	0.89	2.4 (1.4-4.2)
Pre-chemotherapy leukocyte count > 11,000/mm^3	0.77	2.2 (1.2-4)
Body mass index ≥ 35 kg/m^2	0.90	2.5 (1.3-4.7)

*Odds ratios are adjusted for stage.

Patient characteristic	Risk score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count 350 × 10^9/L or more	1
Hemoglobin level less than 100 g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count more than 11 × 10^9/L	1
BMI 35 kg/m^2 or more	1



Khorana et al, Blood, 2008, 111:4902

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