

CANCER PROGNOSIS IN PATIENTS WITH VENOUS THROMBOEMBOLISM (VTE) AND PATIENTS WITH CLINICAL AND LABORATORY BIOMARKERS OF VTE RISK

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DISCLOSURES

- **CONSULTING: PFIZER, BMS, JANSSEN, RIGEL, AMGEN, NOVARTIS, SANOFI, GENZYME**
- **RESEARCH SUPPORT: JANSSEN, PROTOLEX, SYNTIMMUNE**

Incidence of Thrombosis in Carcinoma of Various Organs

Organ in which tumor arose	Total No. Cases	Cases With Thrombosis		Cases With Multiple Thromboses	
		No. Cases	Per cent of Total	No. Cases	%Total
Anywhere in pancreas	47	14	29.7	8	17
Head of pancreas	31	5	16.1	3	9.7
Body or tail of pancreas	16	9	56.2	5	31.3
Lung	81	12	14.8	2	2.5
Liver	22	6	27.2	0	
Gallbladder	30	5	16.6	0	
Stomach	147	32	21.8	2	1.3
Duodenum	16	3	18.7	0	
Colon	94	15	15.9	0	
Kidney	27	7	25.9	0	
Prostate	43	7	16.3	0	
Uterus	27	6	22.2	0	
Ovary	17	4	23.5	0	

WHAT IS THE CONTRIBUTION OF VTE TO CANCER MORTALITY

Autopsy records of 157 patients with pancreatic cancer:

- 34/157 (22%) with VTE/PE
- 8/157 (5%) fatal PE

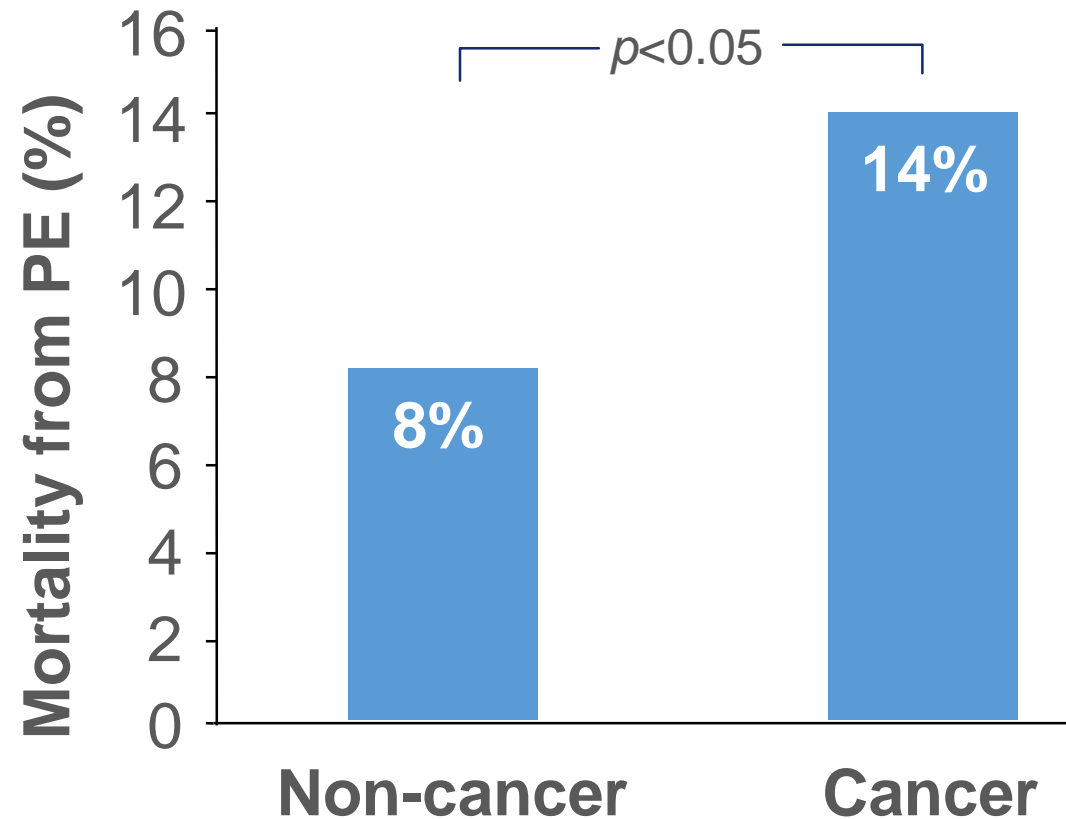
High incidence of arterial thrombosis (13%) including myocardial infarction (6%).

Between 1970 and 1982, 23,796 autopsies performed, representing 84% of in-hospital deaths in the urban Swedish population. Cancer deaths comprised 4739 (20%) cases.

Pulmonary embolism was confirmed by careful examination of the lung specimens. Prevalence was 26% cases.

Examination of clinical history and autopsy finding determined that fatal PE occurred in 387 (8%) of cases.

In-Hospital Mortality Rate Due to Pulmonary Embolism: Results from 578 consecutive autopsies



PROGNOSIS OF CANCERS ASSCOIATED WITH VENOUS THROMBOEMBOLISM

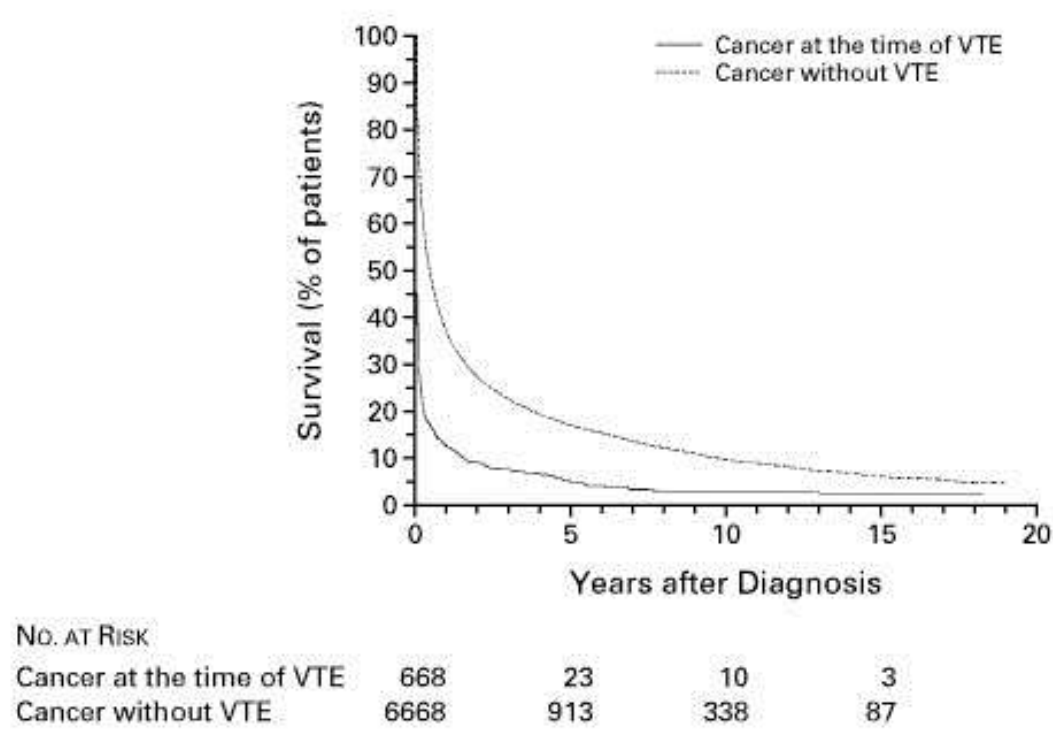


Figure 1. Survival Curves for Patients with a Cancer Diagnosis at the Time of VTE and Matched Controls with Cancer. The control patients, without VTE were matched with the VTE patients according to cancer type, sex, age, and year of diagnosis. $P<0.001$ for the overall curves, by the log-rank test.

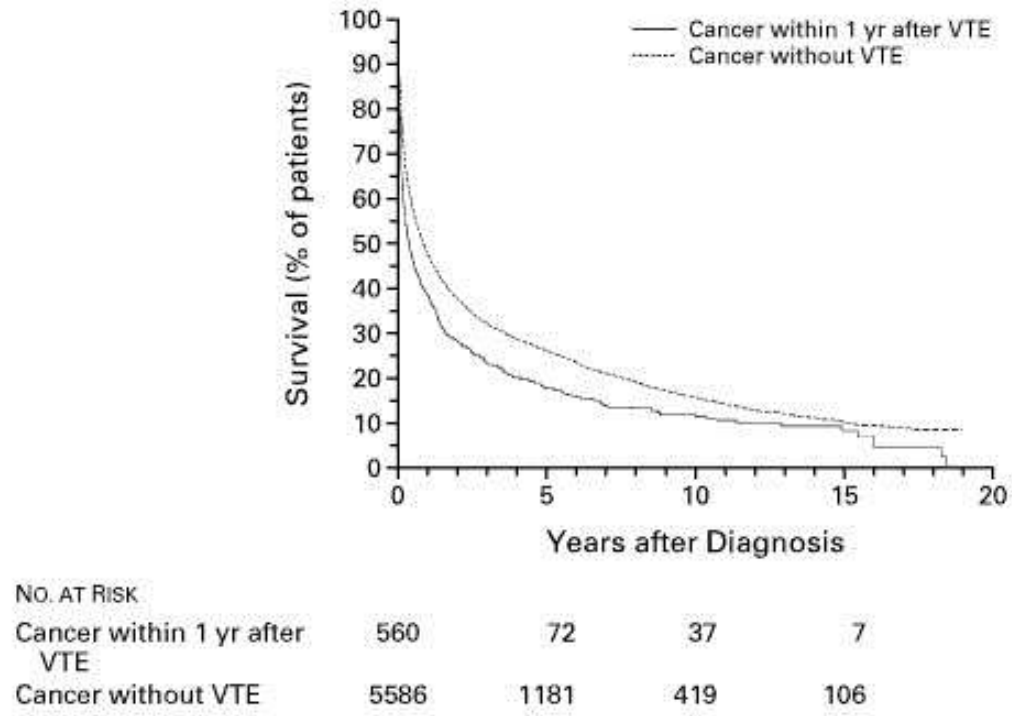
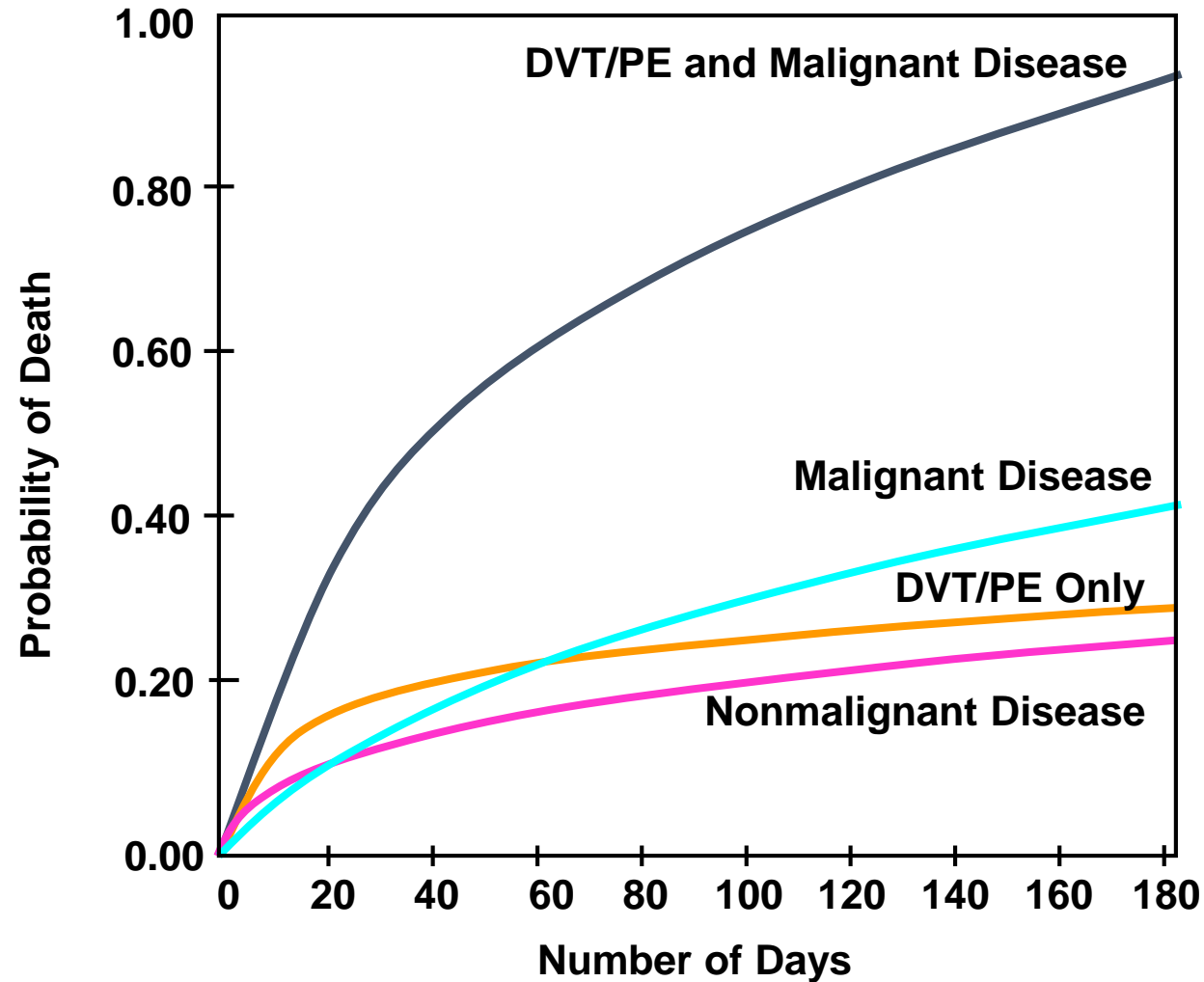
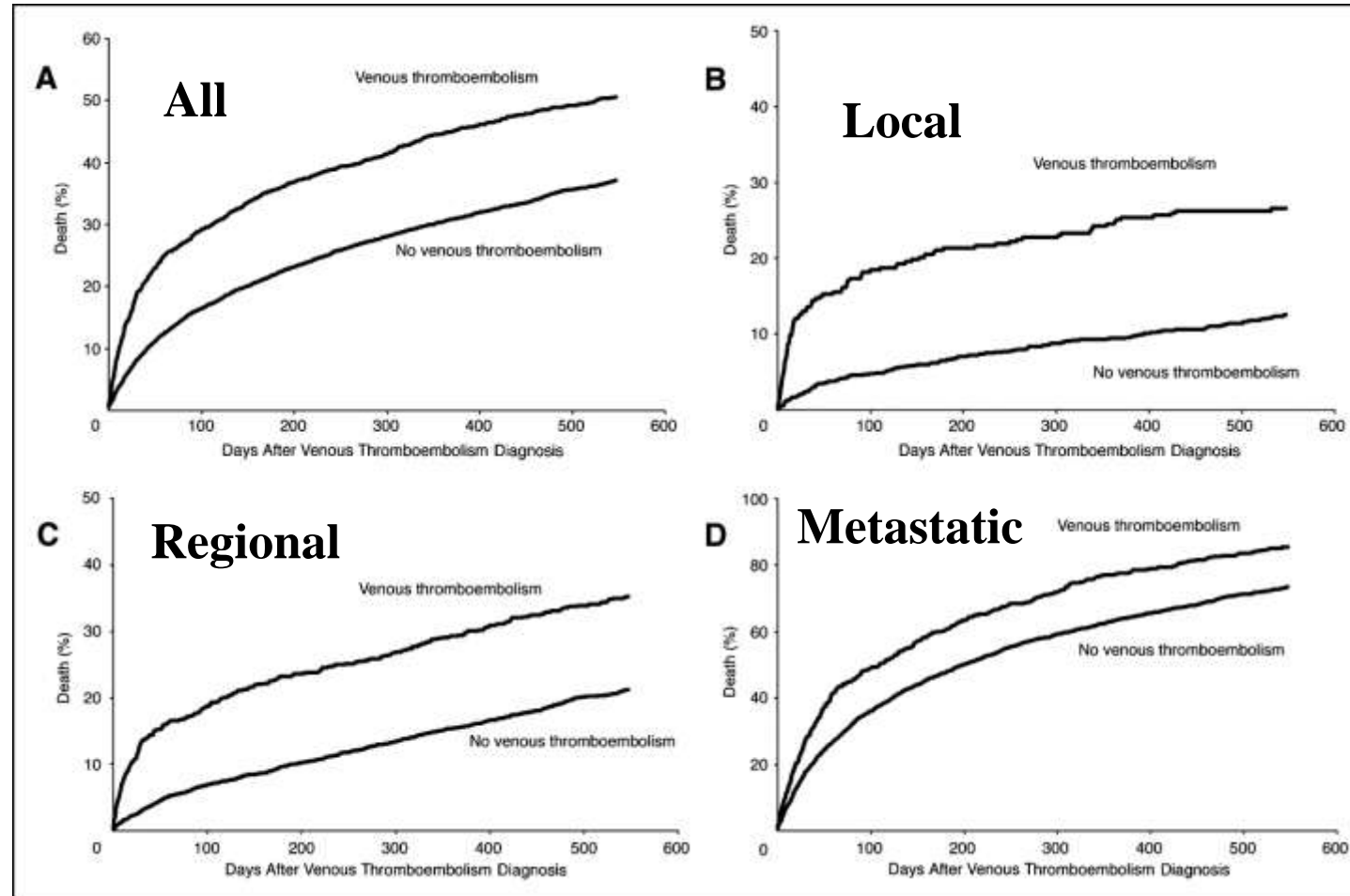


Figure 2. Survival Curves for Patients with Cancer Diagnosis within One Year after VTE and Matched Controls with Cancer. The control patients, without VTE, were matched with the VTE patients to cancer type, sex, age, and year of diagnosis. $P<0.001$ for the overall curves, by the log-rank test.

VTE, Cancer and Survival

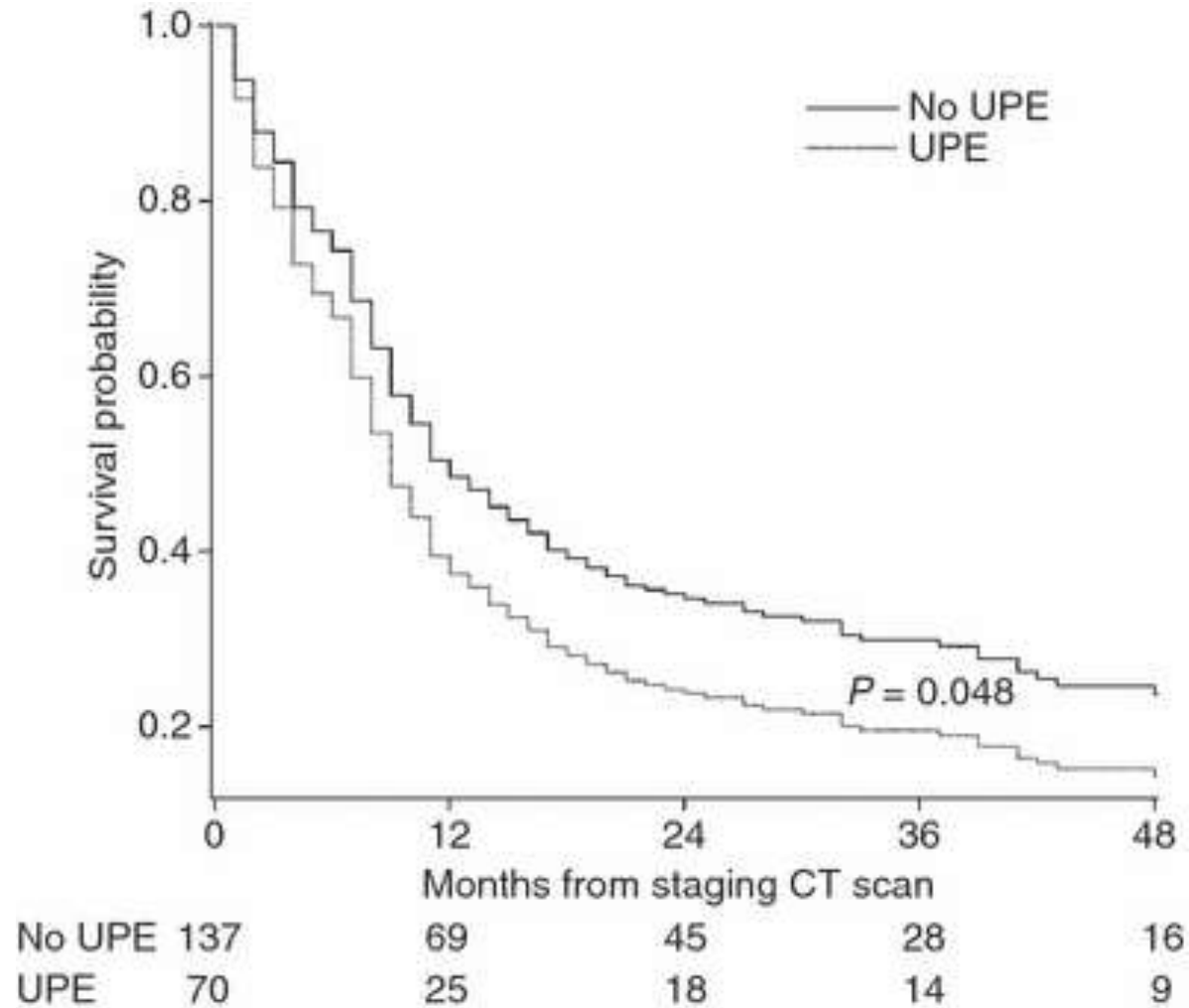


Comparison of the incidence of death after venous thromboembolism (VTE) with the incidence of death in matched patients who never developed VTE



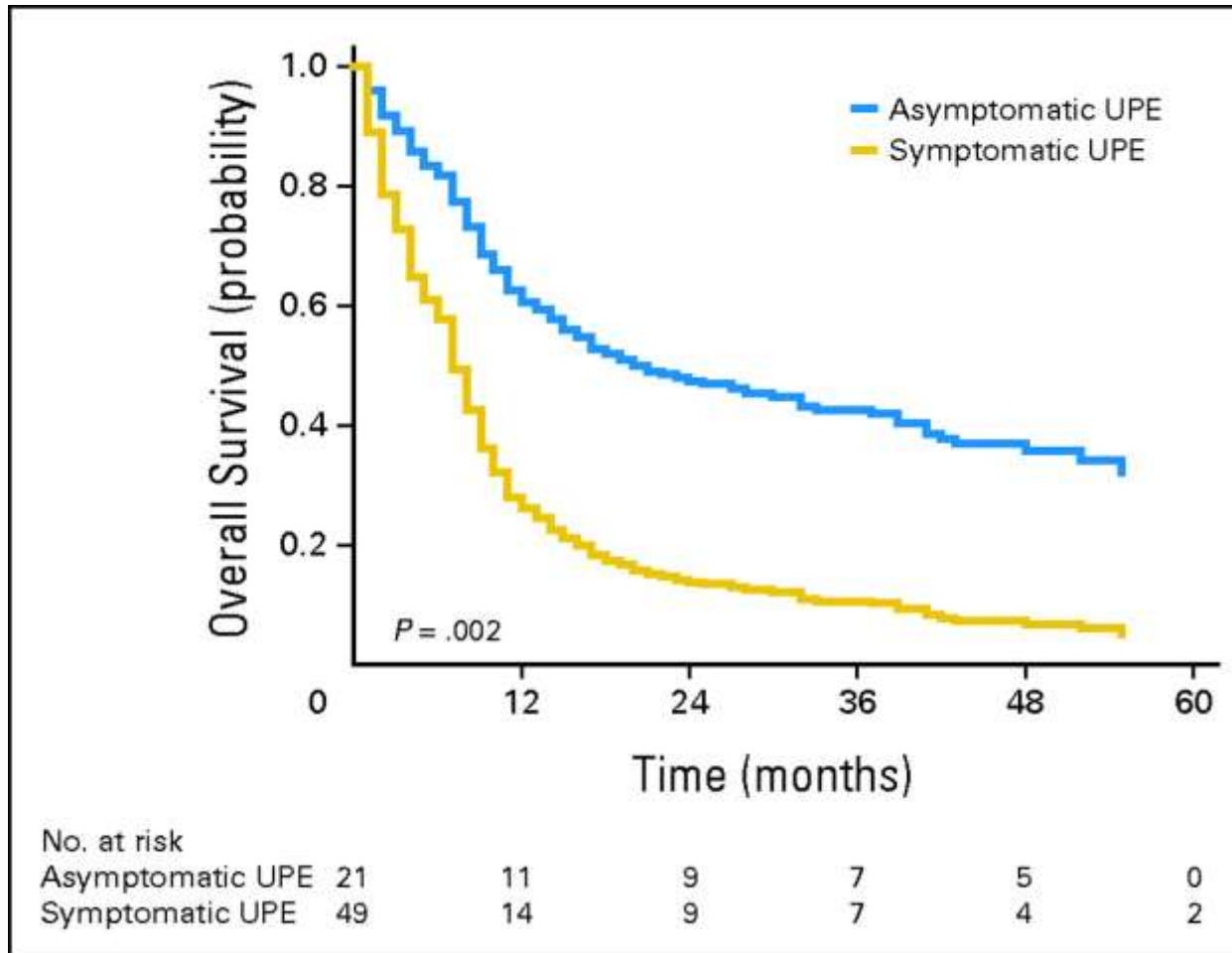
Alcalay, A. et al. J Clin Oncol; 24:1112-1118 2006

SURVIVAL FOR 70 UPE CANCER PATIENTS COMPARED TO 138 MATCHED CONTROLS

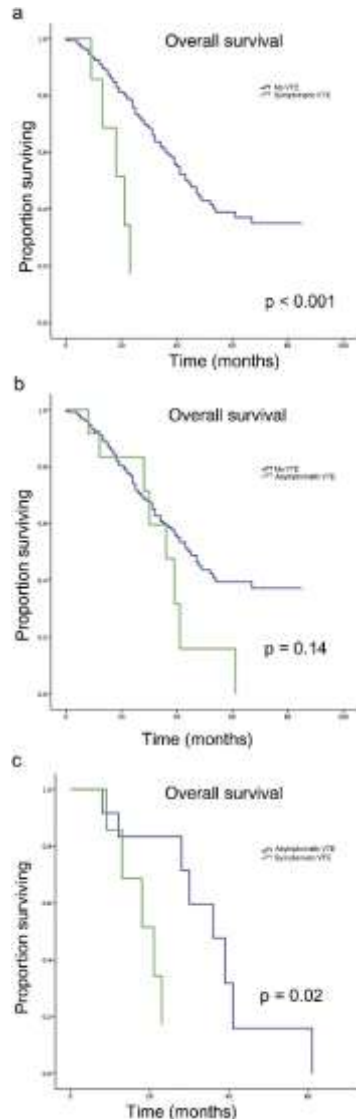


SYMPTOMS DEFINE A PATIENTS POPULATION WITH A WORSE PROGNOSIS

Of the 70 patients with incidental (unsuspected) PE, 49 (70%). Were symptomatic (fatigue, shortness of breath cough).



SURVIVAL IN OVARIAN CANCER: SYMPTOMATIC VS. ASYMPTOMATIC CASES



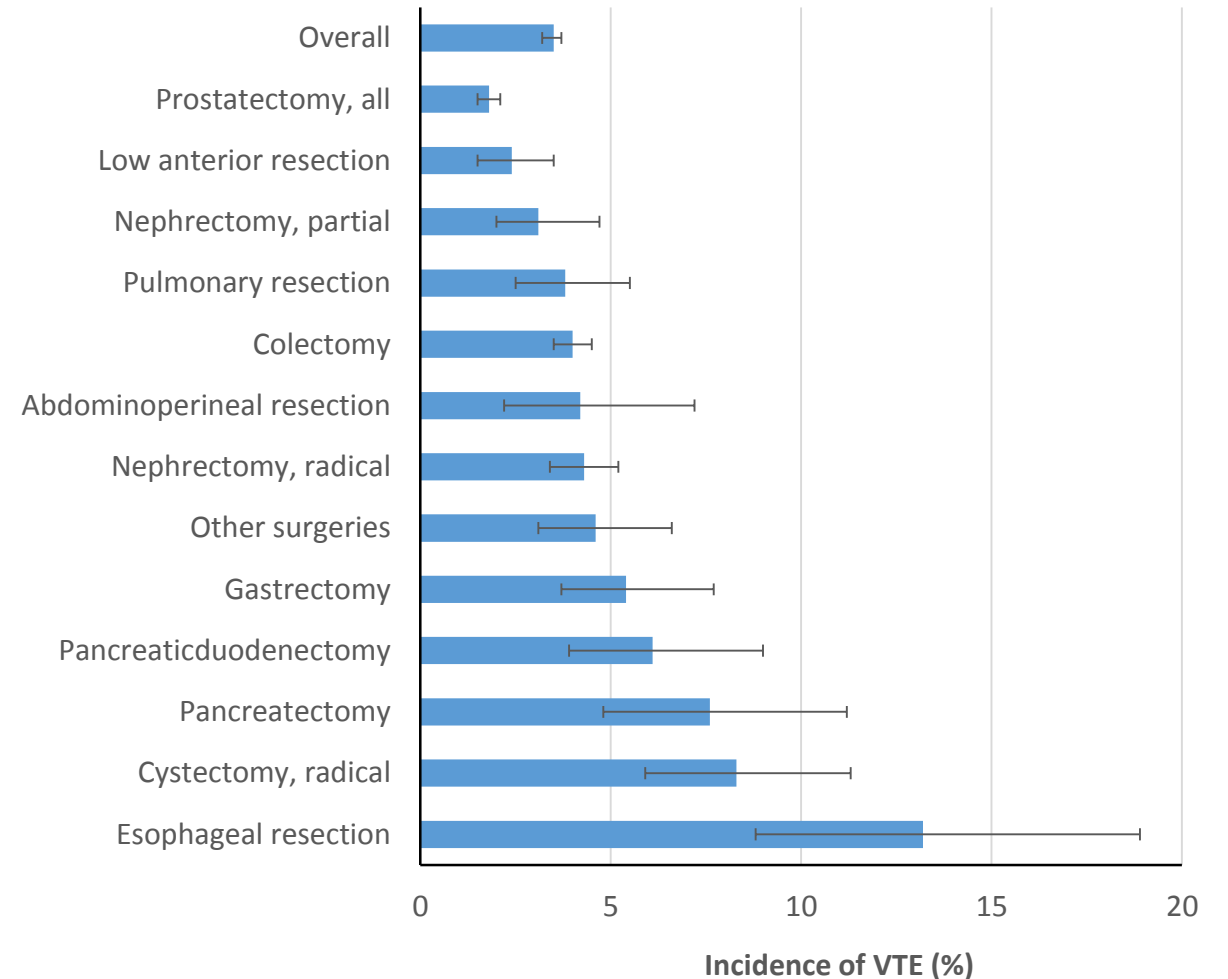
Kaplan–Meier curves comparing patients with symptomatic or asymptomatic VTE and VTE negative groups.

- a) Overall survival differences between symptomatic VTE compared with VTE negative group, log-rank $p < 0.001$.
- b) Overall survival differences between asymptomatic VTE compared with VTE negative group, log-rank $p = 0.14$.
- c) Overall survival differences between symptomatic VTE compared with asymptomatic VTE group, log-rank $p = 0.02$.

**DOES POST-OPERATIVE VTE
IMPACT SURVIVAL IN CANCER
PATIENTS?**

Incidence of VTE after Cancer Surgery

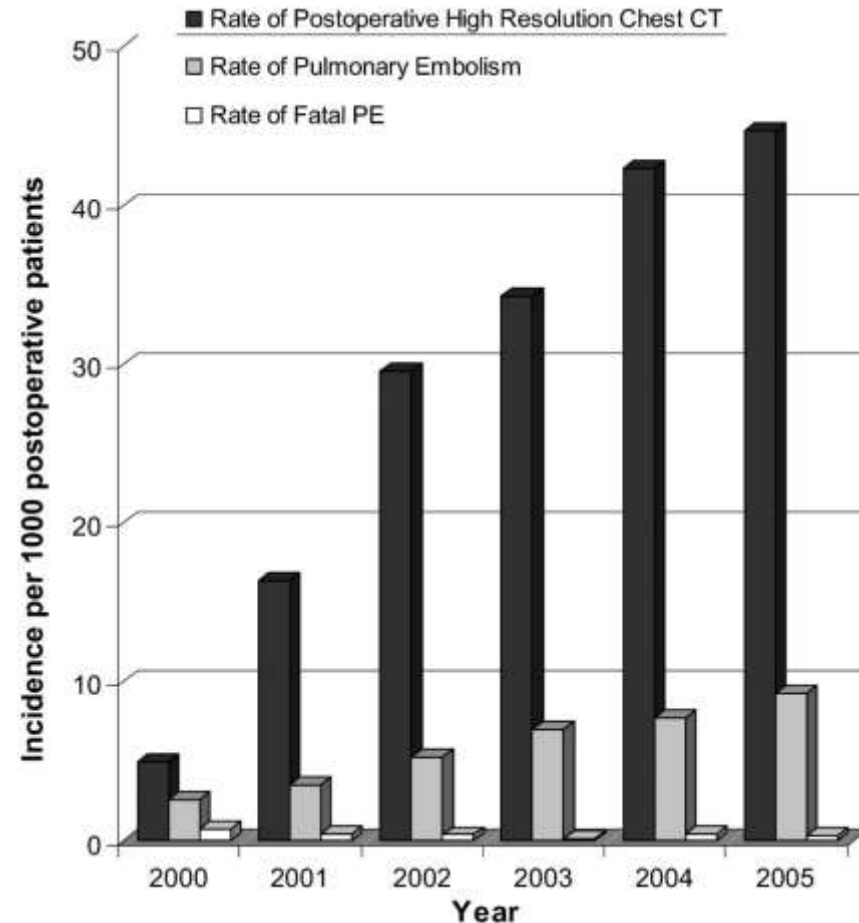
- 20,762 patients undergoing major cancer surgery
- Overall 30-day VTE rate 3.5%



Annual postoperative incidence of multidetector computed tomography (MDCT) scan of the chest, pulmonary embolism (PE), and fatal PE

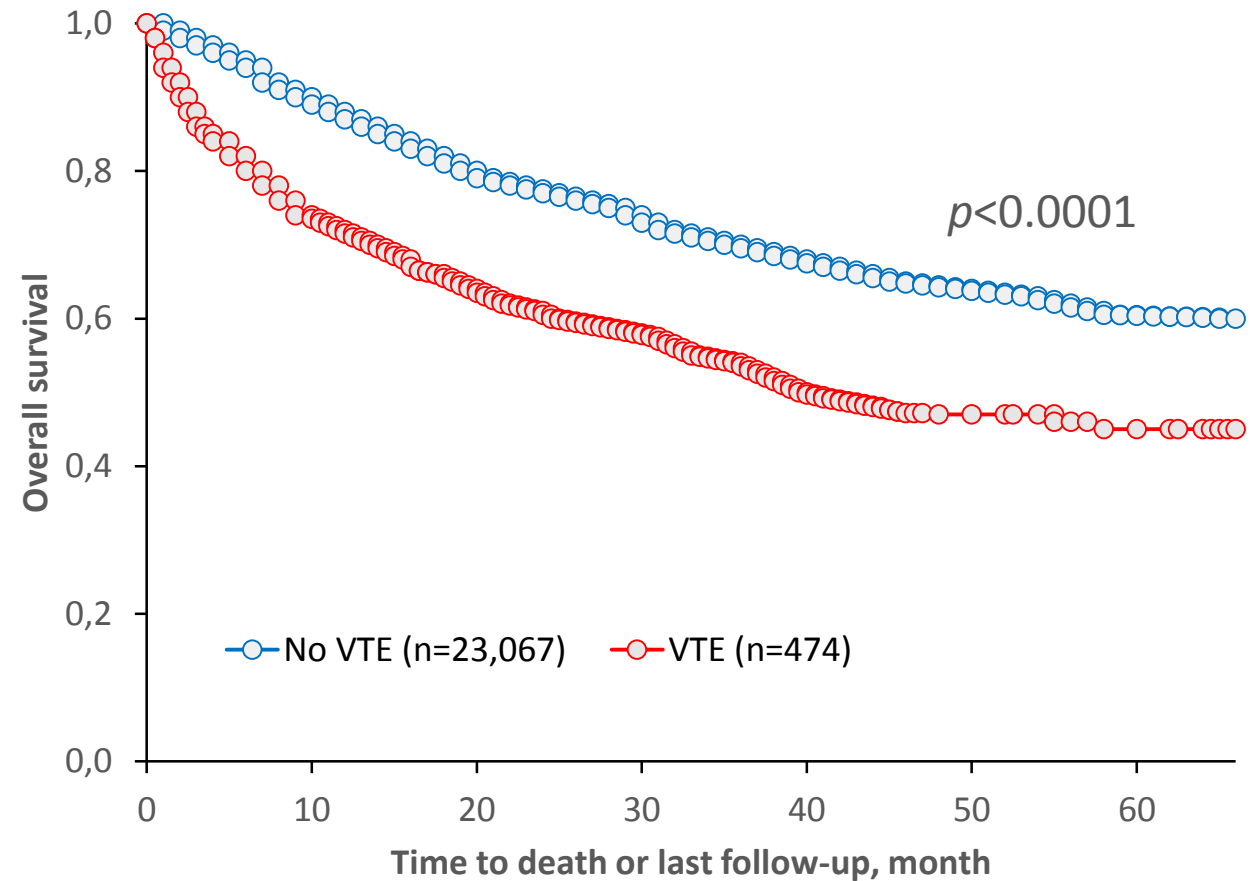
295 PE documented among 47,601 postoperative cancer patients.

The incidence of PE increased yearly from 2.3 per 1000 patients to 9.3 per 1000 patients.



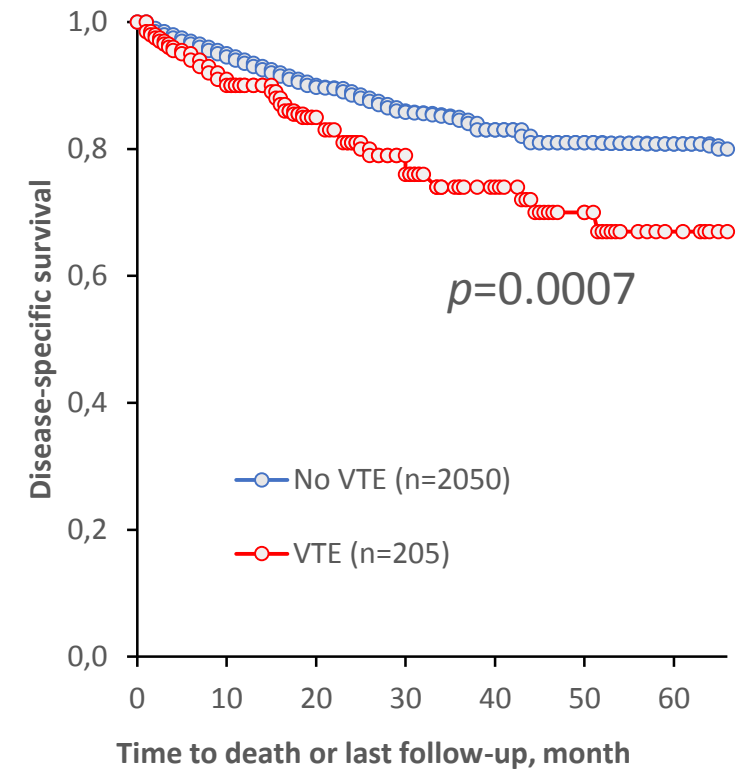
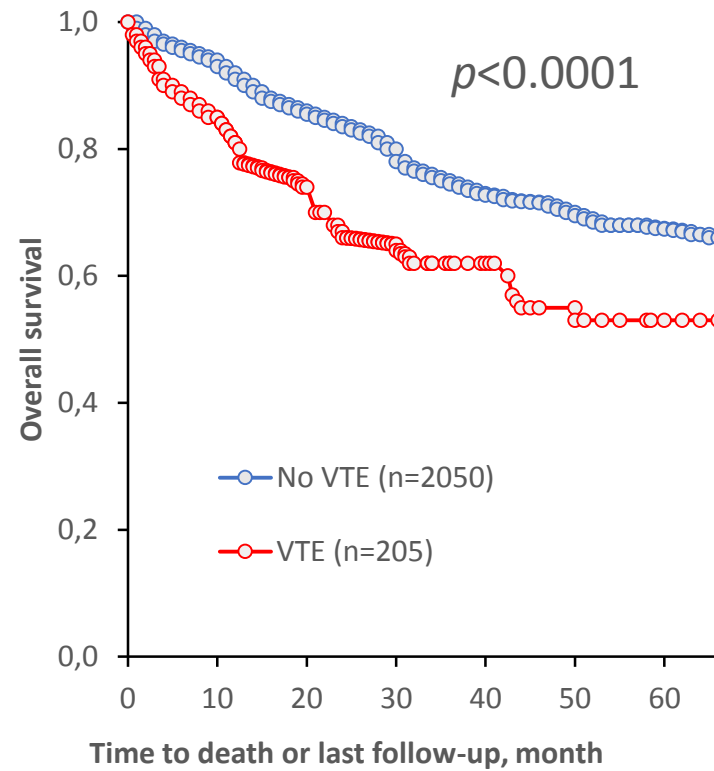
Postoperative VTE and Survival

- 23,541 patients having cancer surgery
- 474 (2%) VTEs
- 5-year overall survival 43.8% vs 61.2%



Postoperative VTE and Survival

- Matched for:
 - Gender
 - Age
 - Year of surgery
 - Type of cancer
 - Stage
 - Procedure
- Worse disease-specific survival in patients with VTE



A GROWING NUMBER OF CLINICAL AND LABORATORY
BIOMARKERS HAVE BEEN FOUND TO BE PREDICTIVE OF AN
INCREASED RISK OF VTE AND/OR RECURRENT VTE IN CANCER
PATIENTS

ARE THEY ALSO PREDICTIVE OF CANCER PROGNOSIS?

CLINICAL AND LABORATORY BIOMARKERS PREDICTIVE OF AN INCREASED RISK OF VTE IN CANCER PATIENTS

Clinical:

Leukocyte count ^{1,2}

Platelet count ²⁻⁴

Anemia (ESAs and Transfusions) ^{2,5,6}

Obesity ^{2,7,8}

VTE Risk Score (Khorana)²

Laboratory Biomarkers:

D-dimer ⁹⁻¹¹

Soluble P-selectin (sPsl) ¹²

Prothrombin 1+2 ¹¹

Tissue Factor (antigen and activity) ¹³⁻¹⁶

CRP ¹⁶⁻¹⁸

Factor VIII ¹⁹

VTE Risk score (Khorana) with biomarkers ²⁰

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2. Khorana AA et al. Blood 2008; 111: 4902
3. Matsuo K et al. Gynecol Oncol 2013; 128: 544
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8. Ashrani AA et al. Thromb Res 2016; 139: 29.
9. Stender MT et al. Dis Colon Rectum 2009; 52: 446.
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11. Ay C et al. J Clin Oncol 2009; 27: 4124
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15. Khorana AA et al. J Clin Oncol 2016; 35: 1078
16. Kroger K et al. Ann Oncol 2006; 17: 297.
17. Jeon HK et al. Eur J Gastroenterol Hepatol 2012; 24: 444
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20. Ay C et al. Blood 2010; 116:5377

CLINICAL AND LABORATORY BIOMARKERS PREDICTIVE OF SURVIVAL IN CANCER PATIENTS

Clinical:

Leukocyte count ^{1,2}

Platelet count ^{3,4}

Anemia (ESAs and Transfusions) ⁵⁻⁷

VTE Risk Score (Khorana) ⁸

Laboratory Biomarkers:

D-dimer ^{4,9-13}

CRP ¹⁴

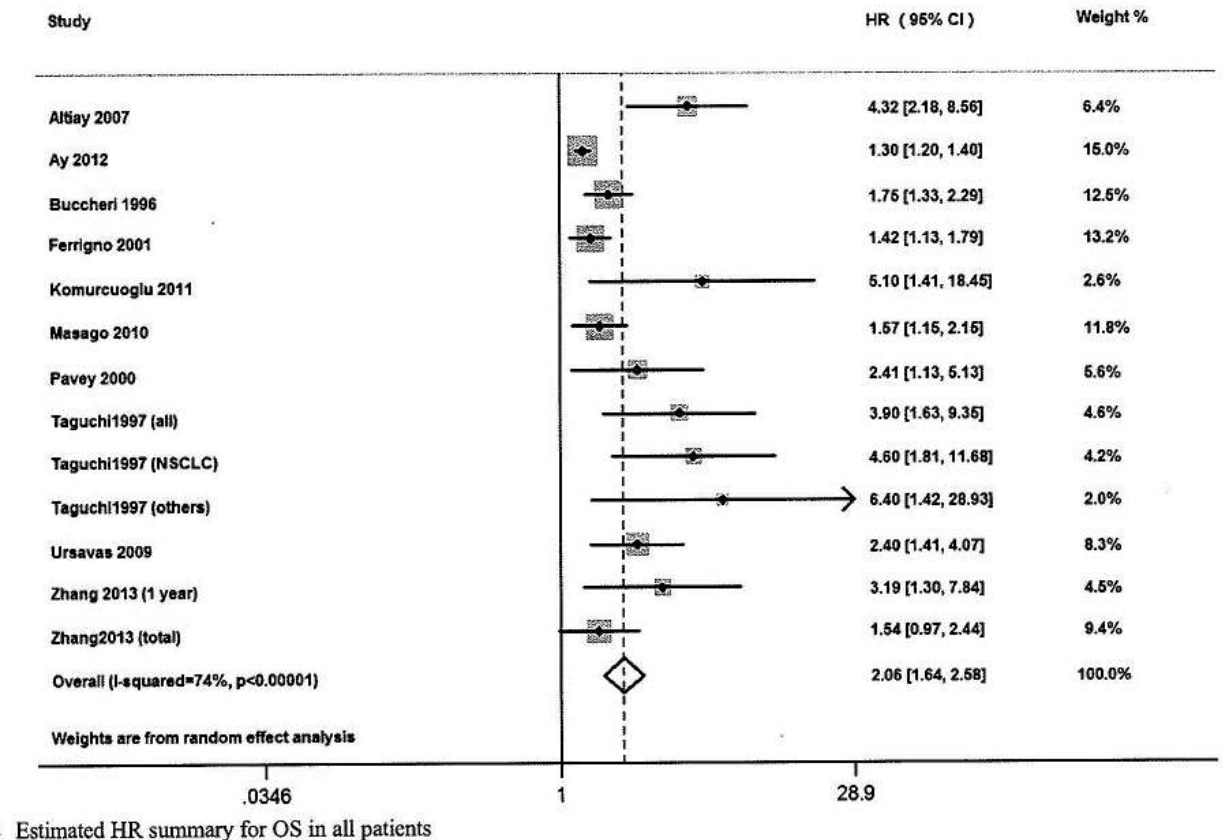
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3. Matsuo K et al. *Eur J Cancer* 2015; 51: 1973
4. Ya-Nan Man MM et al. *Int J Gynecol Cancer* 2015; 25: 24
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6. Khorana et al. *Arch Intern Med*.2008; 168:2377
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8. Kuderer NM et al. *oncologist* 2017; 22: 1
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12. Ma X et al. *Tumor Biol* 2014; 35: 2103
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D-DIMER AND LUNG CANCER PROGNOSIS: A META-ANALYSIS

Table 2 Meta-analyses of D-dimer expression hazard ratios and confidence interval to predict the survival outcome

	Survival outcome	Data sets (number)	Model	HR [95 % CI]	Log-rank <i>p</i>	Heterogeneity (<i>p</i> , <i>I</i> ² %)	Publication bias	Conclusion
Total	OS	13	Random	2.06 [1.64, 2.58]	<0.00001	<0.00001, 74	0.015	Positive
	DFS	1	—	3.38 [1.17, 9.75]	0.02	—	—	Positive
Asia	OS	6	Random	2.48 [1.60, 3.84]	<0.0001	0.03, 59	0.091	Positive
Non-Asia	OS	7	Random	1.89 [1.44, 2.47]	<0.00001	0.0002, 77	0.099	Positive
Histology type (adenocarcinoma/total >25 %)	OS	4	Fixed	1.72 [1.34, 2.19]	<0.0001	0.16, 41	0.042	Positive
Histology type (adenocarcinoma/total <25 %)	OS	3	Fixed	1.62 [1.37, 1.91]	<0.00001	0.16, 46	0.117	Positive
Tumor stage (III + IV/total >80 %)	OS	3	Random	2.91 [1.34, 6.80]	0.01	0.01, 78	0.602	Positive
Tumor stage (III + IV/total <80 %)	OS	5	Fixed	1.64 [1.41, 1.91]	<0.00001	0.21, 32	0.142	Positive
Detection method (ELISA)	OS	7	Random	3.22 [1.99, 5.21]	<0.00001	0.02, 62	0.293	Positive
Detection method (latex assay)	OS	4	Random	1.52 [1.25, 1.86]	<0.0001	0.03, 67	0.042	Positive
Detection method (immunoturbidimetry assay)	OS	2	Fixed	1.79 [1.19, 2.69]	0.005	0.16, 50	0.371	Positive

OS overall survival, RFS/DFS recurrence free survival/disease-free survival, HR hazard ratio, CI confidence interval, ELISA enzyme-linked immunosorbent assay



Survival in metastatic breast cancer correlates with D-dimer levels and associated inflammatory and angiogenic cytokine expression

•107 patients with breast cancer and 30 age matched healthy controls

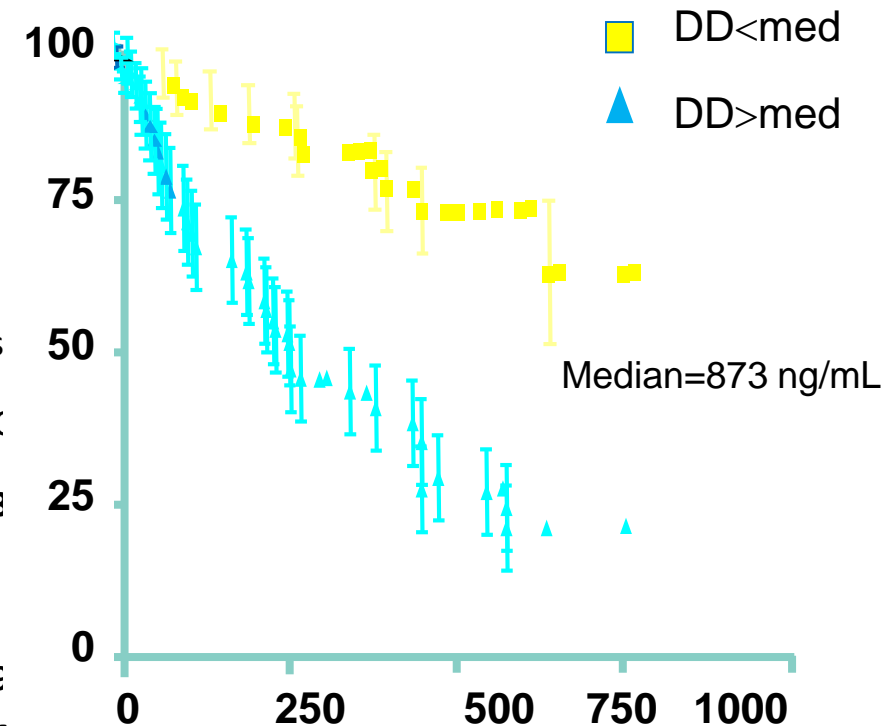
•Breast cancer patients:

- 23 pre-operative
- 84 metastatic disease

•Interrelations between coagulation and angiogenesis markers

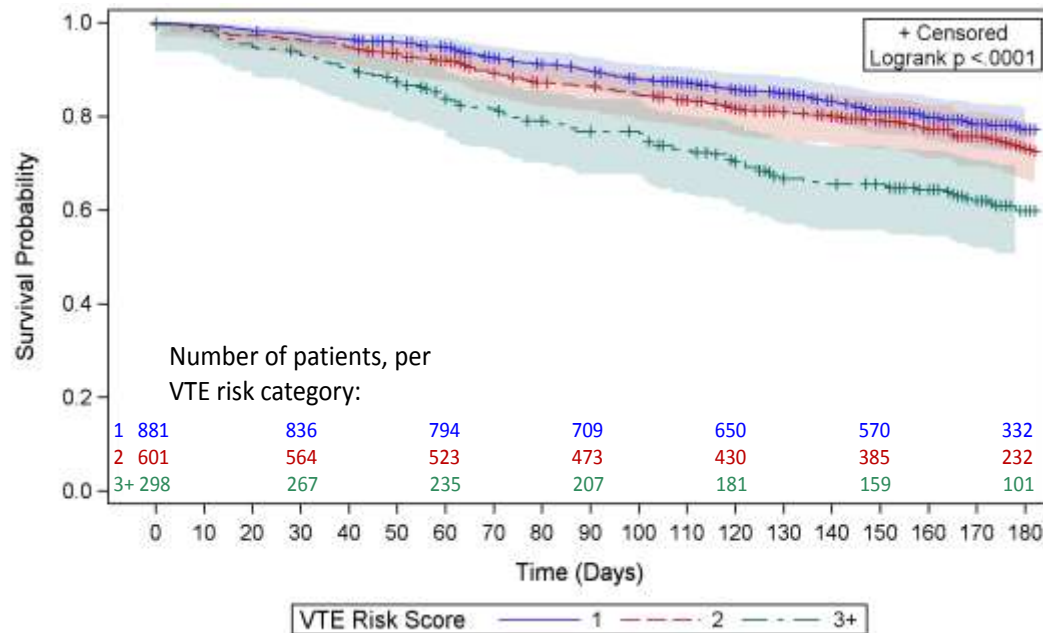
	PLT	FN	D-D	sIL-6	sVEGF	sV/pl	sbFGF	WCC
•PLT		0.25			0.33			0.43
•FN			0.38	0.61	0.43	0.37		
•D-D					0.285	0.37		
•S-IL6					0.59	0.43		0.59
•sV/pl								0.24
•sbFGF								

- Numbers represent Spearman correlations with a P value <0.5.

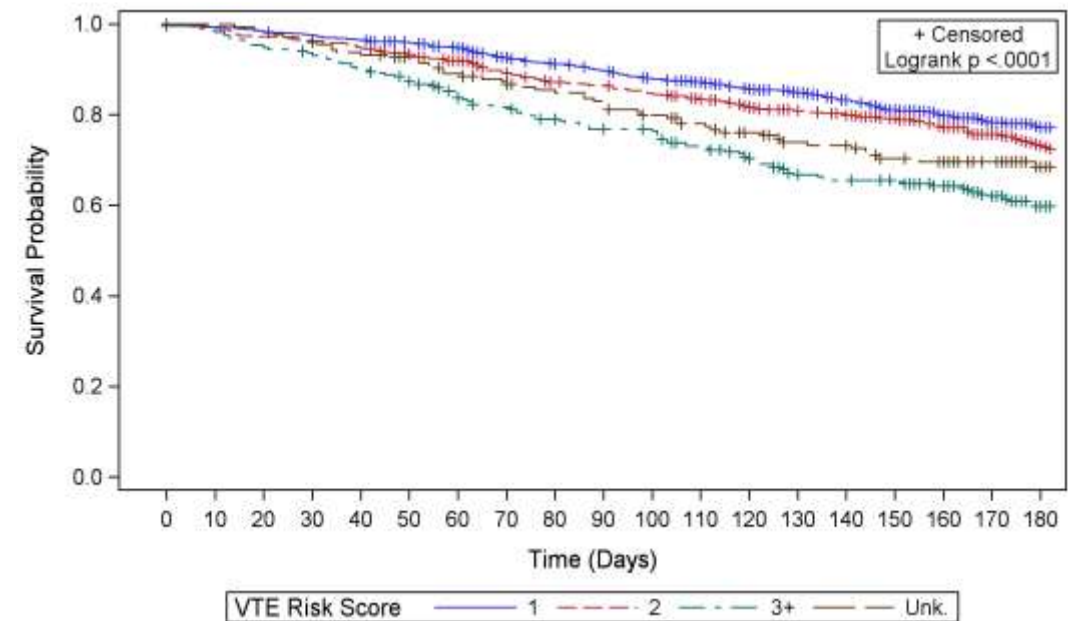


Overall survival (days) in 84 patients with metastatic breast cancer according to D-dimer levels

VTE-RS IS PREDICTIVE OF EARLY MORTALITY IN LUNG CANCER



Survival in patients with calculated VTE Risk Score with 95% Confidence Interval (N=1,780)



Survival in all patients by VTE Risk Score (N=1,980)

SUMMARY

The development of a venous thromboembolic event in a cancer patient are predictive of a more aggressive cancer biology and shorter survival.

Clinical and laboratory biomarkers that have been predictive for an increased risk of VTE may also be predictive of a poorer prognosis in selective malignancies.

These clinical and laboratory biomarkers suggest a significant inflammatory and prothrombotic state induced by the cancer and the host response to the malignancy.