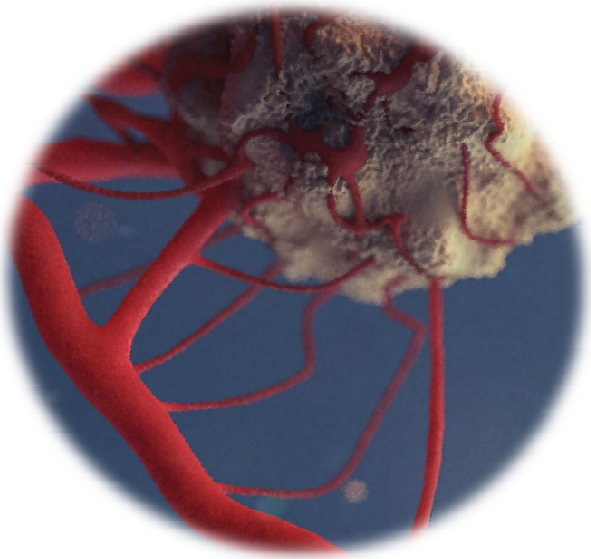
Eventi Tromboembolici nel NSCLC: esiste una minaccia reale?

Marco Platania

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

Esistono dei fattori di rischio particolari per il tumore al polmone?

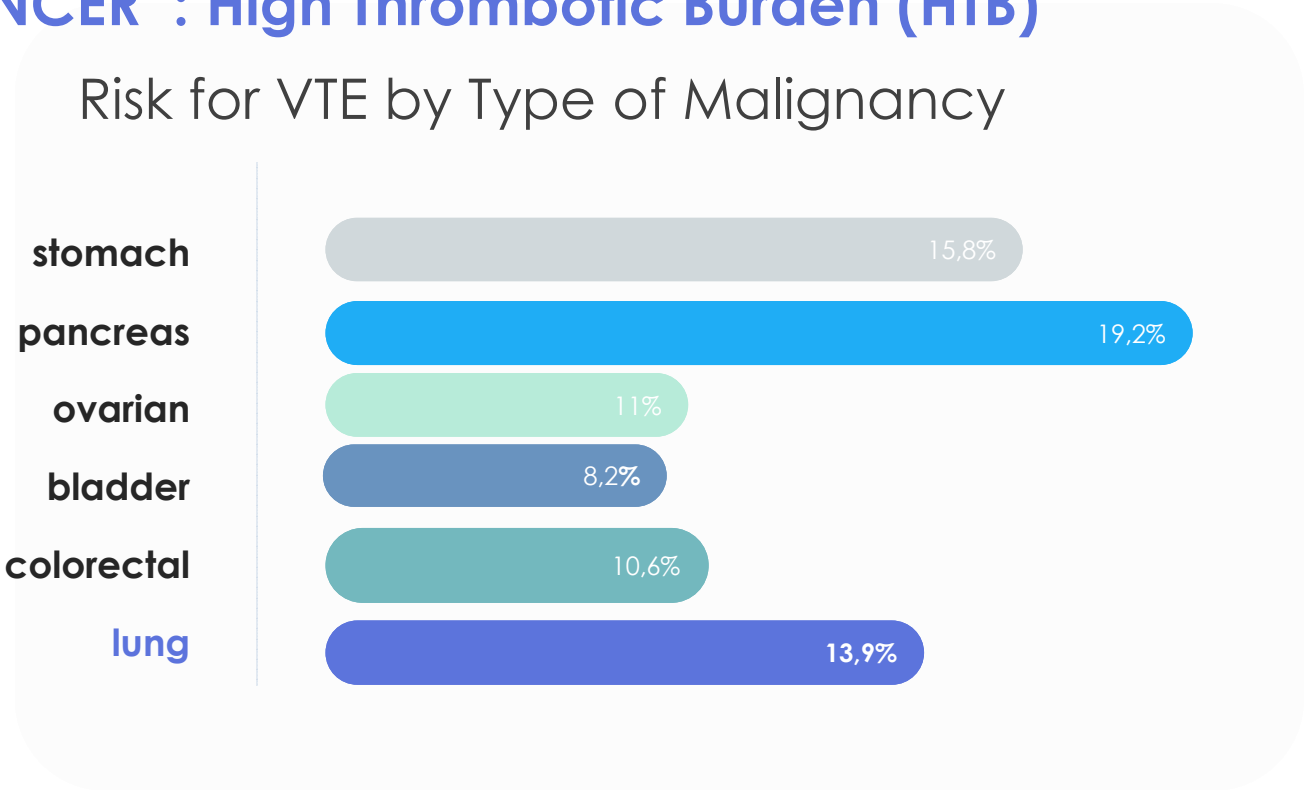


LUNG CANCER – THE FACTS

- One of the most frequent and most deadly tumor entities
- 1.6 million deaths worldwide
- Poor prognosis (5-year OS < 15%)
- Majority of patients diagnosed with advanced stage of disease
- Majority of (caucasian) patients diagnosed without treatable oncogenic alterations
- Majority of patients in need of palliative systemic therapy (=chemotherapy)

Is Thrombosis in patents with active lung cancer a real treat ?

LUNG CANCER : High Thrombotic Burden (HTB)

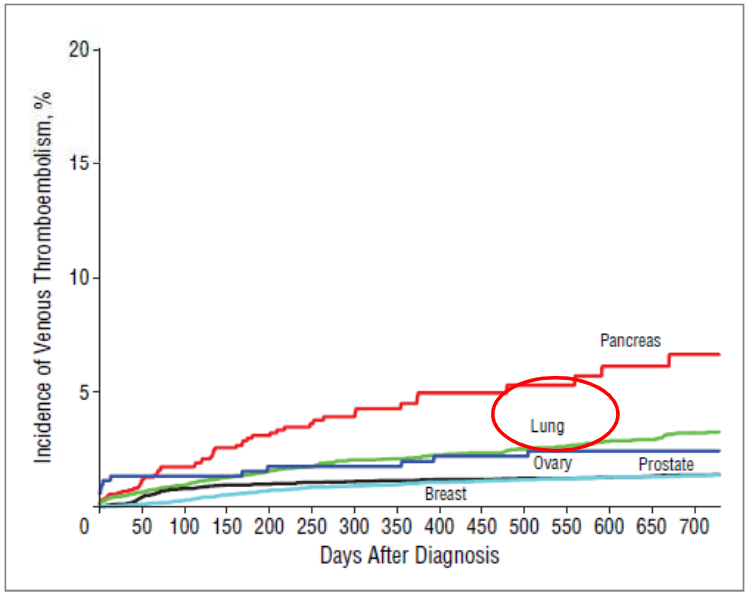


Khorana AA et al, Cancer 2012

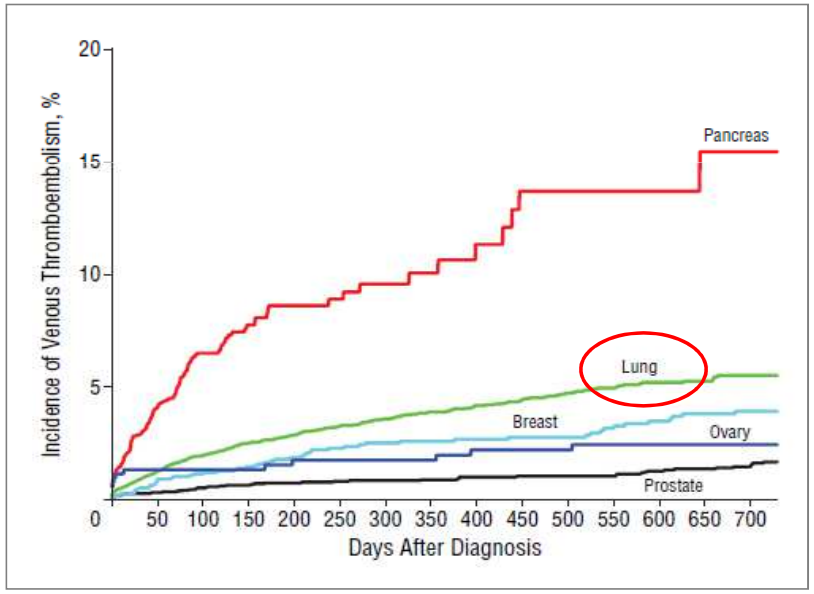
VTE in metastatic NSCLC reported to be 4-fold higher than in patients with localized disease, data from California Registry

Incidence of VTE within 2 years of diagnosis of 5 different types of cancer (235.149 cancer cases), 3775pts (1.9%) of whom 12% at diagnosis sand 88% subsequently

VTE strong predictor of death during first year



Incidence of VTE within 2 years of diagnosis among patients with locoregional disease



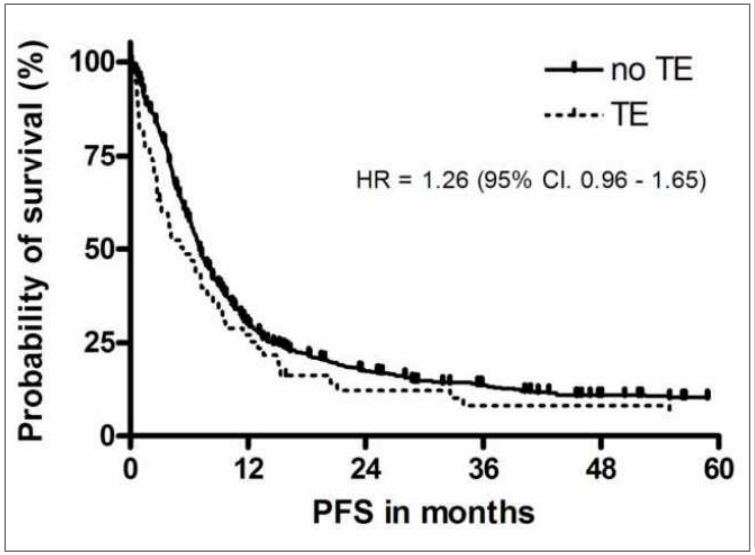
Incidence of VTE within 2 years of diagnosis among patients with metastatic disease

California Cancer Registry. Arch Intern Med. 2006;166:458-464

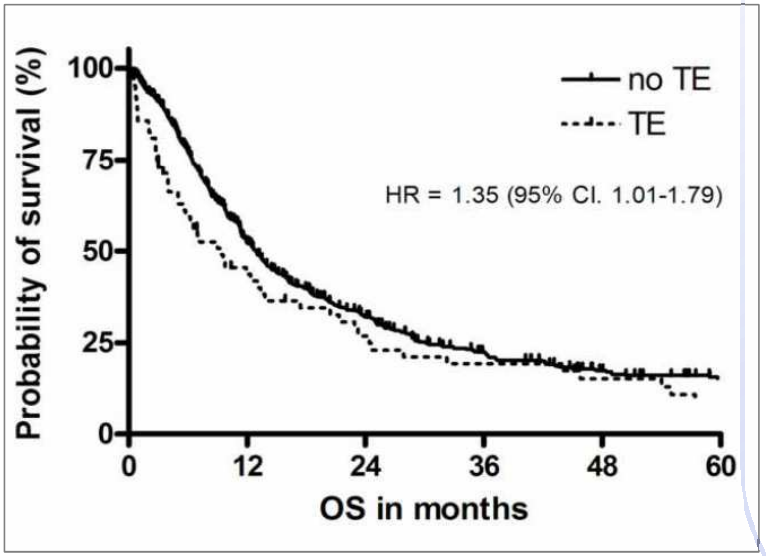
Retrospective evaluation of thromboembolic events in patients with NSCLC treated with platinum-based chemotherapy

748 pts, 63 (8%) had 69 TE events

PFS



Overall survival



PFS was equal in patients with or without TE during treatment, suggesting that TE is not a predictor of more aggressive disease

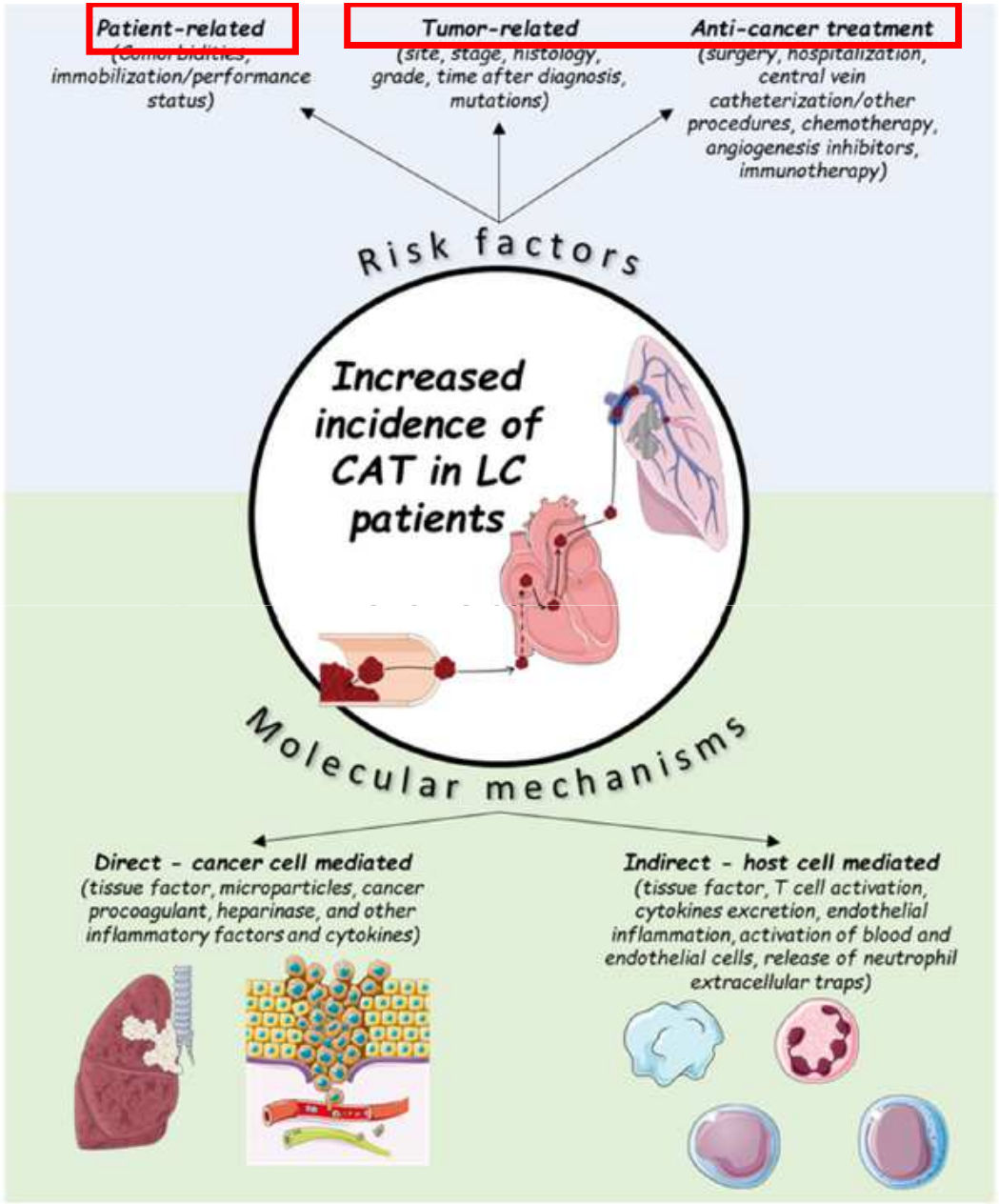
Patients who experienced TE during chemotherapy had a **significant shorter OS** as compared to patients without TE

Median PFS 6.2 vs 7.2 months and OS 9.5 vs 12.9 in pts with and without TE

Lung Cancer (2014), http://dx.doi.org/10.1016/j.lungcan.2014.07.017

Esistono dei fattori di rischio particolari per il tumore al polmone?

Cancer-Associated Thrombosis Risk in Lung Cancer

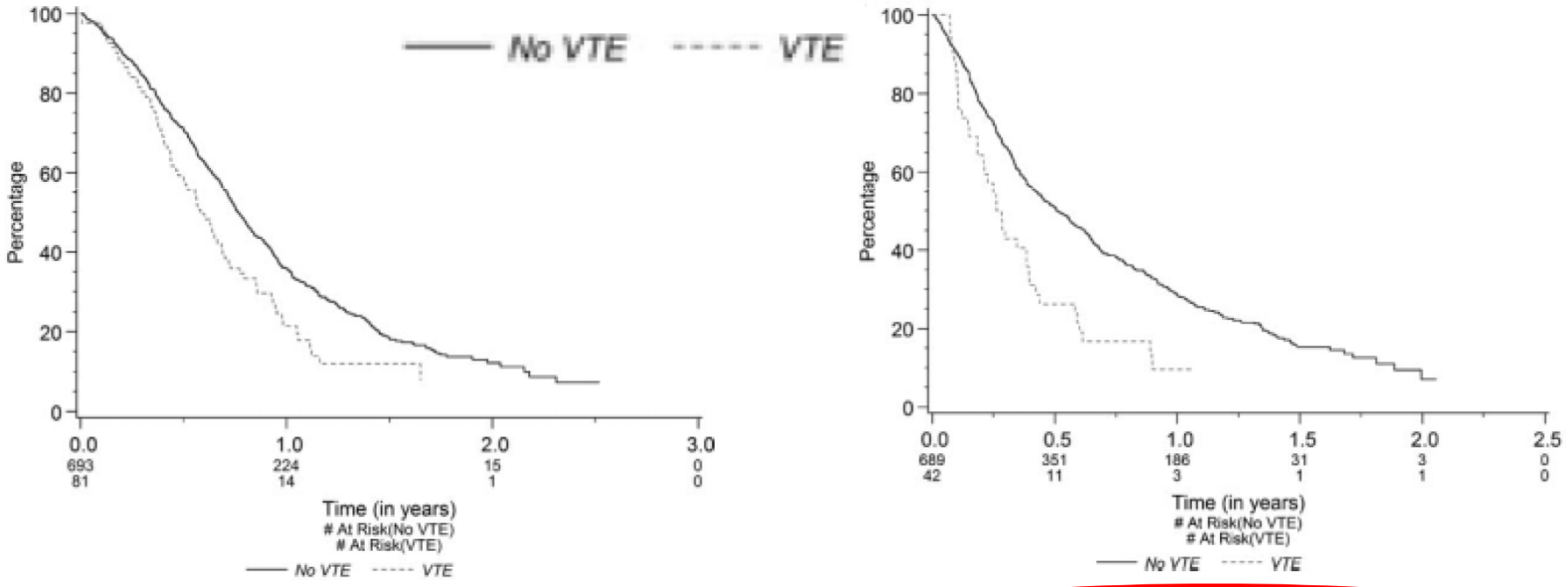


Ay C, et al. Thromb Haemost. 2017;117: 219-230 Cancer-associated Venous Thromboembolism: Burden, Mechan

In Advanced NSCLC, VTE was associated with shorter survival

Individual patient data from 3 NCI of Canada Clinical Trials Group (n = 1987 patients), BR 10 , BR18, BR21 trials

Incidence of VTE from 0% to 7.9%



Hicks LK, et al. Cancer. 2009;115:5516-5525.

Obesity and Previous VTE predictive of VTE

ORIGINAL ARTICLE

High Risk of Deep Vein Thrombosis in Patients with Non-small Cell Lung Cancer: A Cohort Study of 493 Patients

Vicky Tagalakis, MD, MSc, Dahlia Levi,§ Jason S. Agulnik, MD,†‡ Victor Cohen, MD,‡ Goulnar Kasymjanova, MD,† and David Small, MD†‡*

- Of the 493 NSCLC patients included in the cohort, 67 (13.6%) patients developed objectively confirmed DVTs, with an incidence of 110 cases per 1000 person-years
- Advanced stage and, to a lesser extent, male sex, are important predictors of DVT

Journal of Thoracic Oncology • Volume 2, Number 8, August 2007

Atrial Fibrillation (AF) at the time of cancer diagnosis.

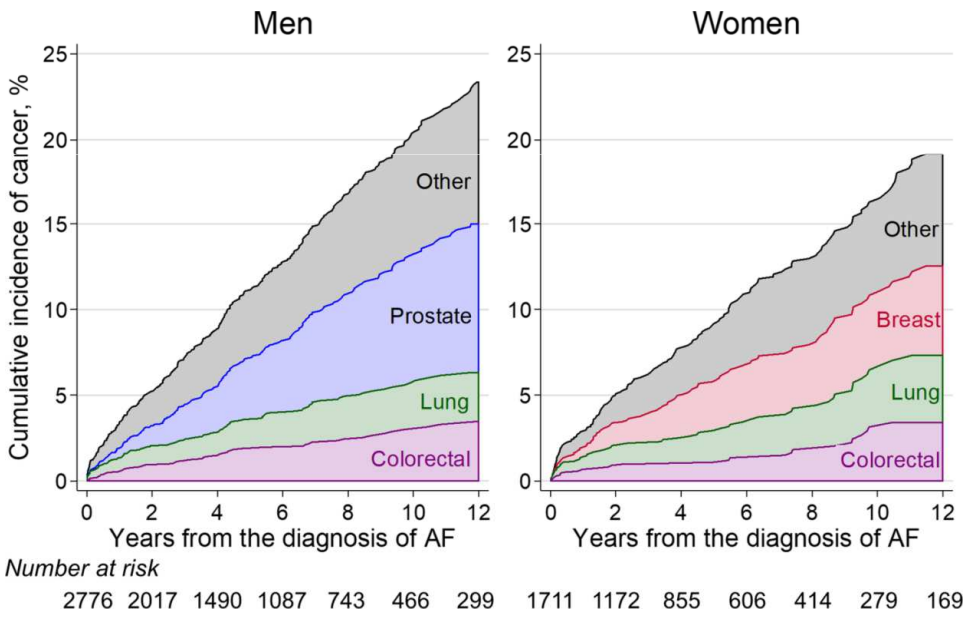
Study including 24.125 patients estimated a prevalence of AF of 2.4% at the time of cancer diagnosis

22.3% of patients will develop Cancer during next 12 years

2,7% LUNG cancer

Atrial Fibrillation

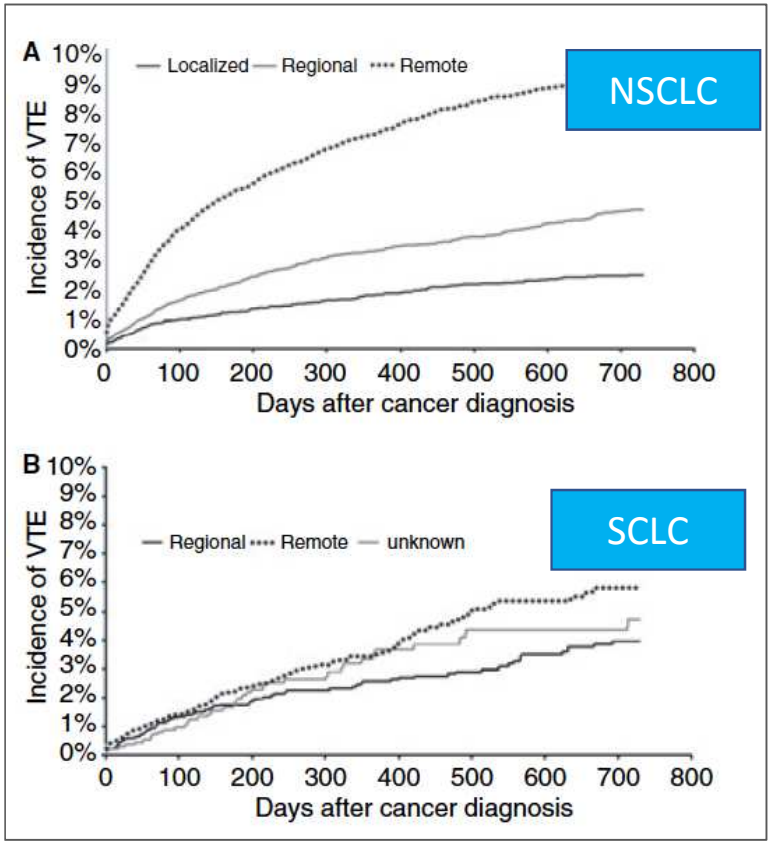
Anticoagulation options include therapeutic low-molecular-weight heparin (LMWH) (as a short- to intermediate-term measure), a vitamin K antagonist (e.g. warfarin) if international normalized ratio control is stable and effective, or a non-VKA oral anticoagulant (NOAC).



Atrial Fibrillation and Risk of Cancer: A Danish Population-Based Cohort Study, Volume: 7, Issue: 17, DOI: (10.1161/JAHA.118.009543)
Esc.cardio guidelines 2016

VTE risk : among patients with NSCLC, high risk for younger age, increasing number of comorbidity, advanced cancer stage, and histology

The California Cancer Registry **91 933** patients with newly diagnosed lung cancer **NSCLC and SCLC**



…he rate of VTE increased among all those patients with NSCLC and SCLC in advancing stage

Possible explanations is more use of medical treatment and more aggressive course of disease

Hisada Y, Mackman N. Cancer-associated pathways and biomarkers of venous thrombosis. Blood. 2017;130:1499-1506.

Journal of Thrombosis and Haemostasis, **2**: 1760–1765

ORIGINAL ARTICLE

The risk of a venous thrombotic event in lung cancer patients: higher risk for adenocarcinoma than squamous cell carcinoma

J. W. BLOM,* S. OSANTO‡ and F. R. ROSENDAAL*†

*Department of Clinical Epidemiology, †Hemostasis and Thrombosis Research Center, ‡Department of Oncology, Leiden University Medical Center, the Netherlands

537 pts Lung cancer: 258 squamous vs 133 Adeno

Table 2 Incidence of venous thrombosis in the total group of lung cancer patients

DVT	17
PE	15
DVT +PE	7
Total	39
Person years of follow up	879
Incidence DVT/PE (per 1000 person-years)	44.4

THE RISK WAS 3-FOLD INCREASED IN Adeno versus Squamous carcinoma

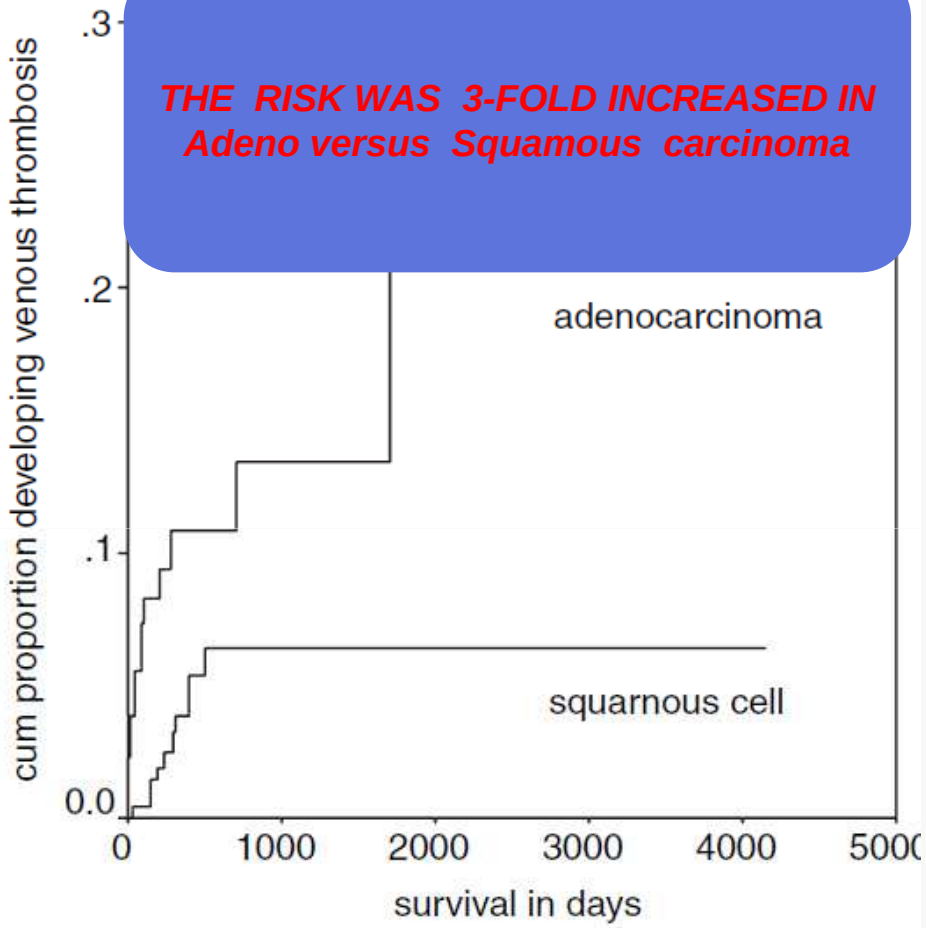
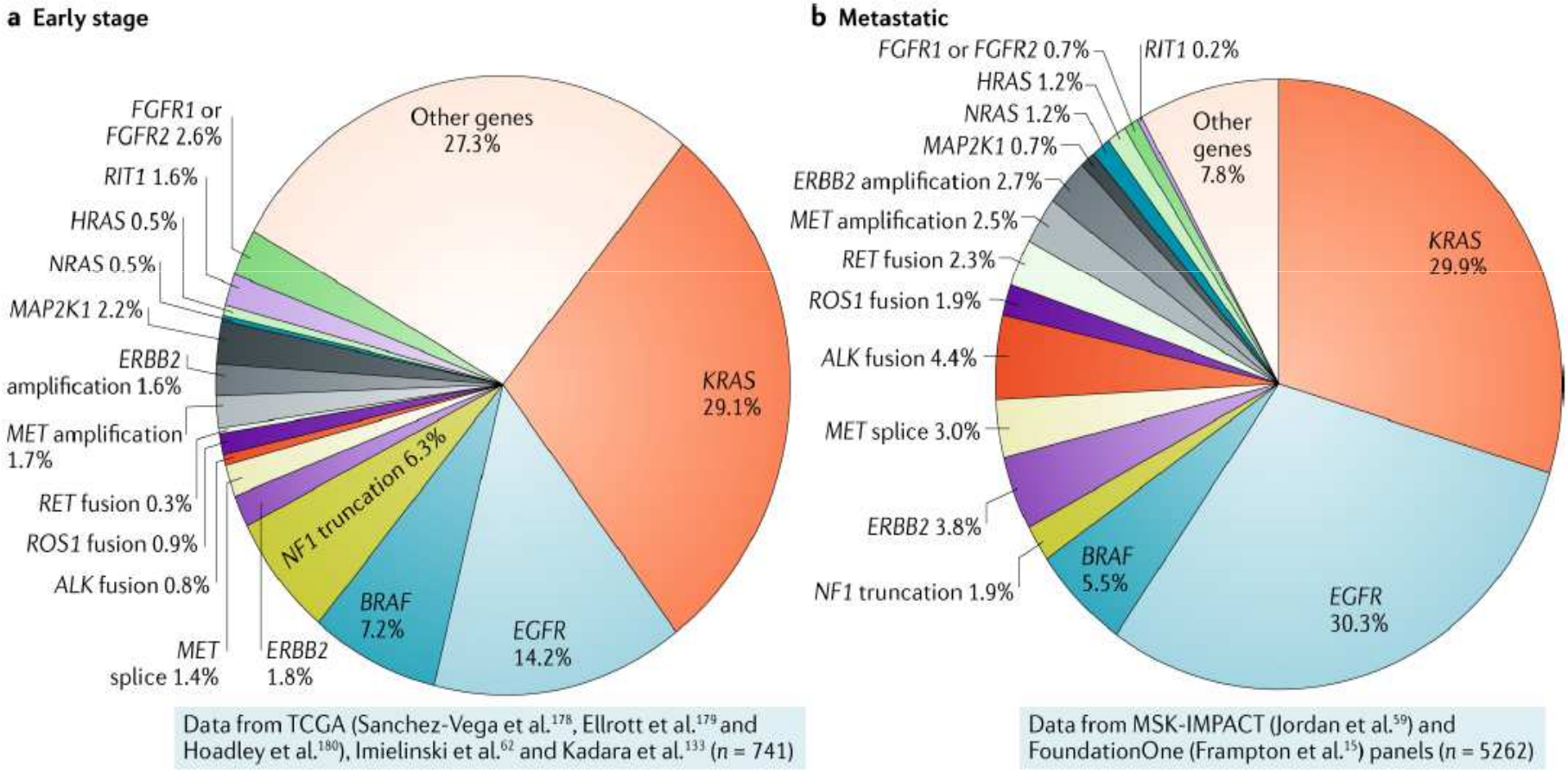


Fig. 1. Cumulative proportion of venous thrombosis in patients with a squamous cell carcinoma vs. patients with an adenocarcinoma.

Targetable Alterations



Data from TCGA (Sanchez-Vega et al.[178], Ellrott et al.[179] and Hoadley et al.[180]), Imielinski et al.[62] and Kadara et al.[133] (n = 741)

Data from MSK-IMPACT (Jordan et al.[59]) and FoundationOne (Frampton et al.[15]) panels (n = 5262)

Genetic mutations risk in NSCLC

- increased thromboembolism (TE) has been reported in ALK+ and ROS1
- systematic review of 8 studies for ALK+ NSCLC, pooled OR as 2.10 for VTE, and 1.24 for arterial thromboembolism (ATE). For ROS1+ NSCLC, pooled OR reported 3.15 for VTE
- VTE is an important predictor for early mortality especially in patients with EGFR/ALK wild-type genes
- **VTE incidence in patients with advanced ROS1-rearranged NSCLC was 3- to 5-fold higher compared to the general population with NSCLC based on METROS**

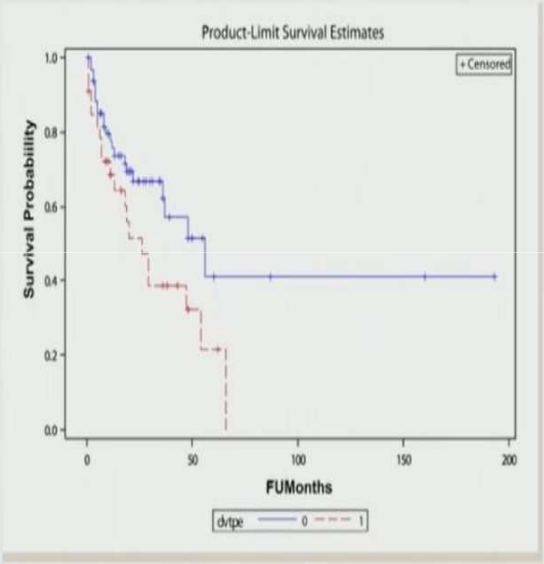
Table 1: DNA damages and their role in VTE risk, adapted from

Genetic damage	Organ	VTE incidence	Effect on VTE risk
ALK rearrangement	Lung	26.9% - 47.1%	2.2 - 5 times increase
EGFR mutation	Lung	9% - 35%	diverging results
KRAS mutation	Lung and colon	16.1% - 54%	2.6 times increase
ROS1 rearrangement	Lung	34.6% - 41.6%	3 - 5 times increase

Thromboembolism in ALK+ and ROS1+ NSCLC patients: A systematic review and meta-analysis," Lung Cancer, vol. 157, pp. 147-155, Jul 2021.
Association of Venous Thromboembolism and Early Mortality in Patients with Newly Diagnosed Metastatic Non-Small Cell Lung Cancer," Cancer Manag Res, vol. 13, pp. 4031-4040, 2021.
ROS1-rearranged Non-small-cell Lung Cancer is Associated With a High Rate of Venous Thromboembolism: Analysis From a Phase II, Prospective, Multicenter, Two-arms Trial (METROS)," Clin Lung Cancer, vol. 21, pp. 15-20, Jan 2020.
Impact of Tumor Genomic Mutations on Thrombotic Risk in Cancer Patients," Cancers (Basel), vol. 12, Jul 19 2020.

ALK & ROS1 – rearranged NSCLC is associated with High Thrombotic Burden

ALK-Rearranged Non Small-Cell Lung Cancer Is Associated With a High Rate of Venous Thromboembolism

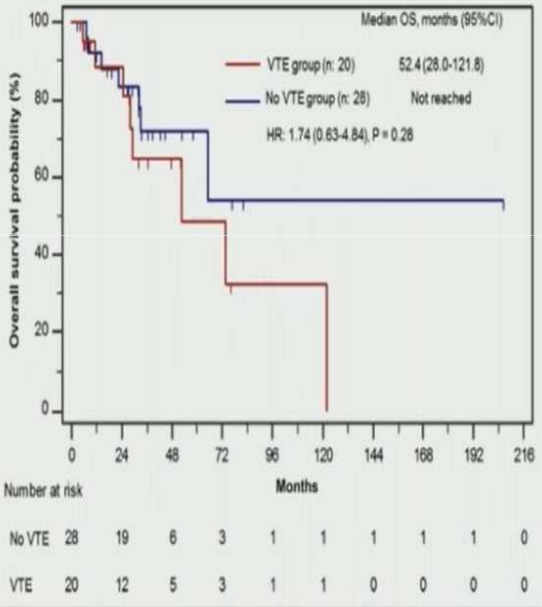


The rate of VTE in our ALK-rearranged cohort was 3- to 5-fold higher than previously reported for the general NSCLC population.

- The VTE rate was 36%
- VTE was associated with shorter overall survival (HR 5.71, P = .01).

Zer et al, Clinical Lung Cancer 2016 http://dx.doi.org/10.1016/j.cllc.2016.10.007

ROS1-rearranged Non-small-cell Lung Cancer is Associated With a High Rate of Venous Thromboembolism: Analysis From a Phase II, Prospective, Multicenter, Two-arms Trial (METROS)



The incidence of VTE is 3- to 5-fold higher in patients harboring ROS1-rearrangment than previously observed for the general population with NSCLC

VTE among 48 pts occurred in 35% at progression, 32% at diagnosis, 14% during crizotinib

Patients with VTE were younger and had a worse PS

Case Report

TJ | Tumori Journal

Recurrent thrombosis followed by Lazarus response in *ROS1* rearranged NSCLC treated with crizotinib: a case report

Tumori Journal
2020, Vol. 106(6) NP41–NP45

DOI: 10.1177/0300891620905665
journals.sagepub.com/home/tmj
SAGE

Teresa Beninato, Giuseppe Lo Russo, Marina Chiara Garassino, Filippo De Braud and Marco Platania

Abstract

Introduction: Patients with cancer have higher risk of thrombosis compared to the general population and particularly lung adenocarcinoma is considered at high risk for venous thromboembolism. Some targetable oncogenic drivers are supposed to further increase this risk.

Case description: A 35-year-old man who had developed a recurrent venous thromboembolism and pulmonary embolism (PE) was diagnosed with *ROS1* rearranged non-small cell lung cancer (NSCLC). While molecular examinations were ongoing, he developed progressive respiratory failure. For PE and thrombosis worsening with detection of right heart thrombus, he underwent therapy with unfractionated heparin. Despite initial good radiologic results, only with the start of crizotinib did the patient's clinical condition significantly improve to configure a Lazarus response.

Conclusions: Cancer diagnosis should always be considered in patients with unprovoked thrombosis and, if NSCLC is diagnosed, genetic alterations should be always sought after. A possible relation between venous thromboembolism and oncogenic drivers, particularly for *ALK* translocations, has been hypothesized. Similarly to ALK-positive NSCLC, *ROS1* rearranged disease has been associated with an increased thromboembolic risk. Further studies are needed to better evaluate this relation and to evaluate the potential benefit of a prophylactic anticoagulating treatment in this subset of patients.

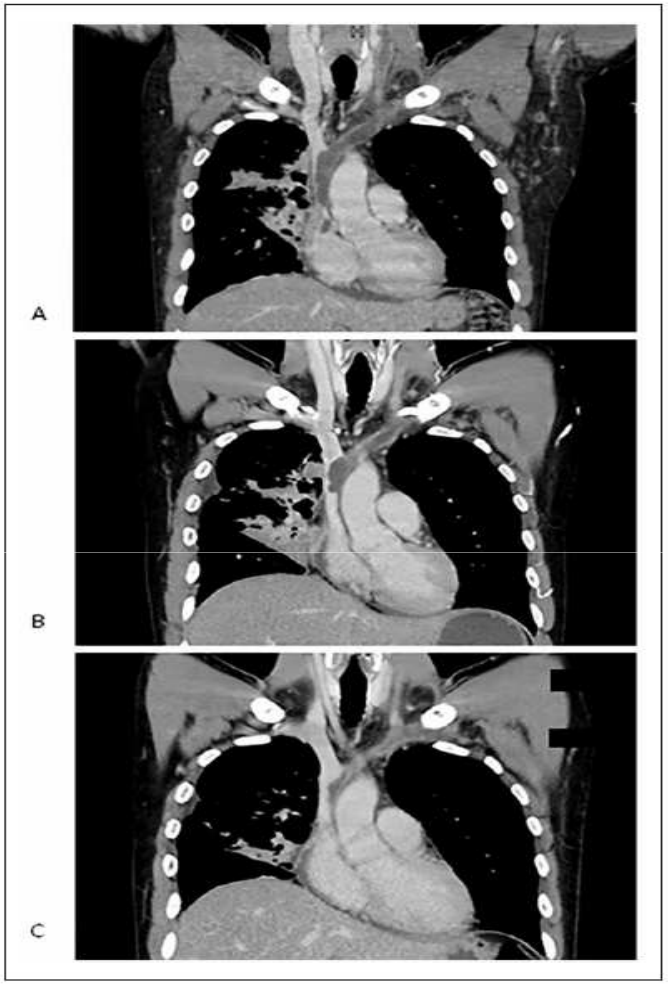
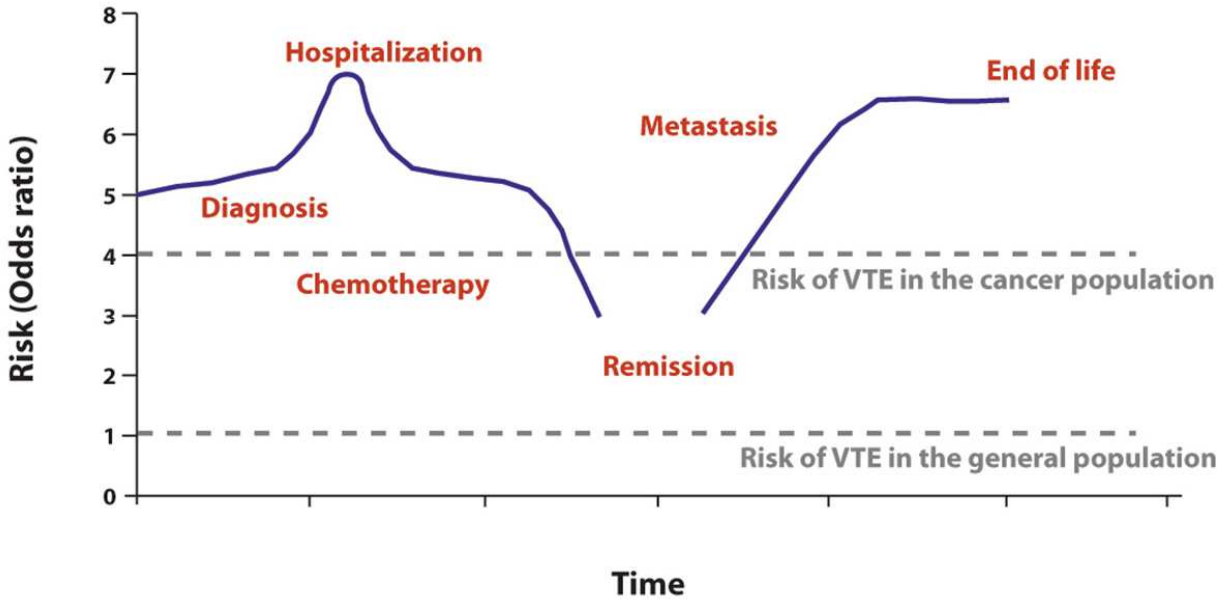


Figure. Superior caval vein thrombosis (A) before starting any treatment; (B) after 5 days of unfractionated heparin (UFH) treatment; and (C) after 1 week of crizotinib, 2 weeks of UFH treatment.

Changes in risk for Thrombosis – Reassessment is needed

Risk factor assessment is an ongoing dynamic process throughout the course of care for the cancer patient.

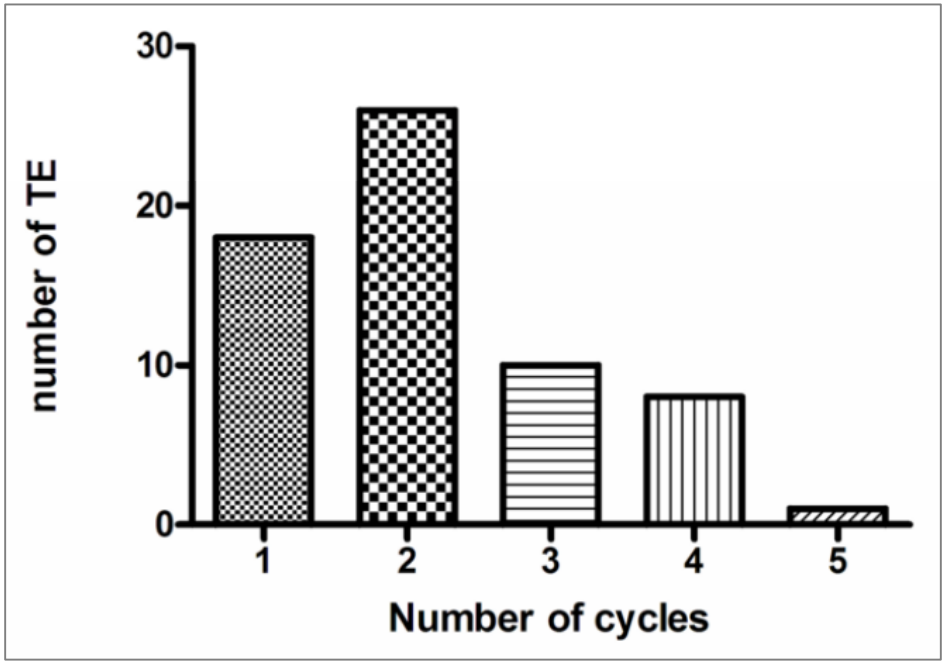


- **Patients with cancer have a 4 to 6-fold increased risk for VTE**
- **Risk factor assessment is an ongoing dynamic process**

JAMA 293: 715–722, 2005.
Arch Intern Med 162: 1245–1248, 2002.
Arch Intern Med 160:809-815, 2000.

Retrospective evaluation of thromboembolic events in patients with NSCLC treated with platinum-based chemotherapy

The number of chemotherapy cycles preceding the first event

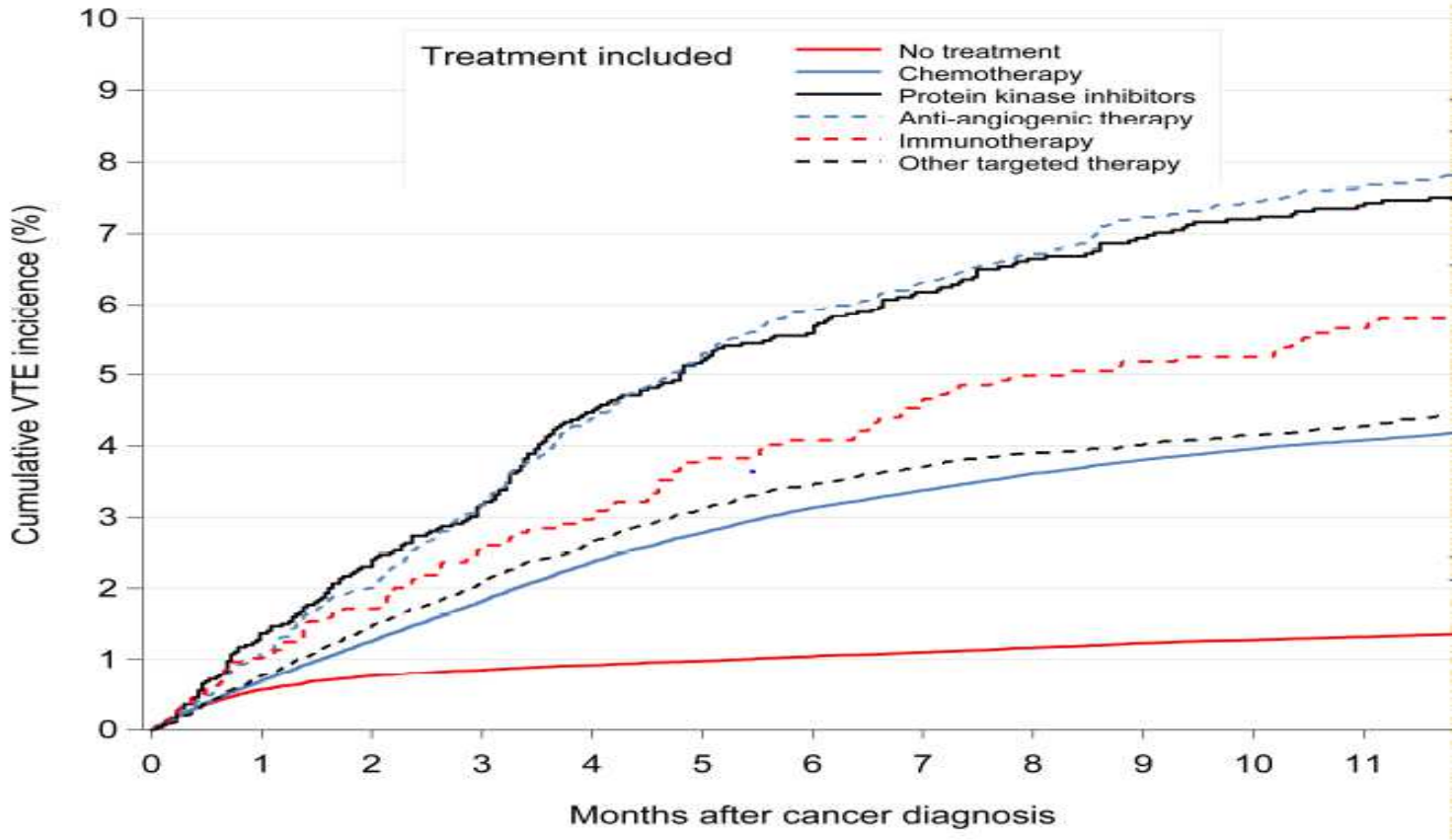


- 70% of TE occurred in the first 2 courses
- Median time to TE from start of chemo 31 days (average)
- Median time to the first VTE 32 days

Lung Cancer (2014), http://dx.doi.org/10.1016/j.lungcan.2014.07.017

The Danish Cancer Registry, 499092 cancer patients 1997-2017

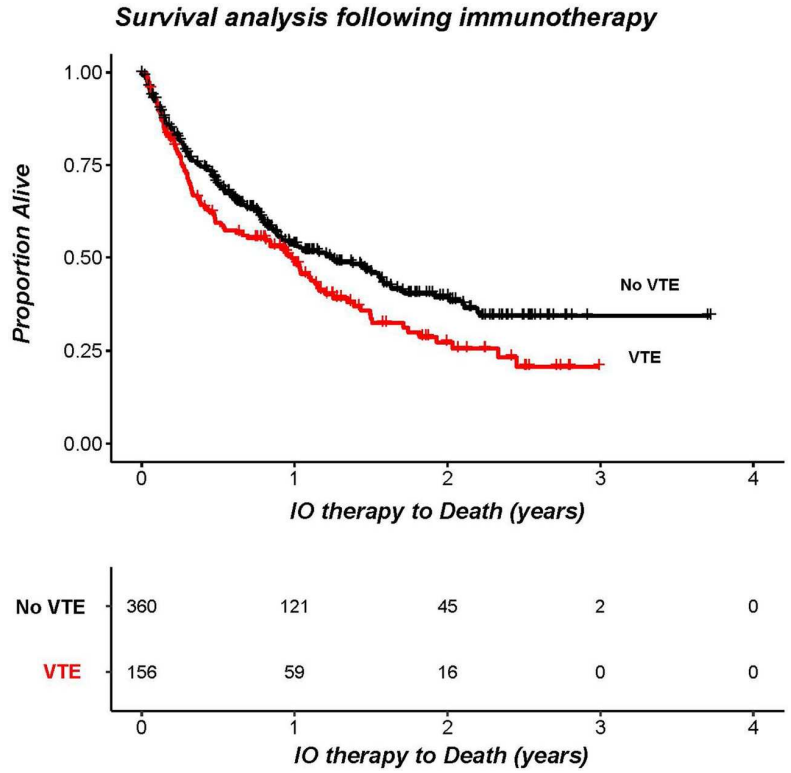
the incidence rates of systemic therapies were 28.4 / 1,000 person-years in the cancer cohort vs 3.6/ 1,000 person-years in the comparison cohort without treatment



2021 Blood VTE in cancer patients – A population-based cohort study

Thrombosis is Common in Lung Cancer Patients Receiving Immunotherapy (Cleveland Registry)

522 pts ,Male 307, median age 64, 88% stage IV, 50% LUNG CANCER

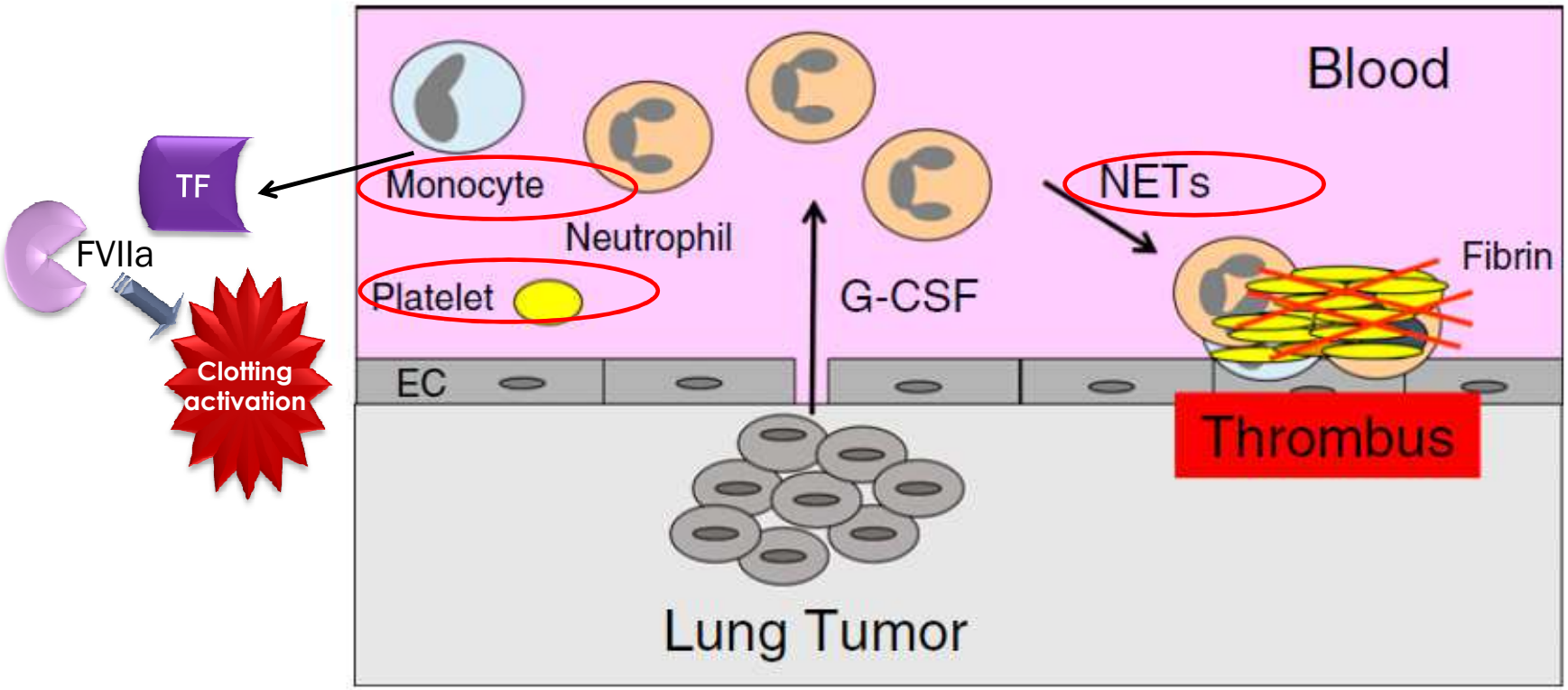


VTE is common in cancer patients receiving immunotherapy either as single-agent or

in combination regimens, affecting nearly one-third of all patients and may potentially be associated with worsened survival

Roopkumar J. et al. Blood. 2018; 132:2510

Different Pathogenic Mechanisms for patients with lung cancer Receiving Immunotherapy



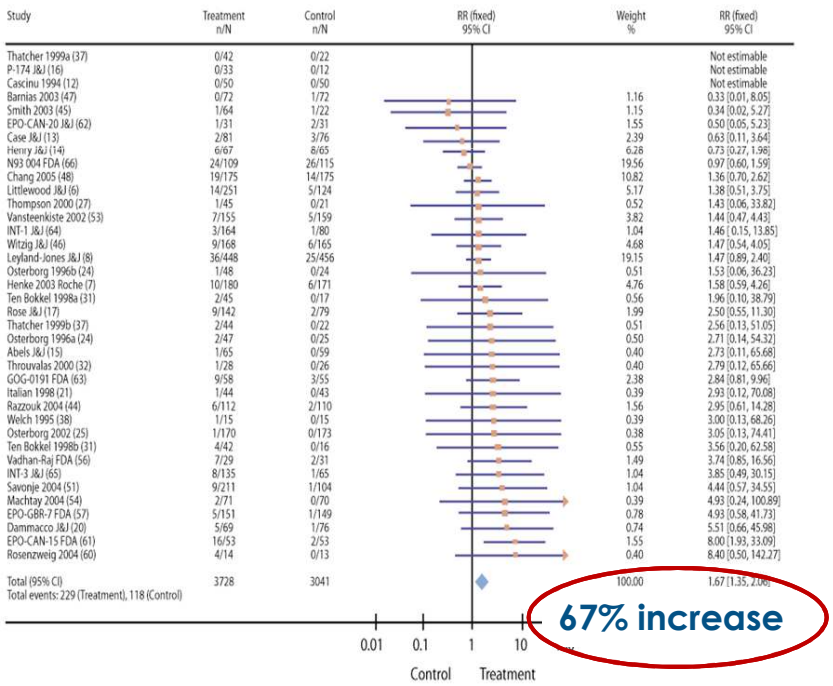
Hisada Y, Mackman N. Blood. 2017;130:1499-1506

Chemotherapy induced thrombosis

Regimen	Contribution to the risk	VTE events rate or RR/Incidence
Cisplatin/platinum based	• elevated von Willebrand factor (vWF) levels • release of procoagulant endothelial microparticles	• ↑Events 18,1%
L-asparaginase	• depletion of key proteins in the regulation of the coagulation pathway • synthesis of plasminogen and antithrombin (AT) is markedly impaired with asparaginase-based therapy	• ↑Incidence 4,2%
5-Fluorouracil (5FU)	• depletion of protein C and increased thrombin activity • endothelial cell damage with the potential to promote thrombus formation	• ↑Incidence (15%) - if combined with hematopoietic G-SFE (29%)
Tamoxifen and Aromatase Inhibitors		• ↑Risk 2,8% - if Tamo+chemo • RR 15,5
Antiangiogenic Agents –bevacizumab	• increased thrombin potential, E-selectin, vWF, and soluble tissue factor • VEGF-targeted therapy is also associated with decreased thrombus resolution	↑Events 23% (bevacizumab with 5-FU and leucovorin)
Immunomodulatory Agents - Thalidomide/lenalidomide	• thalidomide increases the expression of protease-activated receptor 1 • On the endothelium, PAR-1 facilitates platelet and neutrophil rolling and adhesion. • Therefore, PAR-1 may serve as the connection between injury and the coagulation response.	↑Incidence Thalid+anthacycleine 28% , Thalid+Dexamethazone 17%
Corticosteroids Dexamethasone	• increase circulating levels of clotting factors VII, VIII, XI and fibrinogen in healthy volunteers. • decreased thrombolysis associated with increased plasminogen and alpha-2 antiplasmin levels.	↑Incidence Ratio 2,3 -3,4
Erythropoietin stimulating agents	• decrease proteins C and S, increase plasminogen activator inhibitor-1 (PAI-1) production, and increase platelet activation • some evidence of endothelial cell damage/activation with increased serum levels of thrombomodulin and vWF	↑ Relative Risk 1,52 -2,09

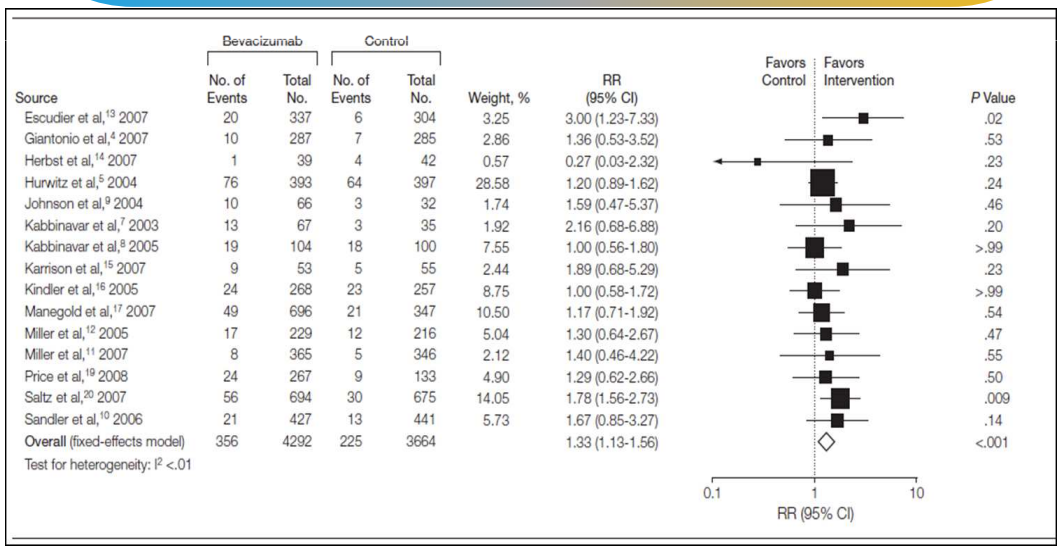
VTE risk is increasing in patients receiving erythropoietin or bevacizumab

VTE complications in cancer patients who received epoetin or darbepoetin



J Natl Cancer Inst. 2006;98:708-714

Relative Risk of VTE associated with Bevacizumab vs Control.



Source	Bevacizumab No. of Events	Bevacizumab Total No.	Control No. of Events	Control Total No.	Weight, %	RR (95% CI)	*P* Value
Escudier et al,[13] 2007	20	337	6	304	3.25	3.00 (1.23-7.33)	.02
Giantonio et al,[4] 2007	10	287	7	285	2.86	1.36 (0.53-3.52)	.53
Herbst et al,[14] 2007	1	39	4	42	0.57	0.27 (0.03-2.32)	.23
Hurwitz et al,[5] 2004	76	393	64	397	28.58	1.20 (0.89-1.62)	.24
Johnson et al,[9] 2004	10	66	3	32	1.74	1.59 (0.47-5.37)	.46
Kabbinavar et al,[7] 2003	13	67	3	35	1.92	2.16 (0.68-6.88)	.20
Kabbinavar et al,[8] 2005	19	104	18	100	7.55	1.00 (0.56-1.80)	>.99
Karrison et al,[15] 2007	9	53	5	55	2.44	1.89 (0.68-5.29)	.23
Kindler et al,[16] 2005	24	268	23	257	8.75	1.00 (0.58-1.72)	>.99
Manegold et al,[17] 2007	49	696	21	347	10.50	1.17 (0.71-1.92)	.54
Miller et al,[12] 2005	17	229	12	216	5.04	1.30 (0.64-2.67)	.47
Miller et al,[11] 2007	8	365	5	346	2.12	1.40 (0.46-4.22)	.55
Price et al,[19] 2008	24	267	9	133	4.90	1.29 (0.62-2.66)	.50
Saltz et al,[20] 2007	56	694	30	675	14.05	1.78 (1.56-2.73)	.009
Sandler et al,[10] 2006	21	427	13	441	5.73	1.67 (0.85-3.27)	.14
Overall (fixed-effects model)	356	4292	225	3664		1.33 (1.13-1.56)	<.001
Test for heterogeneity: I^2 <.01							

Nalluri et al. JAMA. 2008;300(19):2277-2285

Thromboembolism after pneumonectomy for malignancy
Cleveland Clinic Foundation report from 1990-2001

336 patients

- Incidence of postoperative VTE after pneumectomy for malignancy: **7.4 %**
- Peak incidence **within 7 days** after the operation
- Most patients had already been discharged from the hospital
- **Higher pack-years of smoking** were associated with increased risk

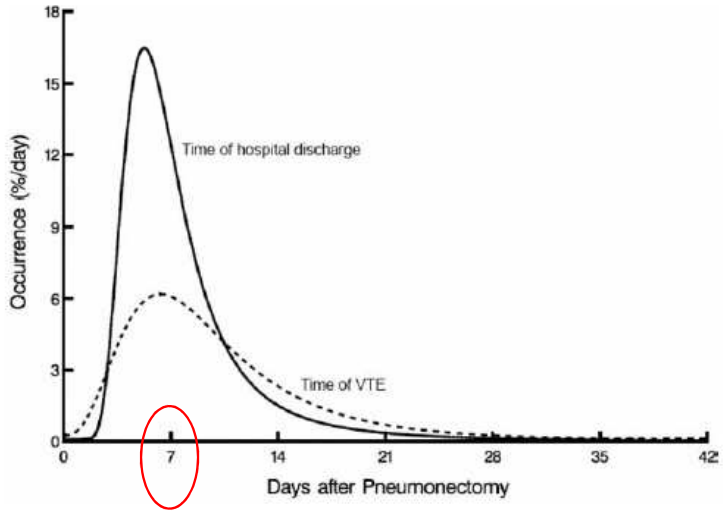


Figure 1. Timing of venous thromboembolism *(VTE)* relative to time of hospital discharge after pneumonectomy.

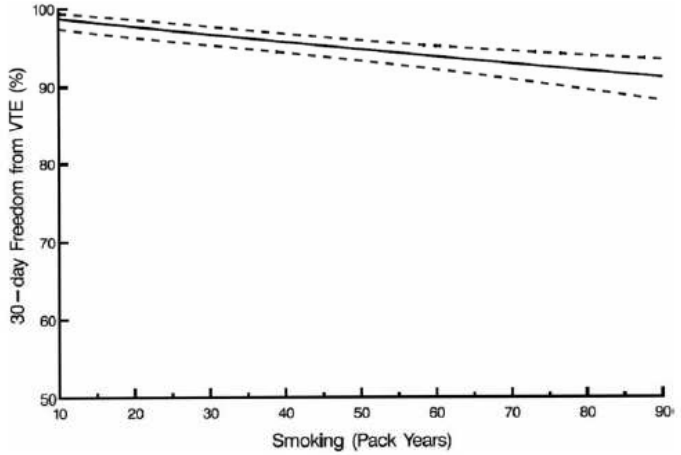


Figure 3. Freedom from venous thromboembolism *(VTE)* at 30 days after pneumonectomy for cancer according to pack-years of smoking (univariable analysis). The *solid line* is the point estimate enclosed within dashed 68% confidence limits.

Thorac Cardiovasc Surg 2006; 131 711-718

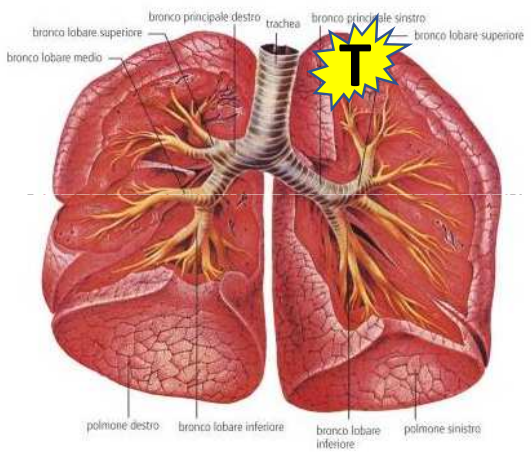
Identify the Thrombotic Burden for each LUNG cancer patient

Cancer Related

- **Histological subtype Adeno vs Squamous vs Small**
- **Stage IV**
- **Molecular Fusion ALK/ROS 1**

Patient Related

- **ECOG PS 2**
- **Medical comorbidities (≥3) (FA)**
- **Immobility for Bone and Brain mts**
- **Male sex, Younger Age, Smoking History**
- Obesity
- Presence of varicose veins
- Prior VTE
- Hereditary Thrombophilia



Treatment Related

- **Platinum-based**
- **Anti-angiogenesis agents**
- **Immunotherapy**
- **Radiotherapy**
- **TYpe of surgery, es Pneumonectomy**
- **Central venous catheter**
- **Response to treatment and Time to Treatment response**
- **Blood transfusion and Eritropoietin**

Biomarkers

D-Dimers

Hematologic (Plts, Lcytes, Hb…)

P-Selectin

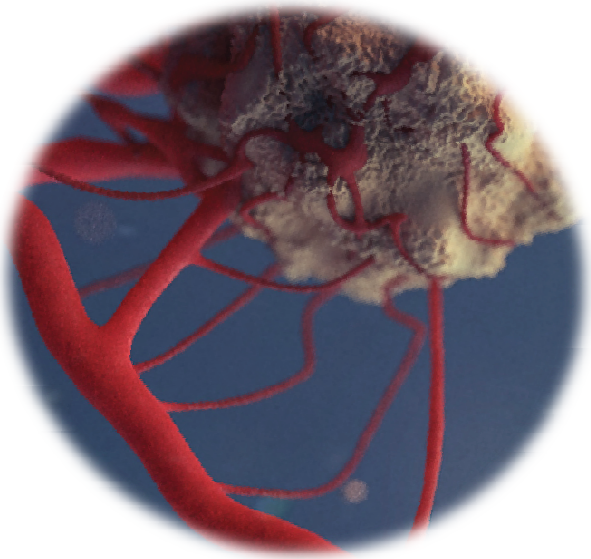
Thrombin Generation Potential

Microparticle-Tissue Factor activity

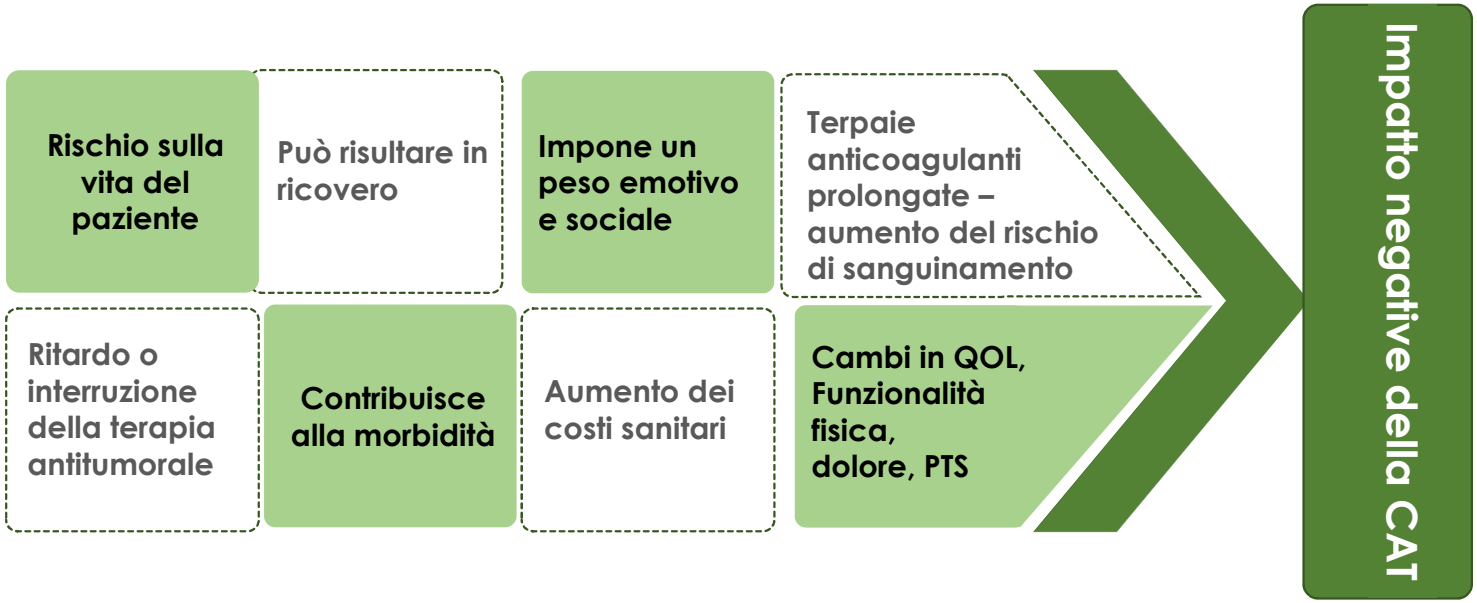
C Reactive Protein

Ay C, et al. Thromb Haemost. 2017;117: 219-230 Cancer-associated Venous Thromboembolism: Burden, Mechanisms, and Management

A chi e per quanto tempo si deve effettuare la profilassi nel tumore al polmone?



Qual è l'impatto della trombosi nei pazienti con tumore attivo?



Noble S et al: patient prefer Adherence 2015
Schaefer JK et al: JTH 2020
ECPC CAT awareness survey 2018 Noble S et al: rPTH 2019
Ambrus JL, et al. J Med. 1975;6:433-458; oncology patients

2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19

2 Primary pharmacological prophylaxis of VTE with LMWH (grade 1A) or with direct oral anticoagulants (rivaroxaban or apixaban; grade 1B) is indicated in ambulatory patients with locally advanced or metastatic pancreatic cancer treated with systemic anticancer therapy and who have a low risk of bleeding. Values and preferences: subcutaneous injections.

3 Primary pharmacological prophylaxis of VTE with LMWH is not recommended outside of a clinical trial for patients with locally advanced or metastatic lung cancer treated with systemic anticancer therapy, including patients who have a low risk of bleeding (guidance).

4 Primary prophylaxis with direct oral anticoagulant (rivaroxaban or apixaban) is recommended in ambulatory patients who are receiving systemic anticancer therapy and are at intermediate-to-high-risk of VTE, identified by a validated risk assessment model (ie, a Khorana score ≥2), and not actively bleeding or not at a high risk for bleeding (grade 1B).

ITAC Advisory Panel Lancet Oncology 2022

Prophylaxis of VTE in surgically-treated patients with cancer

International Advisory Panel ranking: 8·62 out of 9·00

1 Use of low-molecular-weight-heparin (LMWH) once per day (when creatinine clearance is ≥30 mL/min) or low-dose unfractionated heparin three times per day is recommended to prevent postoperative VTE in patients with cancer; pharmacological prophylaxis should be started 2–12 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). Values and preferences: LMWH once per day is more convenient.

2 There is insufficient evidence to support fondaparinux (grade 2C) or direct oral anticoagulants (grade 2B) as an alternative to LMWH for the prophylaxis of postoperative VTE in patients with cancer. Values and preferences: as per the first recommendation.

3 Use of the highest prophylactic dose of LMWH to prevent postoperative VTE in patients with cancer is recommended (grade 1A).

4 Extended prophylaxis (4 weeks) with LMWH to prevent postoperative VTE after major abdominal or pelvic surgery (either laparotomy or laparoscopy) is recommended in patients with cancer who do not have a high risk of bleeding (grade 1A). Values and preferences: longer duration of injections.

5 Mechanical methods are not recommended as mono-therapy except when pharmacological methods are contraindicated (grade 2A). Values and preferences: no injection.

6 Inferior vena cava filters are not recommended for routine prophylaxis (grade 1A).

Prophylaxis of VTE in medically-treated patients with cancer

International Advisory Panel ranking: 8·44 out of 9·00

1 We recommend prophylaxis with LMWH or fondaparinux when creatinine clearance is ≥30 mL/min, or with unfractionated heparin in medically-treated patients with cancer and reduced mobility who are admitted to hospital (grade 1B). In this setting, direct oral anticoagulants are not recommended routinely (guidance). Values and preferences: subcutaneous injections. Costs: in some countries, price differences between LMWH, unfractionated heparin, or fondaparinux might affect the choice.

2 Primary pharmacological prophylaxis of VTE with LMWH (grade 1A) or with direct oral anticoagulants (rivaroxaban or apixaban; grade 1B) is indicated in ambulatory patients with locally advanced or metastatic pancreatic cancer treated with systemic anticancer therapy and who have a low risk of bleeding. Values and preferences: subcutaneous injections.

3 Primary pharmacological prophylaxis of VTE with LMWH is not recommended outside of a clinical trial for patients with locally advanced or metastatic lung cancer treated with systemic anticancer therapy, including patients who have a low risk of bleeding (guidance).

4 Primary prophylaxis with direct oral anticoagulant (rivaroxaban or apixaban) is recommended in ambulatory patients who are receiving systemic anticancer therapy and are at intermediate-to-high-risk of VTE, identified by a validated risk assessment model (ie, a Khorana score ≥2), and not actively bleeding or not at a high risk for bleeding (grade 1B).

5 In patients with myeloma treated with immunomodulatory drugs combined with steroids or other systemic anticancer therapies, VTE primary pharmacological prophylaxis is recommended (grade 1A); in this setting, oral anticoagulants (vitamin K antagonists at low or therapeutic doses and apixaban at prophylactic doses), LMWH at prophylactic doses, or low-dose aspirin (100 mg daily) can be used, and have shown similar effects with regard to preventing VTE (grade 2B). Values and preferences: subcutaneous injections.

Prophylaxis of catheter-related thrombosis

International Advisory Panel ranking: 8·52 out of 9·00

1 Use of anticoagulation for routine prophylaxis of catheter-related thrombosis is not recommended (grade 1A). Values and preferences: bleeding risk with anticoagulants.

2 Catheters should be inserted on the right side, in the jugular vein, and the distal extremity of the central catheter should be located at the junction of the superior vena cava and the right atrium (grade 1B).

3 In patients requiring central venous catheters, we suggest the use of implanted ports over peripherally inserted central catheter lines (guidance).

AIOM recommendations

GRADE Quesito 6: ***Nei pazienti ambulatoriali con tumori solidi selezionati per l'elevato rischio tromboembolico, la profilassi antitrombotica deve essere considerata in tutti i pazienti che ricevono un trattamento chemioterapico?***
RACCOMANDAZIONE: **Nei pazienti ambulatoriali con tumori solidi selezionati per l'elevato rischio tromboembolico, che ricevono un trattamento chemioterapico, la profilassi primaria può essere presa in considerazione sia con EBPM che con apixaban o rivaroxaban**

GRADE Quesito 8: ***Nei pazienti ospedalizzati l'utilizzo della profilassi primaria con anticoagulanti dovrebbe essere preso in considerazione?***
RACCOMANDAZIONE: Nei pazienti oncologici ospedalizzati per una problematica medica e/o allettati, l'utilizzo della profilassi primaria con anticoagulanti (EBPM, Fondaparinux) dovrebbe essere presa in considerazione come prima opzione terapeutica

VTE is an independent risk for Mortality

Table 1. Clinical Risk Score

Factor	Risk score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count ≥350,000/mm^3	1
Prechemotherapy leukocyte count >11,000/mm^3	1
Hemoglobin level <10 g/dL or use of red cell growth factors	1
Body mass index ≥35 kg/m^2	1

Cumulative score: high risk, ≥3; intermediate risk, 1–2; low risk, 0.

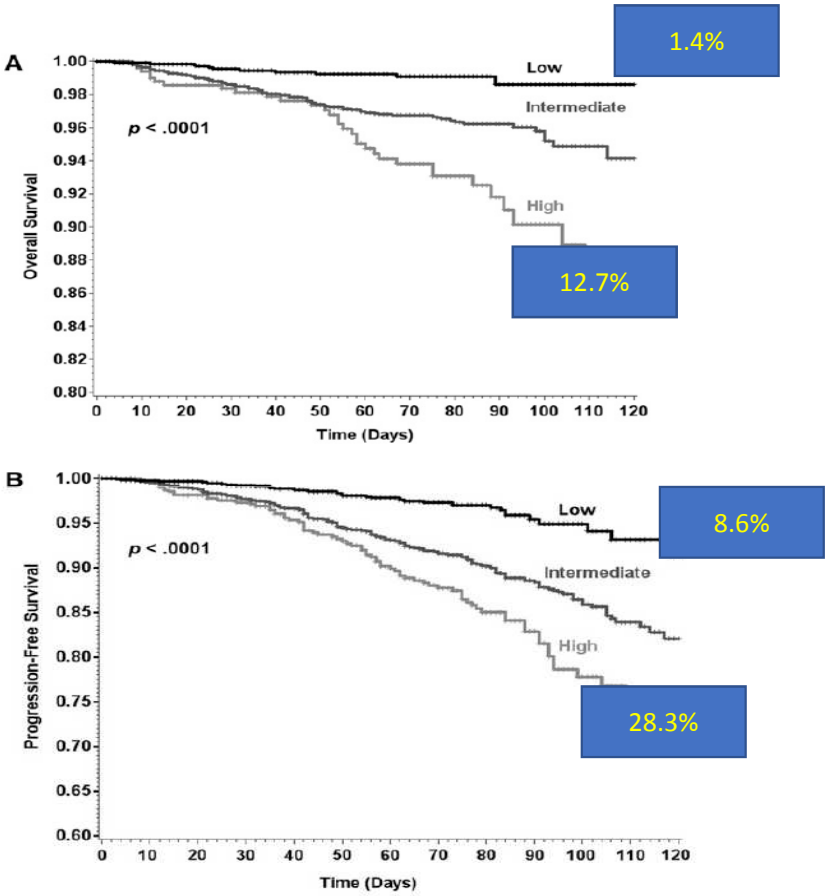


Figure 2. Kaplan-Meier analysis of overall and progression-free survival according to Clinical Risk Score group. **(A):** Overall survival. **(B):** Progression-free survival. Patients with intermediate or high risk based on Clinical Risk Score stratification were found to have worse prognosis than low-risk patients ($p < .0001$ for both).

The clinical risk score predict VTE, early mortality and cancer progression

BUT lung cancer pts little represented and No difference for type of tumor stage and treatment

RAMs: Risk Assessment Models

Hypercan Score in Lung cancer

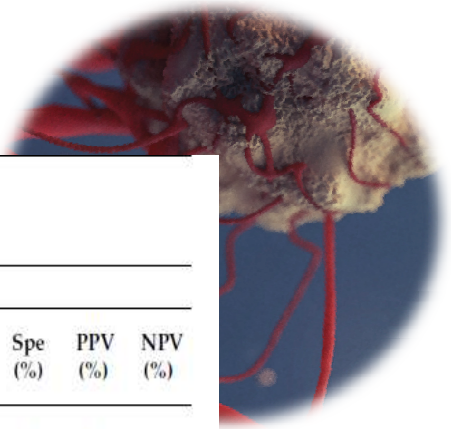


Table 4. Cumulative incidence of VTE and death, and accuracy of RAMs.

RAM	Risk Category	6-Month VTE: Cumulative Incidence (95% CI)	6-Month VTE: Log-Rank (*p*-Value)	6-Month VTE: ROC AUC (*p*-Value)	6-Month VTE: Sen (%)	6-Month VTE: Spe (%)	6-Month VTE: PPV (%)	6-Month VTE: NPV (%)	6-Month Death: Cumulative Incidence (95% CI)	6-Month Death: Log-Rank (*p*-Value)	6-Month Death: ROC AUC (*p*-Value)	6-Month Death: Sen (%)	6-Month Death: Spe (%)	6-Month Death: PPV (%)	6-Month Death: NPV (%)
HYPERCAN • D-dimer/ECOG 2	Low High	6 (4–10) 25 (24–42)	< 0.001	0.734 (<0.001)	63	74	25	93	19 (15–23) 55 (47–63)	<0.001	0.726 (<0.001)	56	80	55	81
KRS • Cancer site/BMI ≥ 35 kg/m^2 • Hemoglobin < 100g/L • Platelet > 350 × 10^9/L • Leukocyte > 11 × 10^9/L	Low Int-High	11 (9–15) 16 (9–30)	0.089	0.543 (0.290)	21	86	16	89	26 (22–30) 49 (39–62)	<0.001	0.609 (<0.001)	25	89	49	74
New-Vienna CATS * • Cancer site/D-dimer	Low-Int High	9 (5–13) 14 (12–22)	0.008	0.642 (0.001)	70	43	14	92	15 (11–20) 40 (35–46)	<0.001	0.670 (<0.001)	79	50	40	85
PROTECHT • Cancer site/BMI ≥ 35kg/m^2 • Hemoglobin < 100g/L • Platelet > 350 × 10^9/L • Leukocyte > 11 × 10^9/L • Gemcitabine/Platinum	Low-Int High	11 (8–17) 12 (9–18)	0.730	0.527 (0.504)	59	42	12	89	24 (18–30) 34 (29–40)	0.012	0.584 (0.002)	66	46	34	76
CONKO • Cancer site/WHO ≥ 2 • Hemoglobin < 100g/L • Platelet > 350 × 10^9/L • Leukocyte > 11 × 10^9/L	Int High	10 (8–14) 19 (13–36)	0.004	0.558 (0.156)	26	85	19	90	25 (21–29) 57 (48–69)	<0.001	0.647 (<0.001)	31	90	56	75

Data shows the cumulative incidence of VTE and death of the five RAMs at different risk stratification. The accuracy of the RAMs by ROC curve and the sensibility, specificity, PPV, and NPV. RAM: risk assessment model; VTE: venous thromboembolism; HYPERCAN: hypercoagulation in cancer; KRS: Khorana risk score; BMI: body mass index; WHO: World Health Organization; ROC: receiver operating characteristics; AUC: area under the curve; Sen: sensitivity, Spe: specificity; PPV: positive predictive value; NPV: negative predictive value; Int: intermediate. * The New-Vienna CATS score set at a VTE cumulative incidence of 10%.

Cancers 2023, 15, 4588. https://doi.org/10.3390/cancers15184588

scientific reports

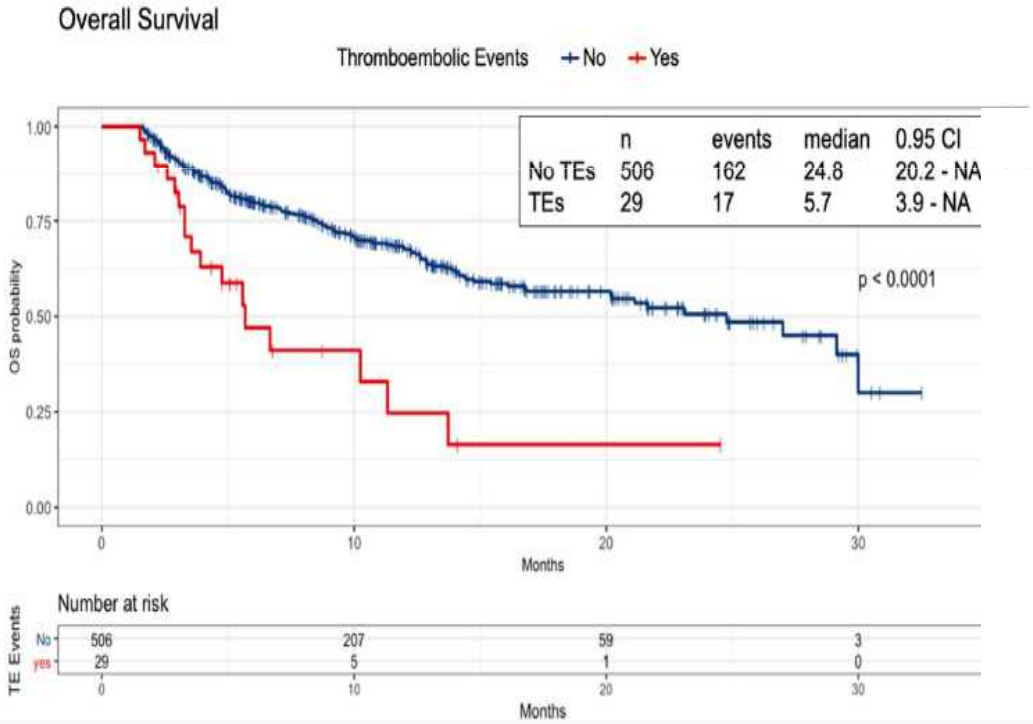
Check for updates

OPEN

Risk assessment of thromboembolic events in hospitalized cancer patients

Federico Nichetti[1,2], Francesca Ligorio[1], Giulia Montelatici[1], Luca Porcu[3], Emma Zattarin[1], Leonardo Provenzano[1], Andrea Franza[1], Luca Lalli[4], Filippo de Braud[1,5] & Marco Platania[1]

- 535 enrolled patients (122 Lung)
- 153 KS =0
- TEs in 7 (4.6%) KS 0
- 27.6% of TEs in Lung Cancer pts



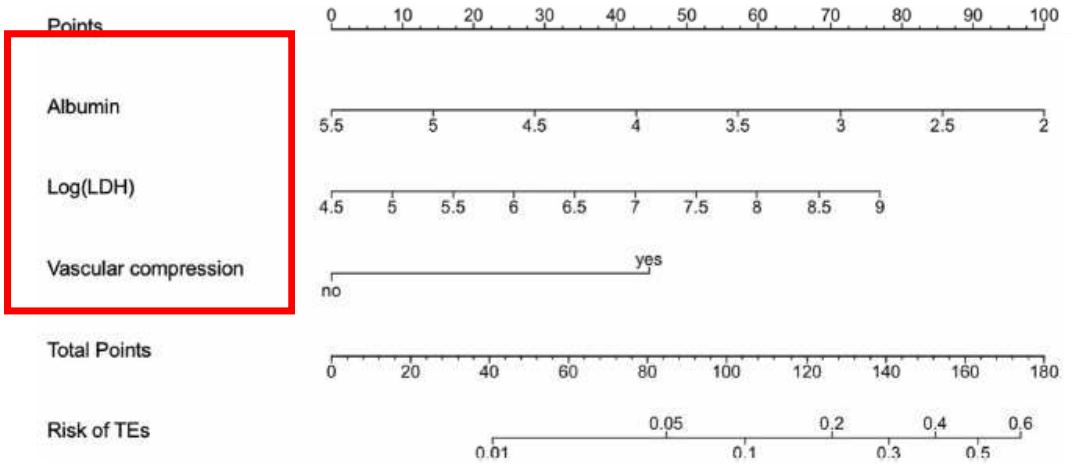
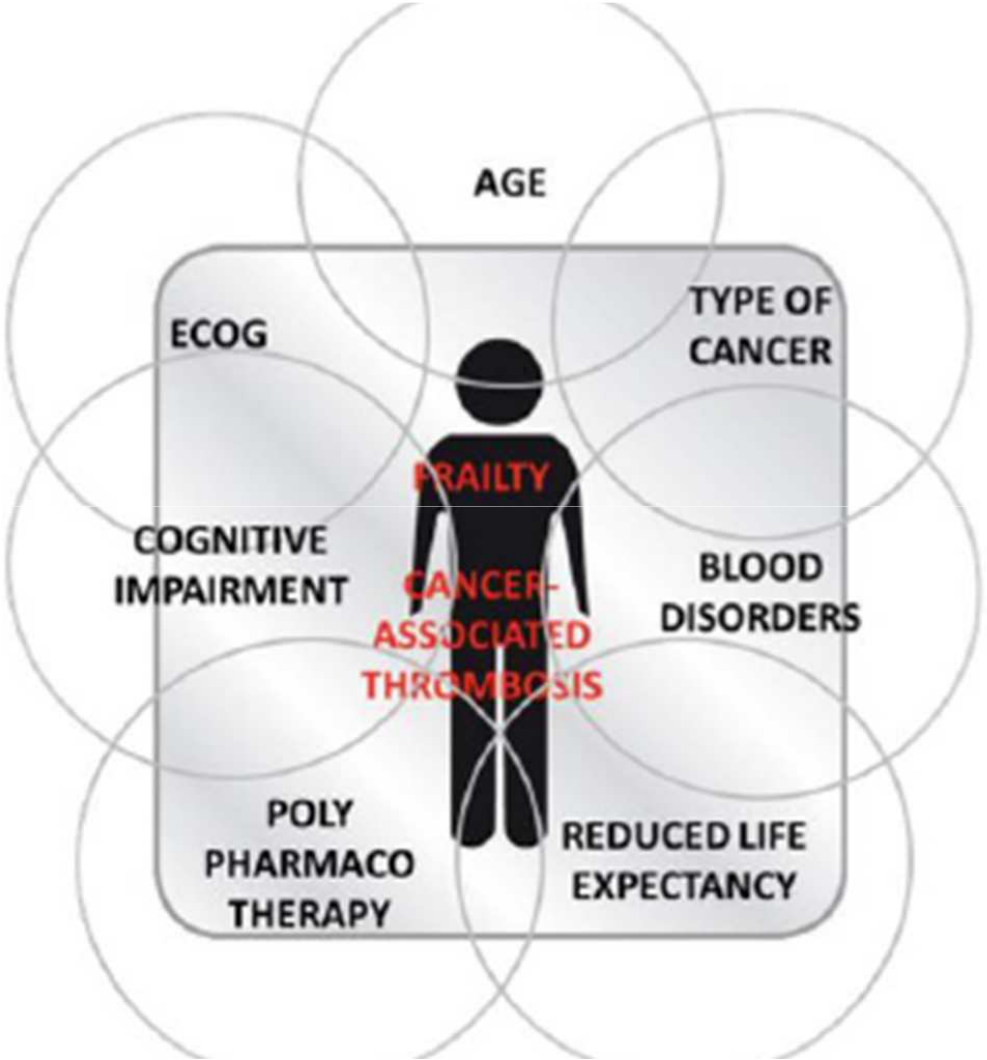


Figure 2. Nomogram predicting the probability of developing a TE during hospitalization and in the next 45 days after discharge. *Log(LDH)* natural logarithm lactate dehydrogenase, *TEs* thromboembolic events.

How confident are we managing thrombosis in patients with Lung cancer ?

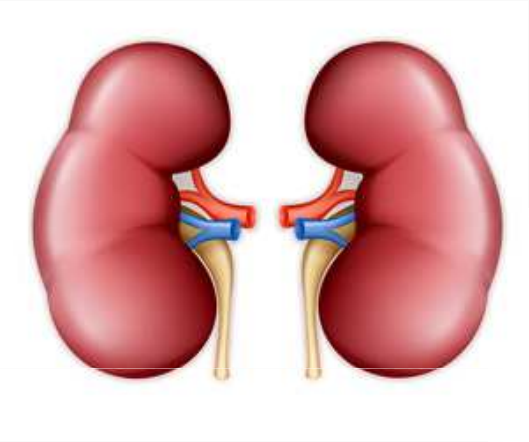
50% pts are elderly and frail

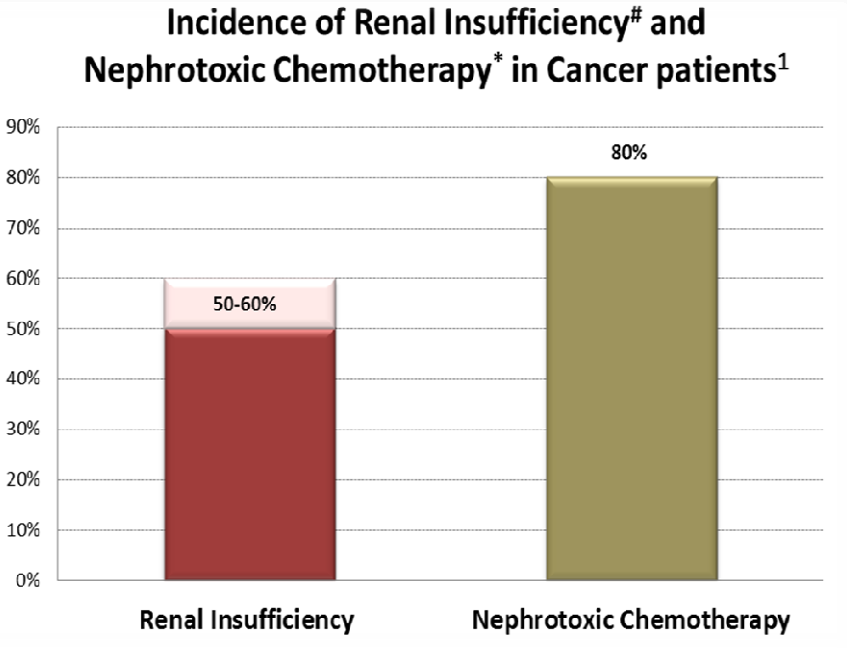


Cancer patients experience frequent Renal Impairment caused by age and use of nephrotoxic chemotherapy

80% of cancer patients receive nephrotoxic anti-cancer agents , such as:

- Classic cytotoxic drugs (eg. cisplatin)
- Modern anti-cancer agents
- ABs
- TKIs
- mTOR inhibitors
- Androgen deprivation therapy





Atrial Fibrillation and Risk of Cancer: A Danish Population-Based Cohort Study, Volume: 7, Issue: 17, DOI: (10.1161/JAHA.118.009543)
Esc.cardio guidelines 2016

Cancer-therapy–specific inhibitors and inducers of CYP3A4 and P-glycoprotein

Cancer-related therapies	Cytochrome p450 CYP3A4	P-glycoprotein
Anthracyclines		
Doxorubicin	↓	↑
Idarubicin	↓	
Antimycotic agents		
Vinblastine	↓	↑
Vincristine	↓	
Vinorelbine	↓	
Paclitaxel	↑	
Topoisomerase inhibitors		
Topotecan	↓	
Etoposide	↓	↑
Alkylating agents		
Cyclophosphamide	↓	
Ifosfamide	↓	
Lomustine	↓	

Cancer-related therapies	Cytochrome p450 CYP3A4	P-glycoprotein
Tyrosine kinase inhibitors		
Afatinib		↓
Alectinib		↓
Ceritinib	↓	
Crizotinib	↓	↓
Dasatinib	↓	
Ibrutinib		↓
Idelalisib	↓	↓
Imatinib	↓	↓
Lapatinib	↓	↓
Nilotinib	↓	↓
Osimertinib	↓	
Vemurafenib	↑	↓
Lenvatinib	↑	↑
Sunitinib		↓
Vandetanib		↓

Blood. 2019;133(4):291-298

Others possible drug to drug interactions with:

Category	Agent	CYP3A4 Interactions	P-gp Interactions
Bisphosphonates and Denosumab	Zoledronic acid	No	No
	Denosumab	No	No
Antiemetics	Ondansetron	Substrate	Substrate
	Palonosetron	Substrate	No
	Metoclopramide	No	No
	Aprepitant	Moderate inhibitor and substrate	No
	Fosaprepitant	Moderate inhibitor and substrate	No
Analgesics and anxiolytics	Oxycodone	Substrate	No
	Hydromorphone	No	No
	Morphine	No	No
	Fentanyl	Weak inhibitor and substrate	No
	Paracetamol	Weak inhibitor and substrate	No
	Lorazepam	No	No
	Clonazepam	Substrate	No
G-CSF	Filgrastim	No	No
ESA	Epoetin alfa/beta	No	No
	Darbepoetin alfa	No	No
Corticosteroids	Dexamethasone	Strong inducer and substrate	No
	Prednisolone	Moderate inducer and substrate	Inhibitor and Substrate

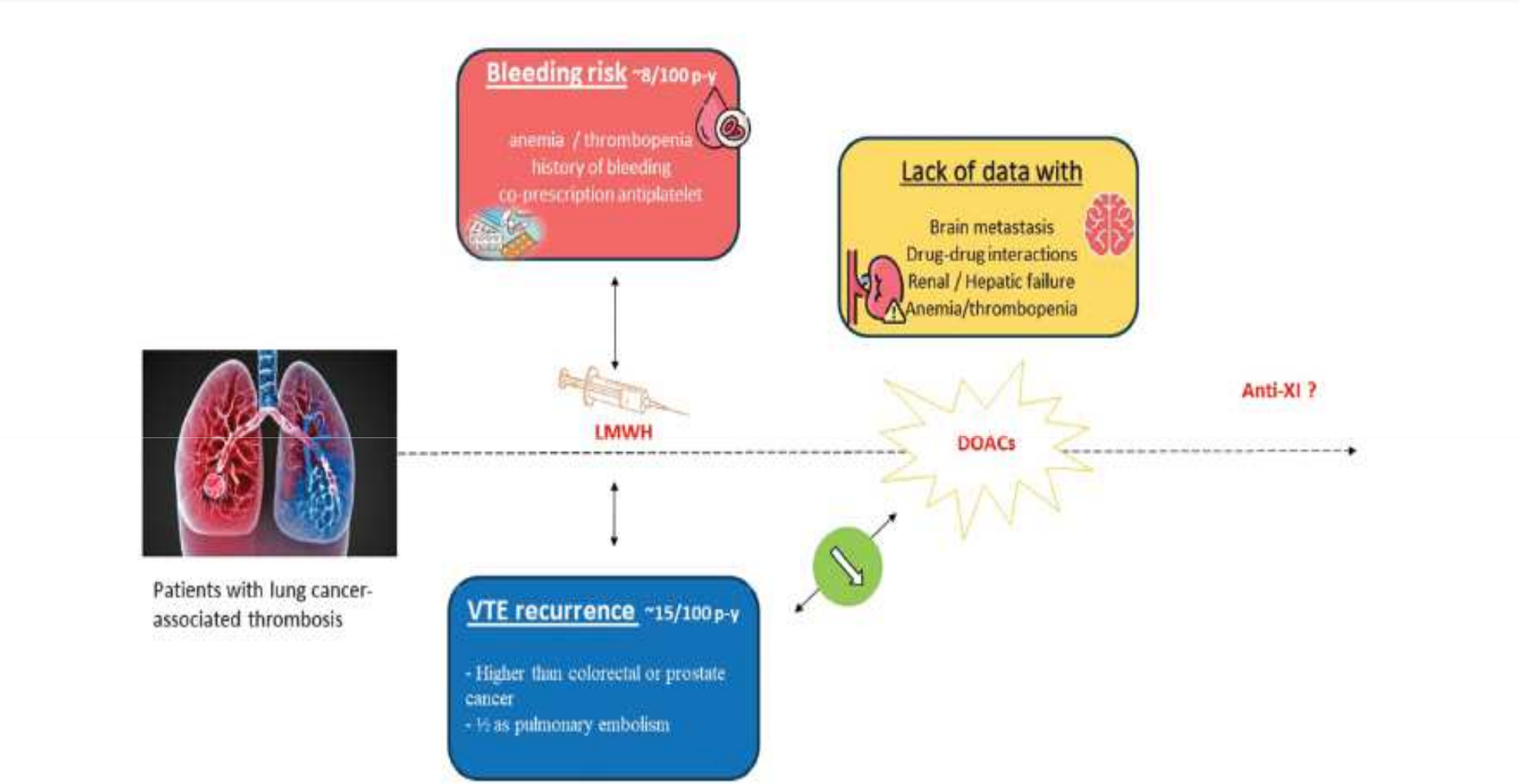
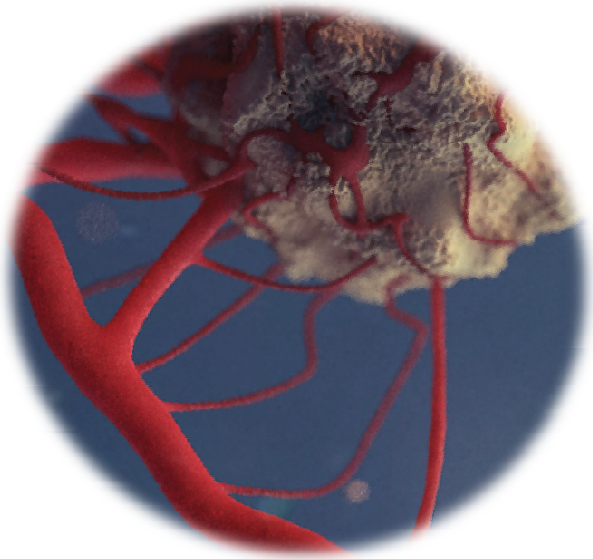


Figure 1. Particularities of Lung-associated thrombosis according to anticoagulant regimen.

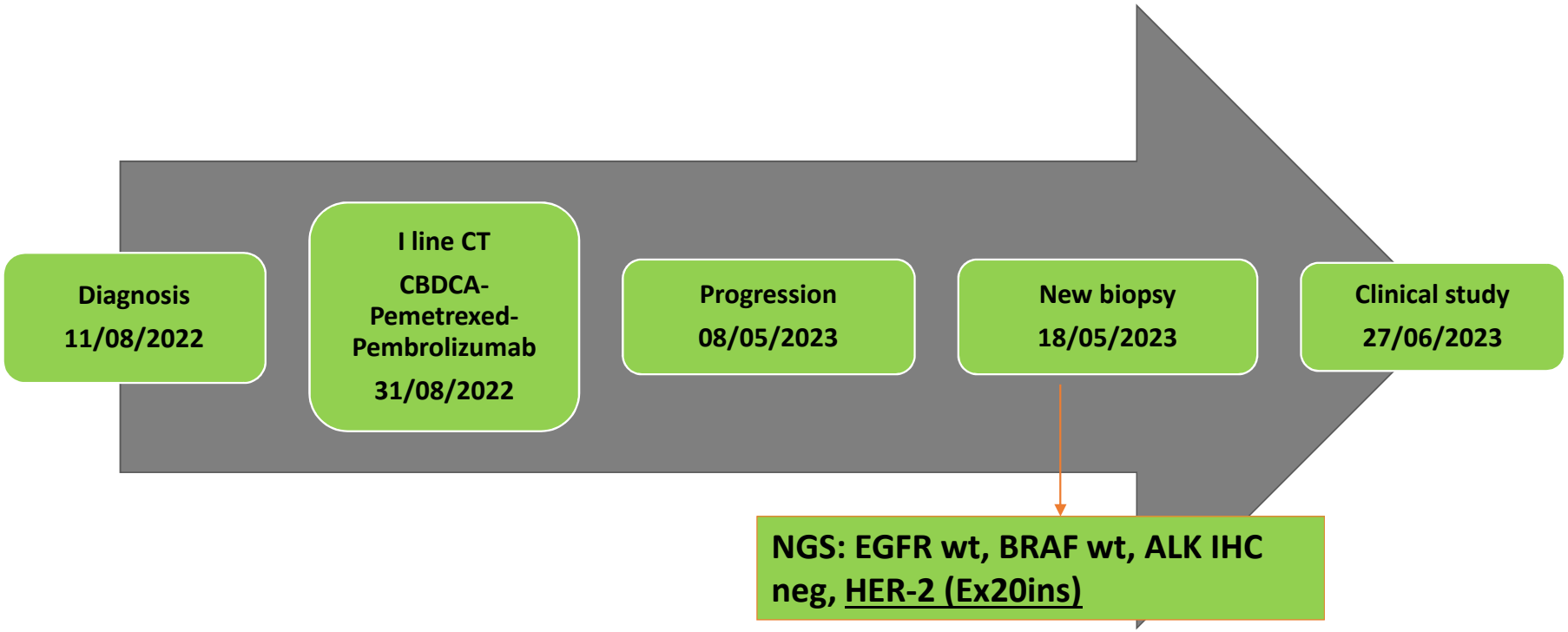
Case report



Case report

At diagnosis
Male, 69 y
NSCLC adenocarcinoma (IVb)
Non-smoker
PD-L1 < 1%. Non oncogene addicted

Concomitant drugs:
Bisoprololo 5mg
Famotidina 40mg
Deltacortene 12,5 mg
Bactrim 160/80 mg



Case report

II line therapy with a new drug
HER2 and EGFR blocker

21/06/2023

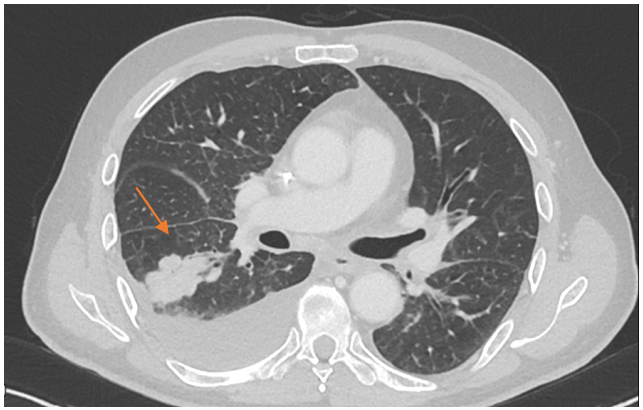
Baseline
Khorana Score 1

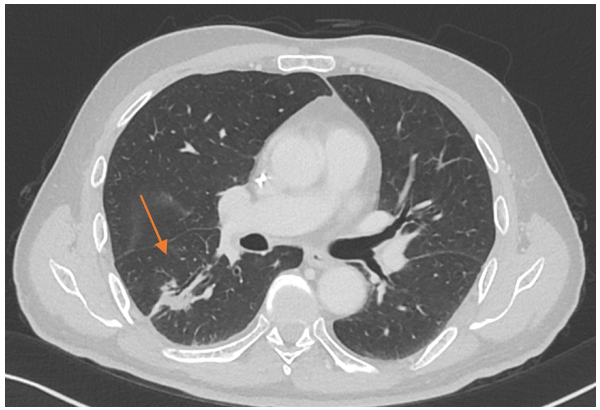
15/12/2023

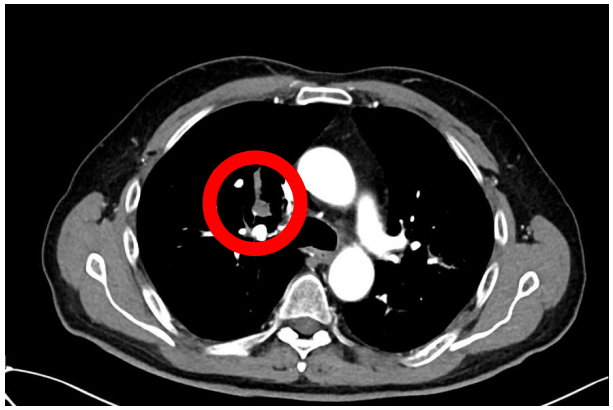
BR
Khorana Score 1

23/04/2024

Progression, thrombosis,
Drug toxicity
Khorana Score 1
HYPERCAN Score 4

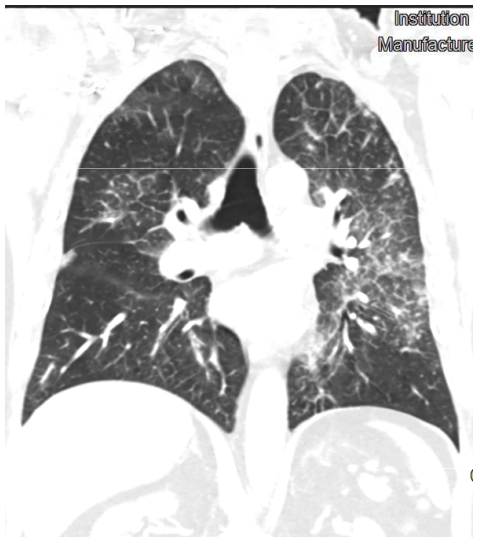


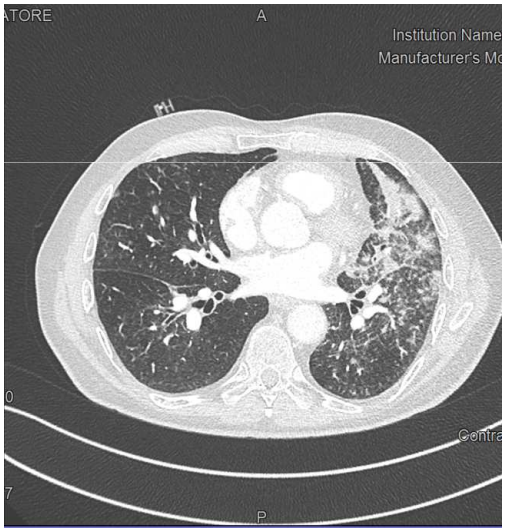




Case report

Hospitalized
Severe respiratory failure due to Concomitant
TEP and Progression disease
Grade 3 Hepatic drug toxicity





DOAC

EPARIN

No epatic metabolism

HFNC

Hospitalization

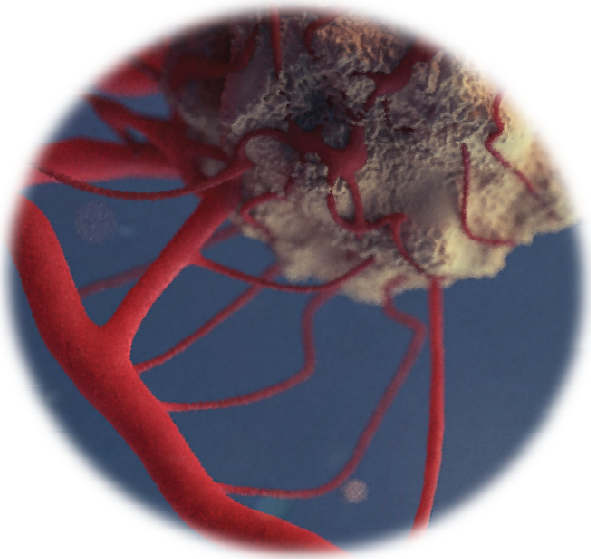
compliance

Tumore al Pancreas e trombosi : quale è la relazione?

Marco Platania

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

Esistono dei fattori di rischio particolari per il tumore al pancreas?



What's to know about *Pancreatic cancer*?

- **Pancreatic cancer is the seventh leading cause of cancer deaths worldwide, 5y OS <10%**
- **Only 20% presents with *potentially resectable* localized disease**
  Hard to diagnose before it is too late for surgery
- Even when resectable at diagnosis, **surgery is rarely curative**
- There is an urgent need to **improve quality of life by integrating best supportive care**

Ironically, Trousseau died of **pancreatic** 6 months after writing to his student, Peter, on January 1st, 1867

"I am lost . . . the phlebitis that has just appeared tonight leaves me no doubt as to the nature of my illness"

Review Article

Pancreatic cancer and thromboembolic disease, 150 years after Trousseau

David Ansari[1], Daniel Ansari[2], Roland Andersson[2], Åke Andrén-Sandberg[3]

[1]Department of Cardiothoracic Surgery, [2]Department of Surgery, Clinical Sciences Lund, Lund University, Skåne University Hospital, Lund, Sweden; [3]Division of Surgery, CLINTEC, Karolinska Institutet at Department of Surgical Gastroenterology, Karolinska University Hospital, Stockholm, Sweden

Correspondence to: David Ansari, MD. Department of Cardiothoracic Surgery, Clinical Sciences Lund, Lund University, Skåne University Hospital, Lund, Sweden. Email: david.ansari@med.lu.se.

HepatoBiliary Surgery and Nutrition, Vol 4, No 5 October 2015

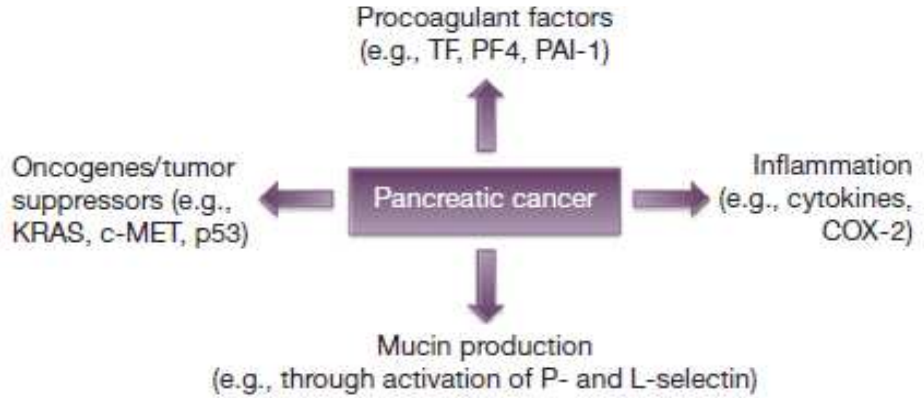
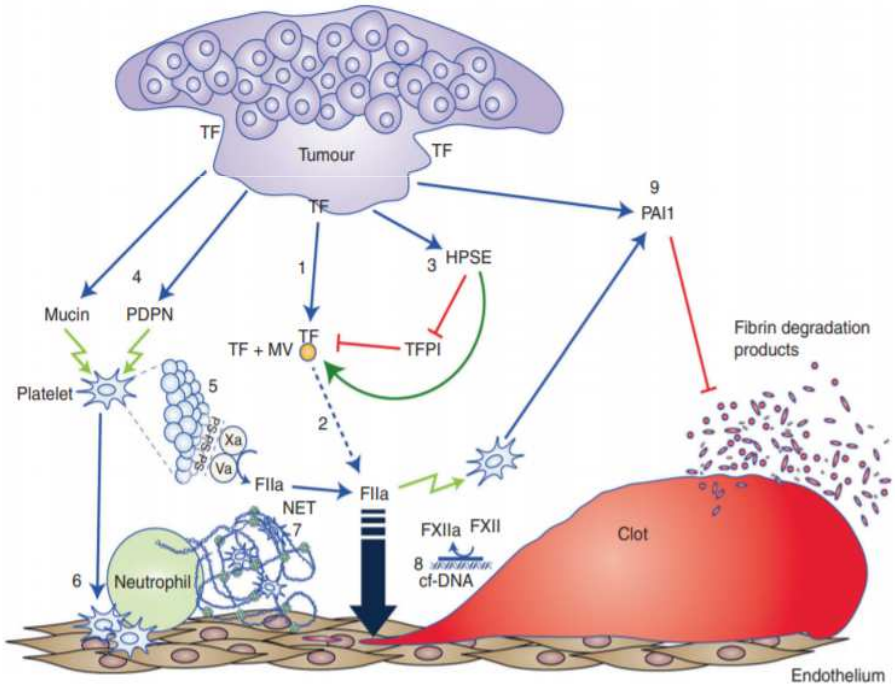
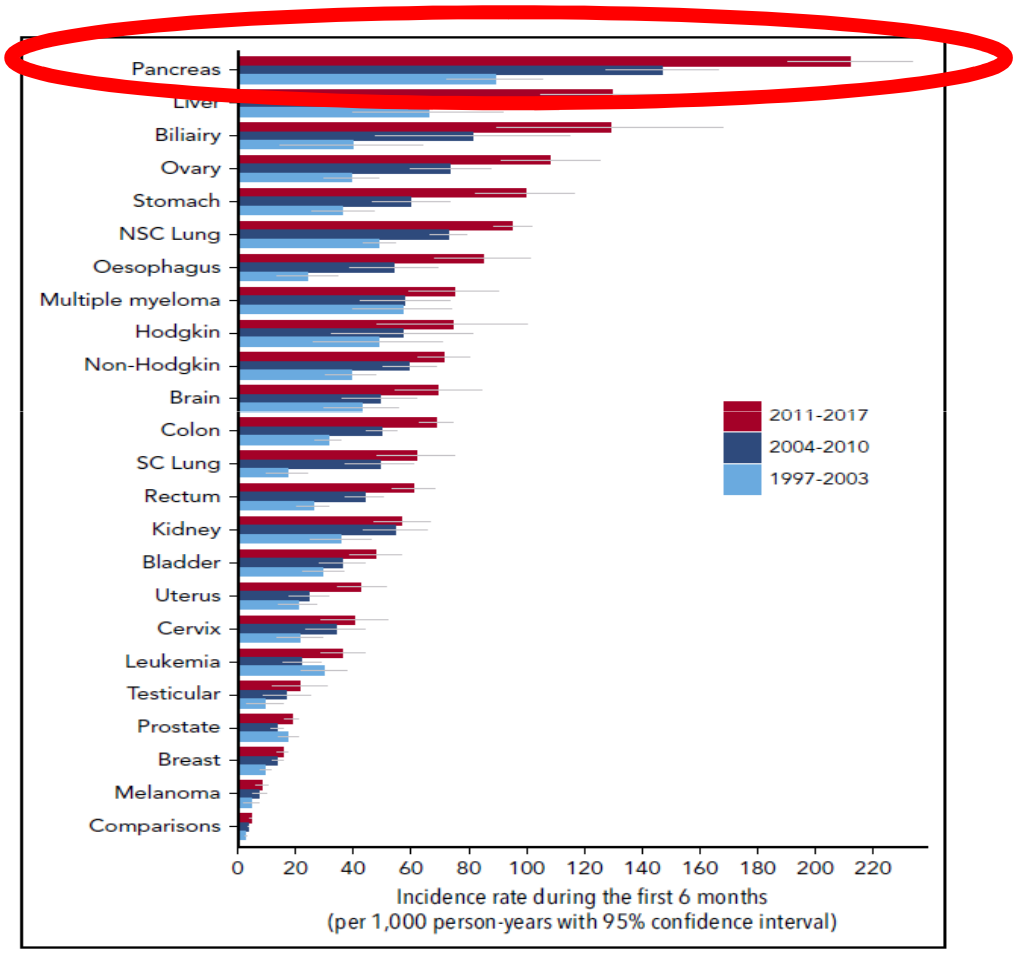


Figure 1 Schematic representation of potential mechanisms involved in the prothrombotic state in pancreatic cancer.



from British Journal of Cancer (2019) 121:359–37

Pancreatic cancers among the top 10 with the highest rate of VTE out of 18 cancers
(the most prothrombotic neoplasms, please note the progressive significant increase over the time)



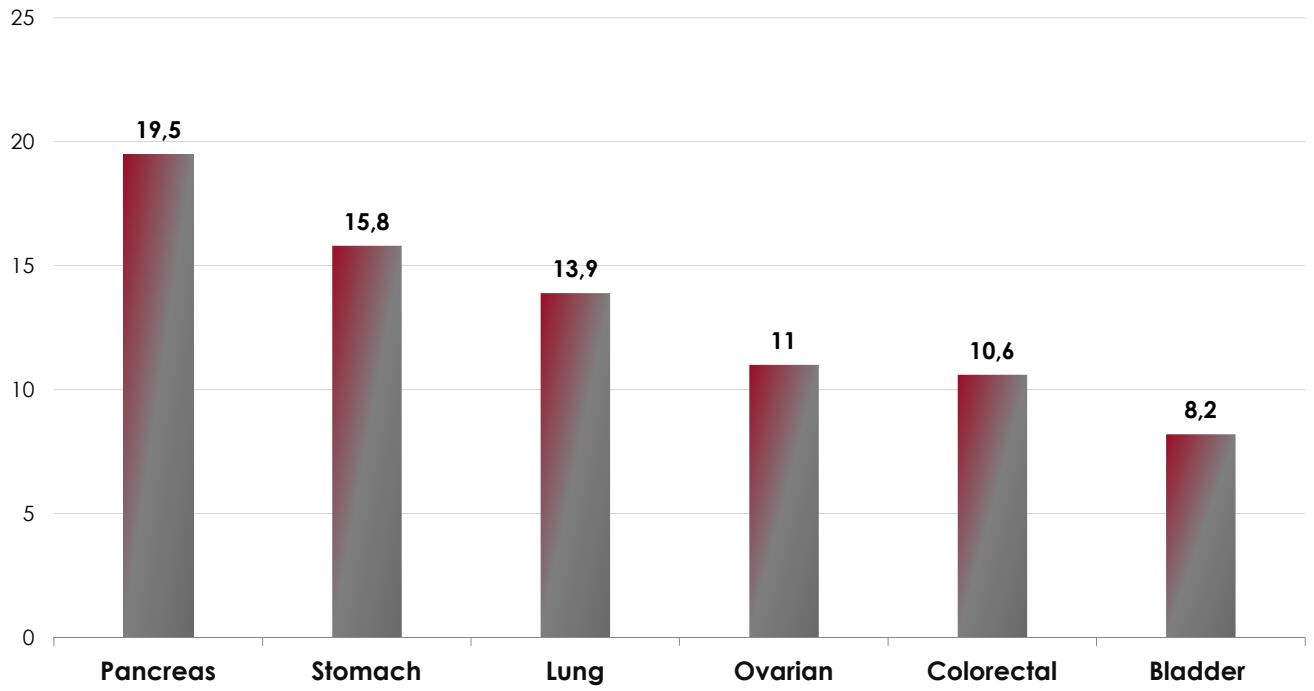
2021 Blood VTE in cancer patients – A population-based cohort study

Review of >1.2 million Medicare patients with malignancy

Cancer	Rate of DVT/PE Per 10,000 patients	Rank out of 18 malignancies
Pancreas	110	3
Stomach	85	5
Colon	76	8
Liver	69	9
Rectal	62	10
Esophagus	43	15

Medicine (Baltimore), 78:285–291, 1999

VTE risk is considerably increased in specific cancer types – pancreas almost 20% but… Great variability from PDAC Borderline operable to inoperably to ADVANCED and Incidentally versus Symtomatic



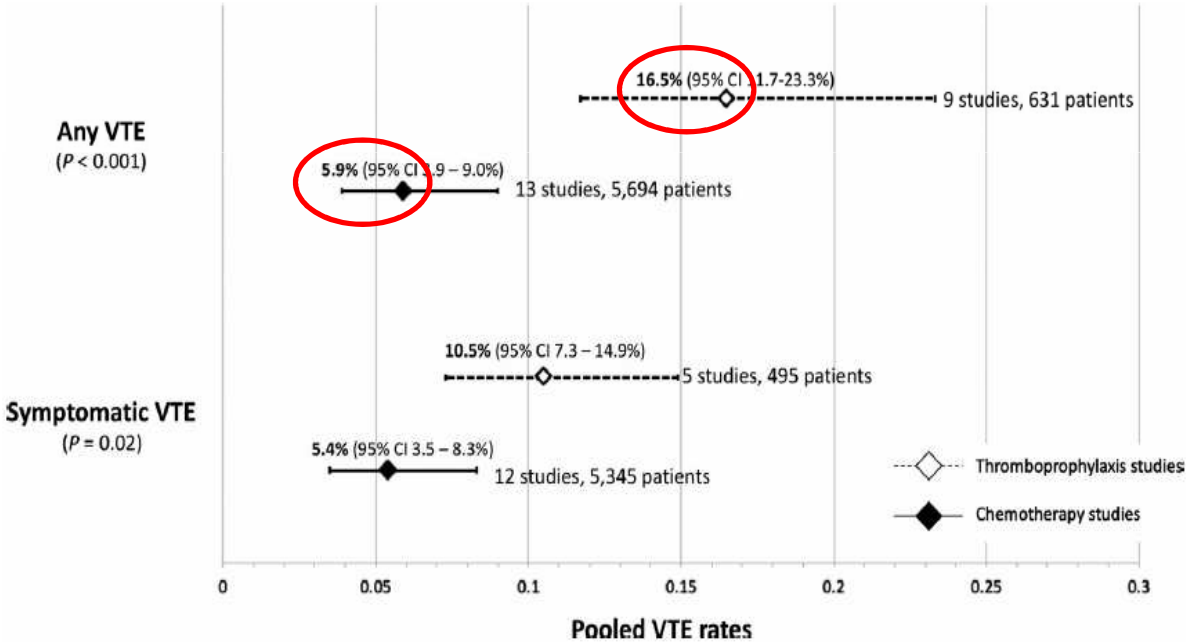
ORIGINAL ARTICLE

Discordant reporting of VTE in pancreatic cancer: A systematic review and meta-analysis of thromboprophylaxis versus chemotherapeutic trials

Thita Chiasakul[1,2] | Rushad Patell[2] | Anthony Maraveyas[3] | Marc Carrier[3,4] | Jeffrey I. Zwicker[2]

Essentials

- Venous thromboembolism (VTE) incidence is inconsistently reported in pancreatic cancer trials.
- Thrombotic events in clinical trials with different objectives were analyzed.
- VTE rate is significantly lower in chemotherapy than in thromboprophylaxis clinical trials.
- Standardized monitoring and reporting of thrombosis in chemotherapy clinical trials is needed.

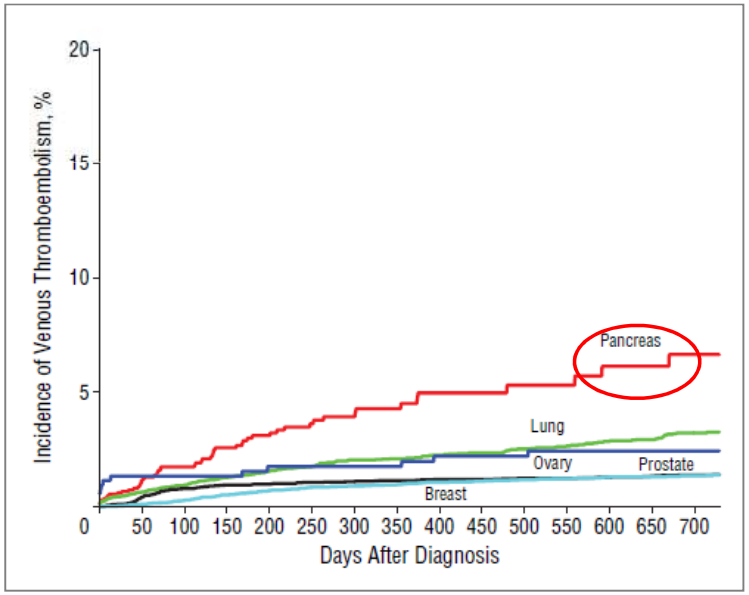


Comparison of pooled VTE rates from thromboprophylaxis studies compared with chemotherapy studies in pancrea venous thromboembolism

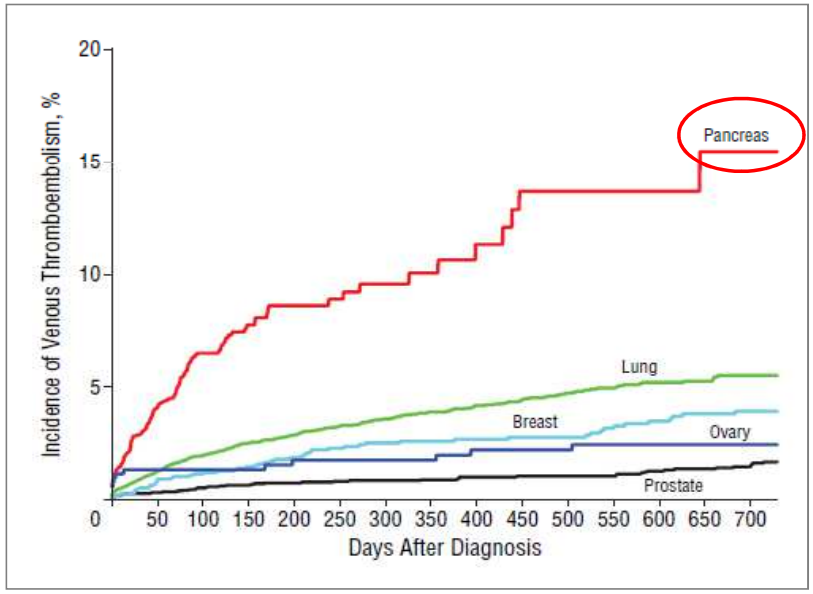
VTE in metastatic Pancreatic Cancer ,data from California Registry
20 events per 100 patients-years

Incidence of VTE within 2 years of diagnosis of 5 different types of cancer (235.149 cancer cases), 3775pts (1.9%) of whom 12% at diagnosis sand 88% subsequently

VTE strong predictor of death during first year



Incidence of VTE within 2 years of diagnosis among patients with locoregional disease



Incidence of VTE within 2 years of diagnosis among patients with metastatic disease

California Cancer Registry. Arch Intern Med. 2006;166:458-464

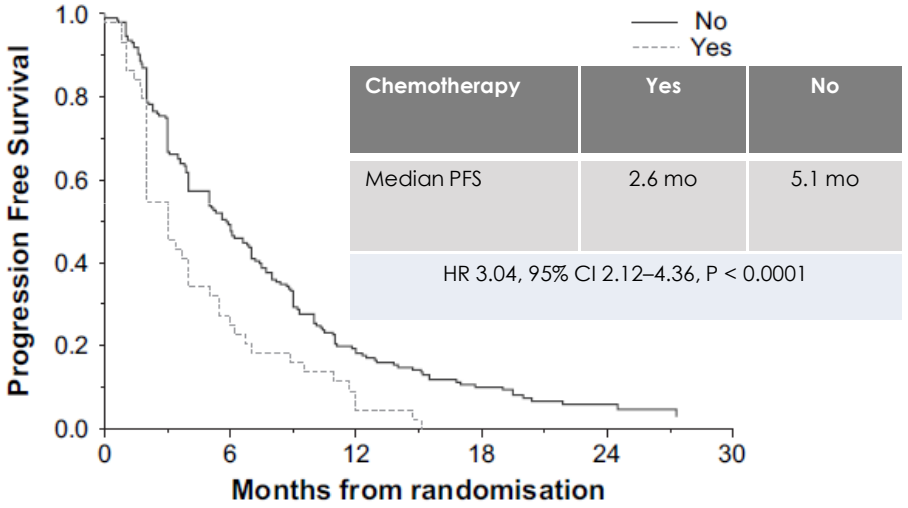
original article

Annals of Oncology 18: 1660–1665, 2007
doi:10.1093/annonc/mdm284
Published online 28 July 2007

Venous thromboembolism predicts poor prognosis in irresectable pancreatic cancer patients

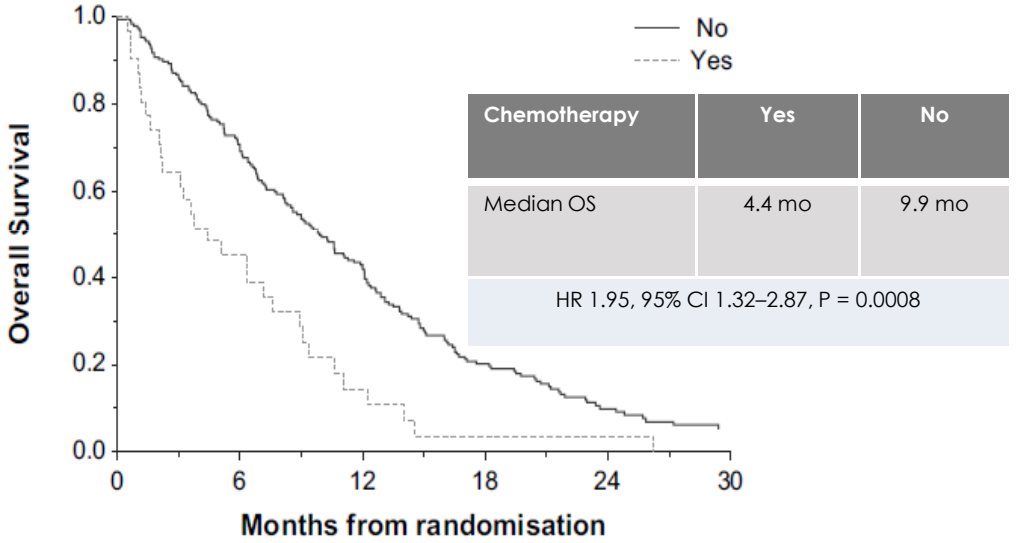
M. Mandalà[1]*, M. Reni[2], S. Cascinu[3], S. Barni[4], I. Floriani[5], S. Cereda[2], R. Berardi[3], S. Mosconi[1], V. Torri[5] & R. Labianca[1]

227 patients locally advanced or metastatic pancreatic cancer with gemcitabine-based chemotherapy



Chemotherapy	Yes	No
Median PFS	2.6 mo	5.1 mo
HR 3.04, 95% CI 2.12–4.36, P < 0.0001		

Patients with occurrence of VTE during chemotherapy had significantly worse PFS vs patients without (median PFS 2.6 vs 5.1 months; HR 3.04, 95% CI 2.12–4.36, P < 0.0001).

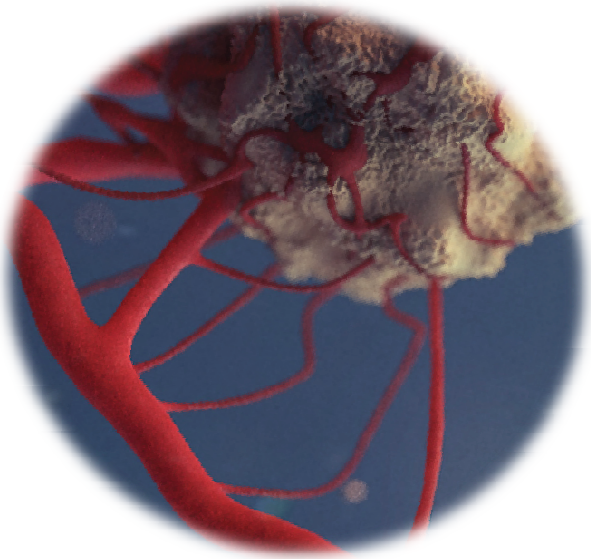


Chemotherapy	Yes	No
Median OS	4.4 mo	9.9 mo
HR 1.95, 95% CI 1.32–2.87, P = 0.0008		

Patients with occurrence of VTE during chemotherapy had significantly worse OS vs patients without (median OS 4.4 vs 9.9 months; HR 1.95, 95% CI 1.32–2.87, P = 0.0008).

Patients with VTE during chemotherapy had significantly worse PFS & OS, but also was a Negative Predictor Factor to response

Esistono dei fattori di rischio particolari per il tumore al pancreas?

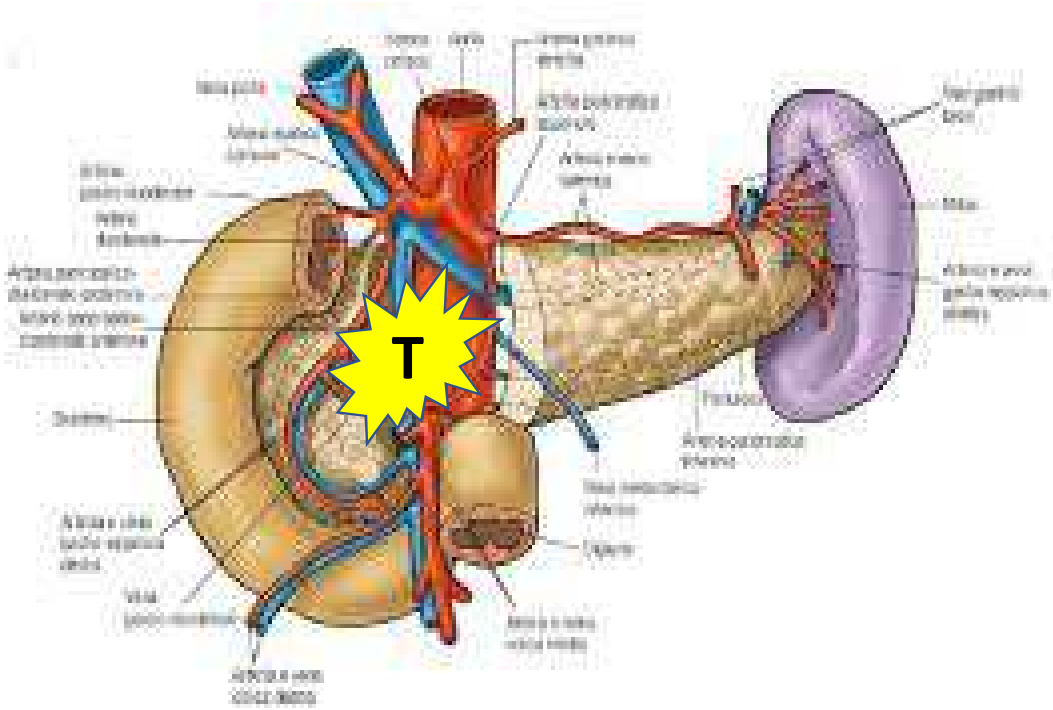


Gastroenterology 2020;158:1346–1358

CLINICAL—PANCREAS

Incidence of Venous Thromboembolism in Patients With Newly Diagnosed Pancreatic Cancer and Factors Associated With Outcomes

Corinne Frere,[1,2,*] **Barbara Bournet**,[3,4,*] Sophie Gourgou,[5] Julien Fraisse,[5] Cindy Canivet,[3,4] Jean M. Connors,[6,7] Louis Buscail,[3,4,§] and Dominique Farge,[8,9,10,§] and the BACAP Consortium



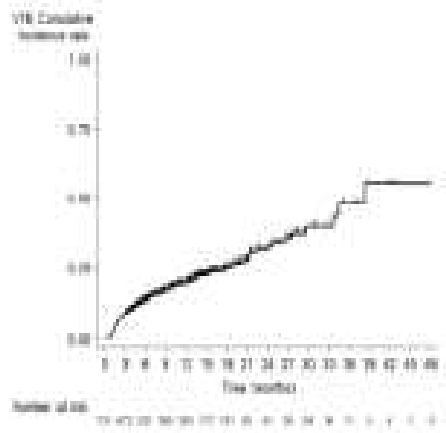
BACAP study, 78:285–291, 1999

- 152 pts/731 (20.79%) developed a VTE, Median Follow time 19.3 months
- Cumulative incidence values of VTE were 8.0% at 3 months and 19.21% at 12 months, MEDIAN TIME 4.49 mts
- DVT, PE, VVT and combined events were 26%,17%,30% and 21%. Overall 46% symptomatic and 54% asymptomatic
- PDAC primary location Isthmus versus head and stage LAD vs Resectable, metastatic vs resectable were indipendent factors for the inset of VTE
- Patients who developed VTE had shorter PFS and OS

Venous Thromboembolism and Pancreatic Cancer

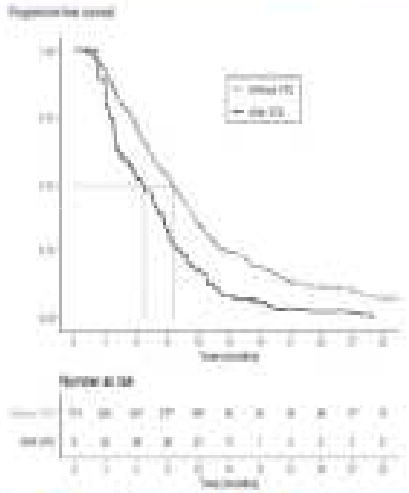
The BACAP-VTE Study : 731 pancreatic cancer patients prospectively followed-up from time of enrollment until last visit or death

Cumulative Incidence of VTE



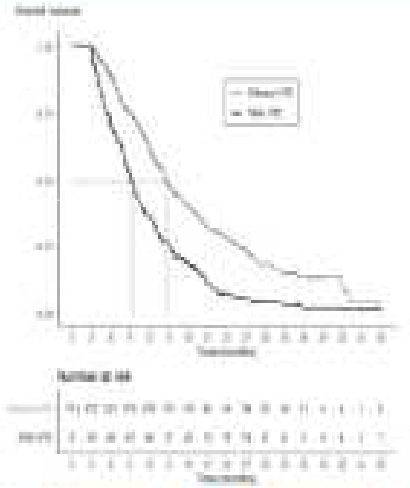
152 patients (20.79%) developed a VTE during a median follow-up of 13.3 months

Progression Free Survival



Patients developing VTE during follow-up had lower PFS (HR 1.74, 95%CI 1.19-2.54, P=.004)

Overall Survival



Patients developing VTE during follow-up had lower OS (HR 2.02, 95%CI 1.57-2.60, P<.001).

Abbreviations : VTE, Venous Thromboembolism; PFS, progression free survival; OS, overall survival; HR, Hazard Ratio

- PFS 6.66 VTE + vs 9.56 VTE-
- OS 9.13 VTE + vs 14.56 VTE-

Venous Thromboembolism

Risk factors	No. of events/No. of patients		HR (95% CI)
	Yes	No	
Women (vs. Men)	64/152	281/579	**0.75 (0.53-1.04)**
Previous DVT (vs. non previous DVT)	10/152	25/579	**1.73 (0.89-3.33)**
Tumor Location (vs. Head as reference)			
Isthmus	11/152	23/579	**2.06 (1.09-3.91)**
Body	18/152	74/579	**0.97 (0.57-1.64)**
Tail	16/152	44/579	**1.35(0.78-2.35)**
Overlapping lesion	26/152	85/579	**1.29(0.81-2.04)**
Tumor stage (vs. resectable as reference)			
Locally advanced	49/152	163/579	**1.66 (1.10-2.51)**
Metastatic	54/152	139/579	**2.50 (1.64-3.79)**

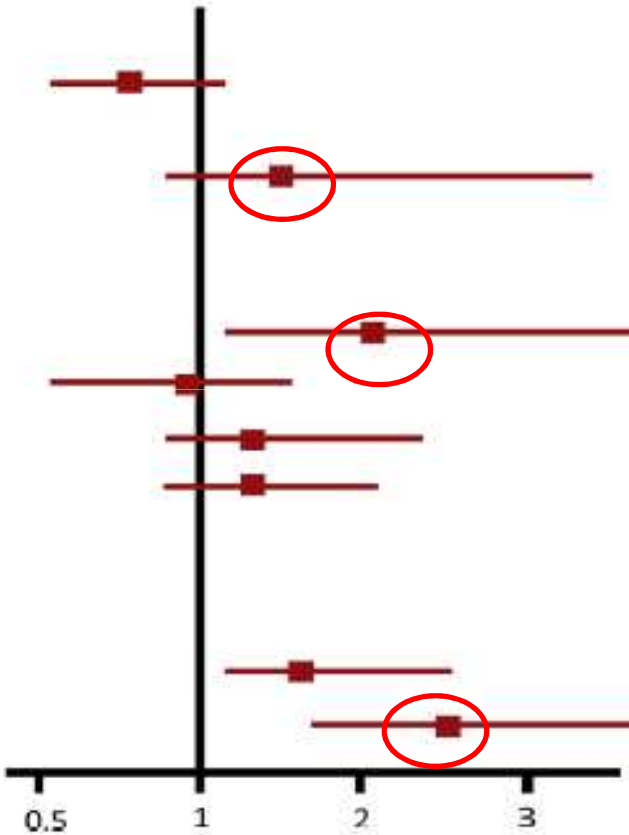
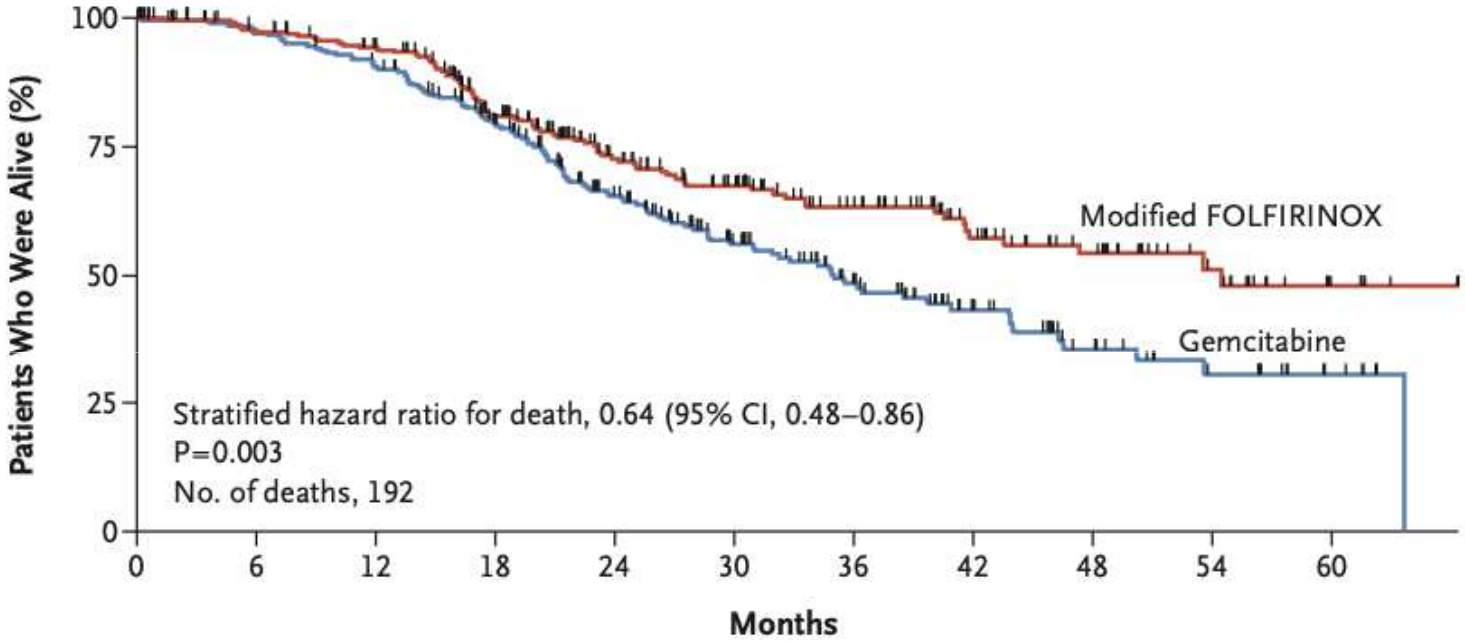


Figure 2. Risk factors for VTE identified by multivariate analysis. Factors with an HR of <1 are protective, and those with an HR of >1 are risk factors.

RESECTABLE DISEASE – THE STANDARD

Update a ESMO 2021: 5y OS 43.2% vs 31.4%; mOS 53.5 months vs 35.5 months
Metastasis free survival: 5yMFOS 31.9% vs 21.5%; 29.4 mo vs 17.7 mo

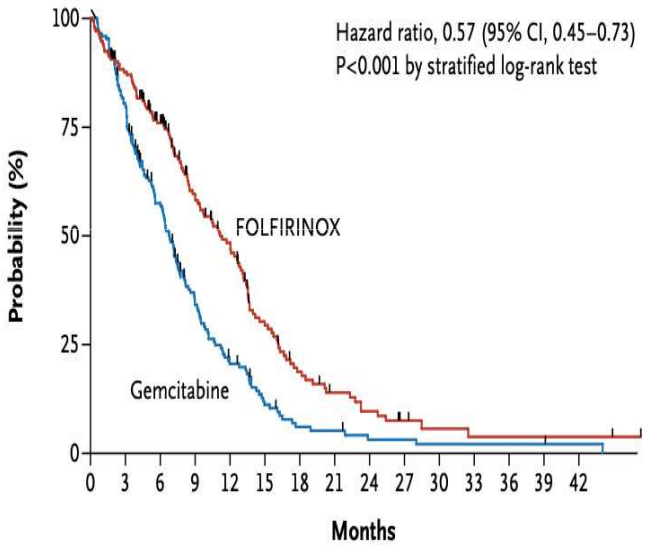


No. at Risk											
Modified FOLFIRINOX	247	223	210	165	119	91	68	46	32	16	4
Gemcitabine	246	233	215	171	120	81	55	33	18	9	4

Conroy et al NEJM 2018

FIRST LINE THERAPY –OLD STORY

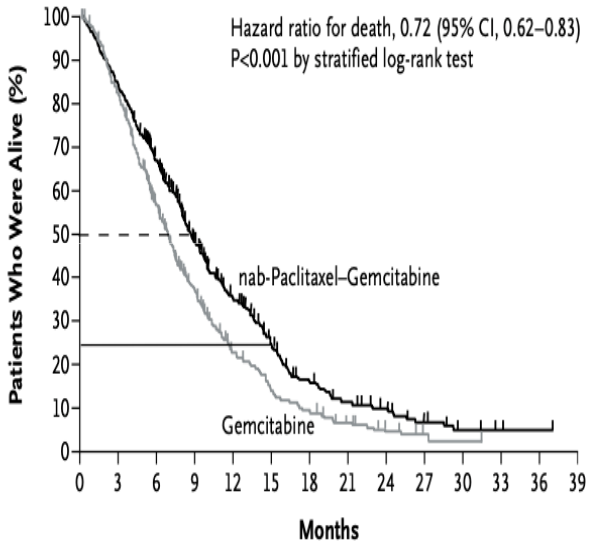
FOLFIRINOX (2011)



No. at Risk

Gemcitabine	171	134	89	48	28	14	7	6	3	3	2	2	2	1
FOLFIRINOX	171	146	116	81	62	34	20	13	9	5	3	2	2	2

GEMCITABINE + NABPACLITAXEL (2013)



No. at Risk

nab-Paclitaxel–Gemcitabine	431	357	269	169	108	67	40	27	16	9	4	1	1	0
Gemcitabine	430	340	220	124	69	40	26	15	7	3	1	0	0	0

Conroy et al NEJM 2011; Von Hoff et al NEJM 2013

Is NALIRIFOX a new option?

Lancet 2023; 402: 1272–81

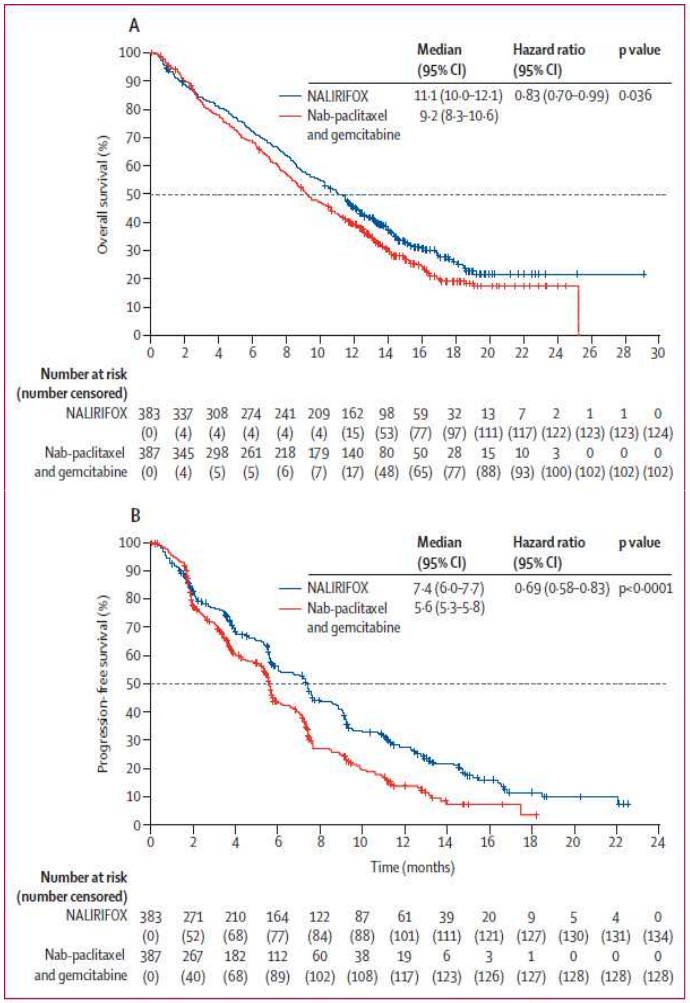


Figure 2: **Kaplan-Meier estimates of overall survival (A) and progression-free survival (B)**
NALIRIFOX=liposomal irinotecan in combination with fluorouracil, leucovorin, and oxaliplatin.

Chemotherapy induced thrombosis

Regimen	Contribution to the risk	VTE events rate or RR/Incidence
Cisplatin/platinum based	• elevated von Willebrand factor (vWF) levels • release of procoagulant endothelial microparticles	• ↑Events 18,1%
L-asparaginase	• depletion of key proteins in the regulation of the coagulation pathway • synthesis of plasminogen and antithrombin (AT) is markedly impaired with asparaginase-based therapy	• ↑Incidence 4,2%
5-Fluorouracil (5FU)	• depletion of protein C and increased thrombin activity • endothelial cell damage with the potential to promote thrombus formation	• ↑Incidence (15%) - if combined with hematopoietic G-SFE (29%)
Tamoxifen and Aromatase Inhibitors		• ↑Risk 2,8% - if Tamo+chemo • RR 15,5
Immunomodulatory Agents - Thalidomide/lenalidomide	• thalidomide increases the expression of protease-activated receptor 1 • On the endothelium, PAR-1 facilitates platelet and neutrophil rolling and adhesion. • Therefore, PAR-1 may serve as the connection between injury and the coagulation response.	↑Incidence Thalid+anthacycleine 28% , Thalid+Dexamethazone 17%
Corticosteroids Dexamethasone	• increase circulating levels of clotting factors VII, VIII, XI and fibrinogen in healthy volunteers. • decreased thrombolysis associated with increased plasminogen and alpha-2 antiplasmin levels.	↑Incidence Ratio 2,3 -3,4
Erythropoietin stimulating agents	• decrease proteins C and S, increase plasminogen activator inhibitor-1 (PAI-1) production, and increase platelet activation • some evidence of endothelial cell damage/activation with increased serum levels of thrombomodulin and vWF	↑ Relative Risk 1,52 -2,09

Oppelt P, et al. Vasc Med 2015;20(2):153–61.

High prevalence of incidental and symptomatic venous thromboembolic events in patients with advanced pancreatic cance under palliative chemotherapy: A retrospective cohort study

Anne Katrin Berger, MD [a,*], Hans Martin Singh, MD [a], Wiebke Werft, PhD [b], Alexander Muckenhuber, MD [c], Martin R. Sprick, PhD [d,e,f], Andreas Trumpp, PhD [d,e,f], Wilko Weichert, MD [c], Dirk Jäger, MD [a], Christoph Springfeld, MD, PhD [a]

Incidental and symptomatic VTEs Grade 2 or higher were found in 37 patients (24.7%) of which 19 patients were treated with FOLFIRINOX (21.4% of the FOLFIRINOX group) and 18 with GEM (29.5% of the GEM group) ($p = 0.34$). Median time to diagnosis of VTE was 57 days after first diagnosis of APC, or, in patients who

No difference for Type of Chemotherapy regimen

FOLFIRINOX vs Gemcitabine

Pancreatology 17 (2017) 629–634

Table 1
Patient characteristics for all patients

	All (n)	%	FOLFIRINOX (n)	%	GEM (n)	%
Number of patients	150	100.0	89	100.0	61	100.0
Sex						
m	93	62.0	58	65.2	35	57.4
w	57	38.0	31	34.8	26	42.6
p = 0.39						
Localisation						
head	84	56.0	51	57.3	33	54.1
corpus	39	26.0	22	24.7	17	27.9
tail	27	18.0	16	18.0	11	18.0
p = 0.92						
Metastases						
yes	138	92.0	80	89.9	58	95.1
no	12	8.0	9	10.1	3	4.9
p = 0.36						
Prior Operation						
yes	39	26.0	23	25.8	16	26.2
no	111	74.0	66	74.2	45	73.8
p = 1.00						
Prior adjuvant therapy						
yes	28	18.7	14	15.7	14	22.9
no	122	81.3	75	84.3	47	77.0
p = 0.29						
ECOG PS						
0	66	44.0	50	56.2	16	26.2
1	[illegible]	41.3	36	[illegible]	[illegible]	42.6
2	18	12.0	3	3.4	15	[illegible]
3	4	2.7	0	0.0	4	6.6
p < 0.0001						
VTE						
yes	37	24.7	19	21.4	18	29.5
[illegible]	113	75.3	70	78.7	43	70.5
Dead						
yes	138	96.5	80	94.1	58	100.0
no	5	3.5	5	5.9	0	0.0
all	143	100.0	85	100.0	58	100.0
p = 0.08						

cancers

MDPI

Review

Venous Thromboembolism and Primary Thromboprophylaxis in Perioperative Pancreatic Cancer Care

R. A. L. Willems [1,2,3,4,5], N. Michiels [6], V. R. Lanting [7,8,9], S. Bouwense [10,11], B. L. J. van den Broek [12], M. Graus [4,13], F. A. Klok [14], B. Groot Koerkamp [12], B. de Laat [1,5,15], M. Roest [15], J. W. Wilmink [16,17], N. van Es [7,8], J. S. D. Mieog [6], H. ten Cate [2,3,5] and J. de Vos-Geelen [4,13,*]

- Preoperative VTE incidences ranging from 11 to 14% for patients with borderline resectable PDAC to 8-21% treated with different neoadjuvant chemotherapy regimens

- The study perfomed by Krepline et al showed lower rate of neoadjCT in pts who developed VTE (54%) vs who did not (75%)

- Median OS was found to be decreased

  17 (VTE pos) vs 25 (VTE neg) months

Table 1. Incidence of VTE in patients with localized PDAC (treated with neoadjuvant chemotherapy).

Study	Study Size	Cancer Stage, *n* (%)	Chemotherapy, *n* (%)	VTE Incidence • Stage, *n* (%)	VTE incidence • Chemotherapy, *n* (%)
Prospective					
Frere et al., 2020 [22]	731	RPC: 208 (29.0) BRPC: 105 (14.6) LAPC: 212 (26.9)	-	Total: 97 (19) • RPC: 31 (21) • BRPC: 17 (11) • LAPC: 49 (33)	-
Krepline et al., 2016 [27]	260	RPC: 109 (42) BRPC: 151 (58)	5-FU: 98 (37) Gemcitabine: 84 (32) Platinum agent: 110 (42)	Total: 26 (10) • RPC: 9 (8) • BRPC: 17 (11)	• 5-FU: 13/98 (13) • Gemcitabine: 5/84 (6) • Platinum agent: 13/110 12)
Walma et al., 2021 [28]	326	LAPC: 326 (100)	FOLFIRINOX: 252 (77) Nab-paclitaxel/gemcitabine: 33 (10) Gemcitabine: 41 (13)	Total: 20/326 (6)	• FOLFIRINOX: 17/252 (7) • Nab-paclitaxel/ gemcitabine: 2/33 (6) • Gemcitabine: 1/41 (2)
Katz et al., 2016 [29]	22	BRPC: 22 (100)	mFOLFIRINOX: 22/22 (100)	Total: 3 (14)	• mFOLFIRINOX: 3/22 (14)
Retrospective					
Barreau et al., 2021 [30]	174	LAPC: 56 (32)	-	Total: 46 (26) LAPC: 13 (23)	
Tahara et al., 2018 [31]	27	LAPC: 21 (78) Metastatic: 6 (22)	FOLFIRINOX: 10 (37) Nab-paclitaxel/gemcitabine: 11 (41)	Total: 6/27 (22) [a]	• FOLFIRINOX: 5 (42) • Nab-paclitaxel/gemcitabine 1 (7)
Hanna-Sawires et al., 2021 [32]	361	I: 62 (17) II: 152 (42) III: 61 (17)	FOLFIRINOX: 6 Gemcitabine/radiotherapy: 11	Total: 64/361 (18) I: 7/62 (11) II: 24/152 (38) III: 9/61 (14) During neoadjuvant therapy: 2 (3)	

[a] VTE incidence for both locally advanced and metastatic PDAC, VTE incidence for only LAPC was not reported in study. BRPC: borderline resectable pancreatic cancer; LAPC: locally advanced pancreatic cancer; mFOLFIRINOX: modified FOLFIRINOX; RPC: resectable pancreatic cancer; VTE: venous thromboembolic event.

Khorana score Pitt falls in PDAC

Table 1. Clinical Risk Score

Factor	Risk score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count $\geq$350,000/mm^3	1
Prechemotherapy leukocyte count $>$11,000/mm^3	1
Hemoglobin level $<$10 g/dL or use of red cell growth factors	1
Body mass index $\geq$35 kg/m^2	1

Cumulative score: high risk, $\geq$3; intermediate risk, 1–2; low risk, 0.

- All Patients with PDAC Have a score of 2 or more by definition
- The number of patients with PADC was less than 2% in original cohort study
- The presence of BMI >35 is unrealistic for PDAC
- No difference for site, stage type of chemotherapy
- No difference OS and PFS for Intermediate and High Risk KRS in BACAP study

Criteria	KRS	Vienna-CATS	CONKO	ONCOTEV	PROTECHT	COMPASS-CAT
Very high-risk tumor (stomach, pancreas)	2	2	2		2	
High-risk tumor (lung, lymphoma, gynecologic, bladder, testicular)	1	1	1		1	
Pre-ChT platelet count $\geq 350 \times 10^9$/L	1	1	1		1	2
Hb ≤ 100 g/L or use of red cell growth factors	1	1	1		1	
Pre-ChT WBC $\leq 11 \times 10^9$/L	1	1	1		1	
BMI ≥ 35 kg/m^2 or more	1	1	1		1	
D-dimer > 1.44 µg/L		1				
Soluble P-Selectin > 53.1 ng/L		1				
WHO performance status ≥ 2			1			
Gemcitabine ChT					1	
Platinum-based ChT					1	
KRS > 2				1		
Previous VTE				1		1
Metastatic disease				1		
Vascular/lymphatic macroscopic compression				1		
Anti-hormonal therapy for BC or anthracycline ChT						6
Time since cancer diagnosis ≤6 months						4
Central venous catheter						3
Advanced disease						2

Table 3. *Cont.*

Criteria	KRS	Vienna-CATS	CONKO	ONCOTEV	PROTECHT	COMPASS-CAT
Cardiovascular risk						5
Recent hospitalization for acute medical illness						5
Low	0	0	0	0	0	0–6
Intermediate	1–2	1–2	1–2	1	1–2	
High	≥3	≥3	≥3	≥2	≥3	≥7

The Oncologist®

Gastrointestinal Cancer

ONKOTEV Score as a Predictive Tool for Thromboembolic Events in Pancreatic Cancer—A Retrospective Analysis

João Godinho,[a] Mafalda Casa-Nova,[a] João Moreira-Pinto,[a] Pedro Simões,[a] Francisco Paralta Branco,[a] Luísa Leal-Costa,[a] Ana Faria,[a] Fábio Lopes,[a] José Alberto Teixeira,[a] José Luís Passos-Coelho[a,b]

[a]Hospital Beatriz Ângelo, Loures, Portugal; [b]Hospital da Luz, Lisboa, Portugal

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Venous thromboembolism • Pancreatic cancer • Risk prediction • ONKOTEV

Table 1. Patient demographics and tumor characteristics

Variable	All (n = 165), n (%)	VTE (n = 51), n (%)	No VTE (n = 114), n (%
Age, years, median (IQR)	73.0 (13.0)	72.0 (12.0)	73.0 (13.0)
Gender: female	75 (45.5)	29 (56.9)	46 (40.4)
ECOG PS at diagnosis			
0	39 (23.6)	12 (23.5)	27 (23.7)
1	55 (33.3)	17 (33.3)	38 (33.3)
2	37 (22.4)	10 (19.6)	27 (23.7)
3	27 (16.4)	9 (17.6)	18 (15.8)
4	7 (4.3)	3 (5.9)	4 (3.5)
Stage			
I	18 (10.9)	2 (3.9)	16 (14.0)
II	23 (13.9)	3 (5.9)	20 (17.5)
III	32 (19.4)	6 (11.8)	26 (22.8)
IV	92 (55.8)	40 (78.4)	52 (45.6)
Location within the pancreas			
Head/uncinate	102 (61.8)	26 (51.0)	76 (66.7)
Body/tail	63 (38.2)	25 (49.0)	38 (33.3)
Chemotherapy[a]			
Yes	109 (66.1)	35 (68.6)	74 (64.9)
Gemcitabine-based	94 (56.9)	29 (56.9)	65 (57.0)
Platinum-based	35 (21.2)	12 (23.5)	23 (20.2)
Surgical resection: yes	40 (24.2)	7 (13.7)	33 (28.9)
Radiologic vascular invasion: yes	55 (33.3)	27 (52.9)	25 (21.9)
ONKOTEV score			
0	30 (18.2)	1 (2.0)	29 (25.4)
1	63 (38.2)	8 (15.7)	55 (48.2)
2	55 (33.3)	28 (54.9)	27 (23.7)
≥3	17 (10.3)	14 (27.4)	3 (2.7)
Vascular/lymphatic compression: yes	67 (40.6)	36 (70.6)	31 (27.2)
Presence of metastasis: yes	92 (55.8)	41 (80.4)	51 (44.7)
Previous history of VTE: yes	7 (4.2)	7 (13.7)	0 (0)
Khorana score			
>2	59 (35.8)	23 (45.1)	36 (31.6)
2	106 (64.2)	28 (54.9)	78 (68.4)

The incidence of VTE increased with increasing ONKOTEV score, with a cumulative VTE incidence of 3.3%, 12.7%, 50.9%, and 82.4% for ONKOTEV scores of 0, 1, 2, and ≥3, respectively (p < .001). These differences are sufficiently wide to support a useful predictive role for ONKOTEV score in patients with pancreatic cancer. There are no other studies validating the predictive impact of ONKOTEV, other than the original publication [12].

Abbreviation: VTE, venous thromboembolism.

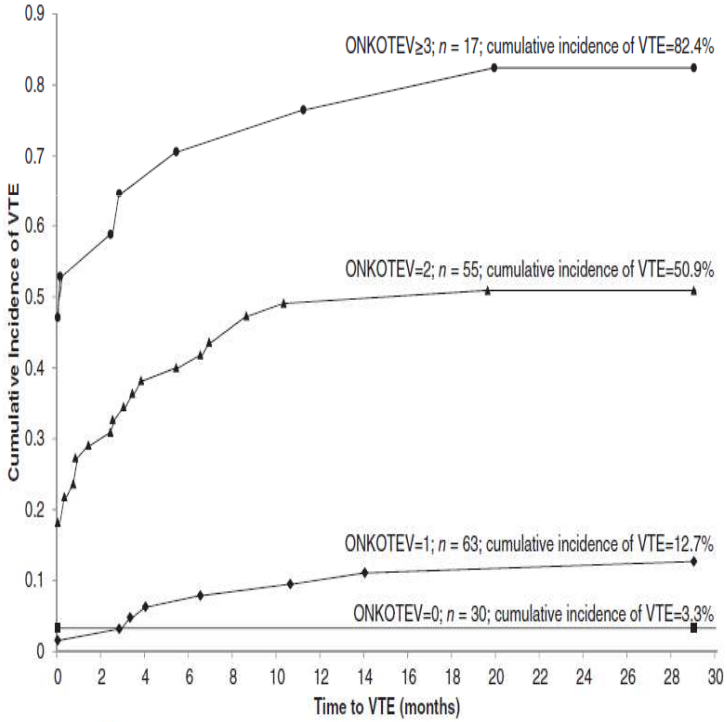
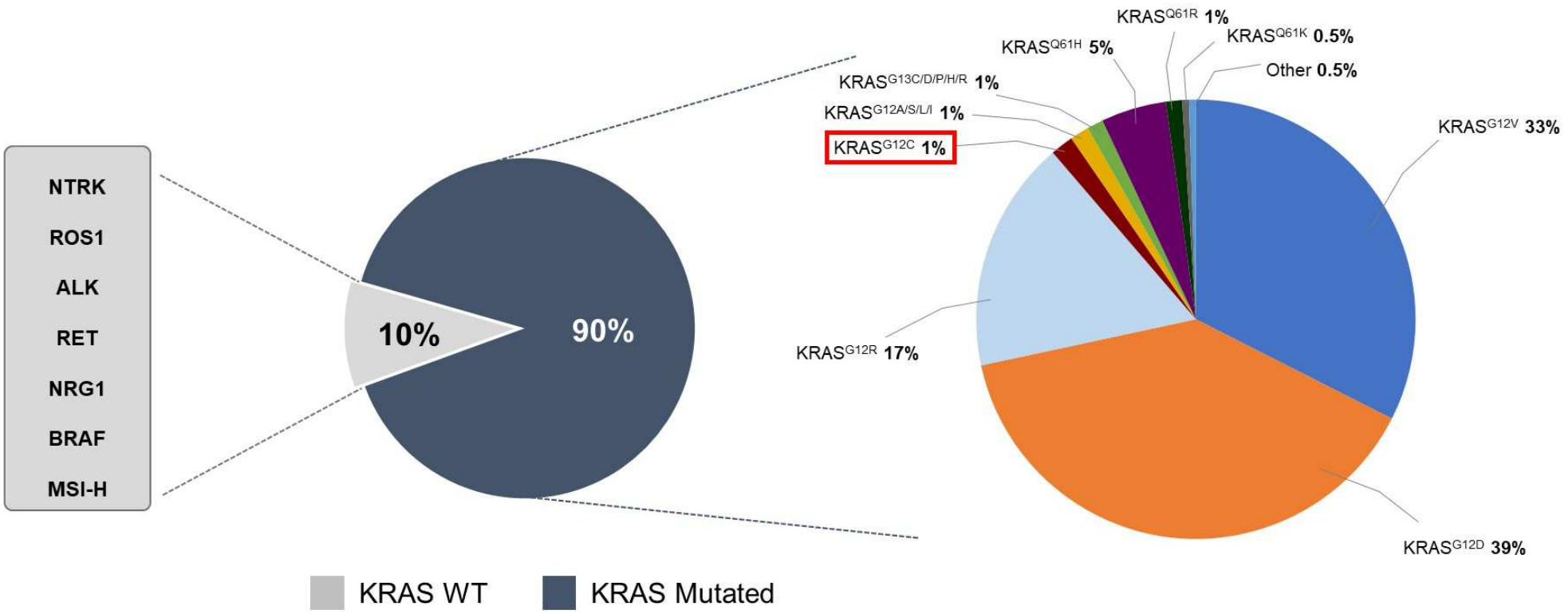


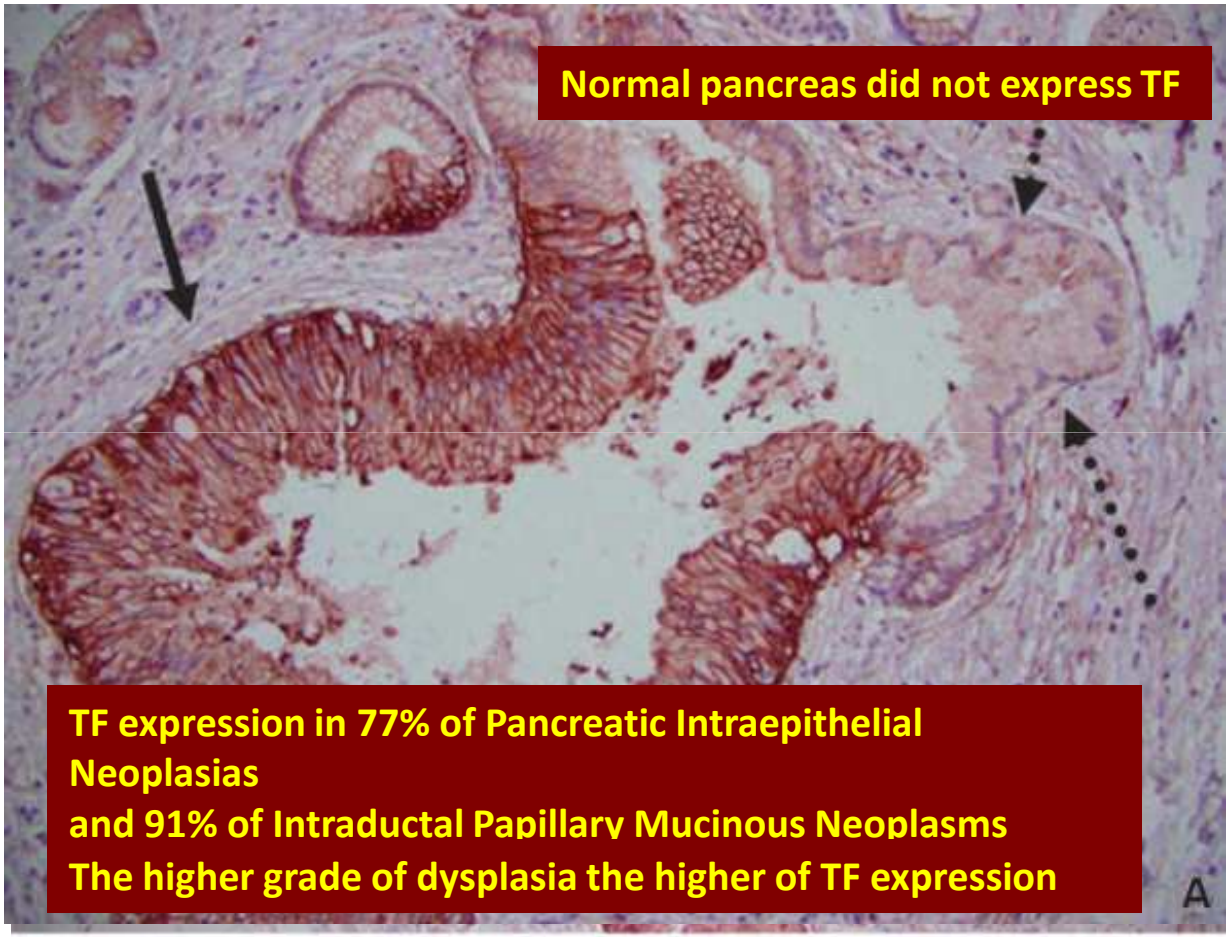
Figure 1. Cumulative incidence of VTE by ONKOTEV score.
Abbreviation: VTE, venous thromboembolism.

KRAS Mutations are a hallmark of PDAC



Zehir A, et al. Nat Med 2017. Salem ME, et al. JCO Precis Oncol 2022. Luo J. Semin Oncol 2021 [data analyzed using cBio Cancer Genomics Portal (http://cbioportal.org); Cerami E, et al. Cancer Discov. 2012; Gao J, et al. Sci Signal. 2013]. Hosein AN, et al. Nat Cancer 2022

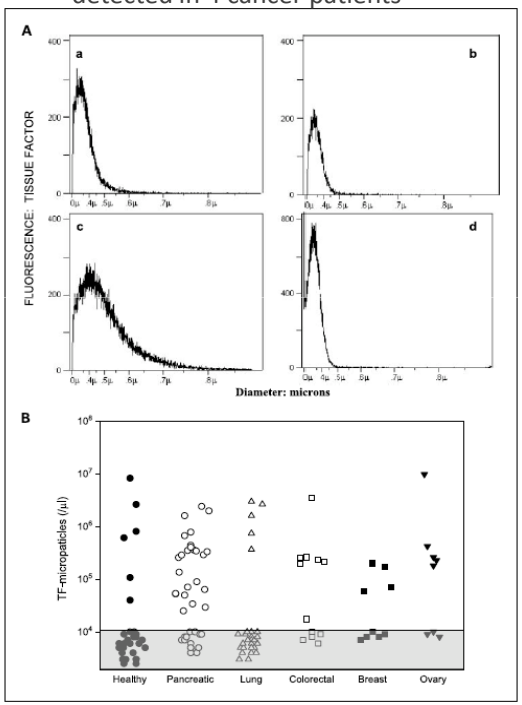
TF expression is an important early event in malignant transformation of the pancreas



Clin Cancer Res 2007;13:2870-2875

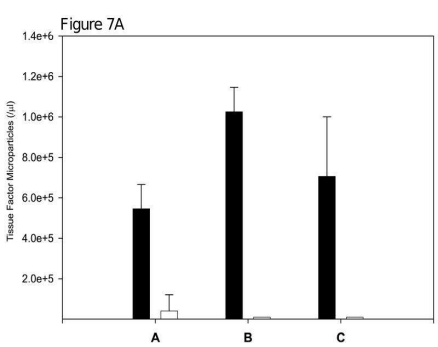
TF-MPs were detected in 2/3 of patients with pancreatic carcinoma

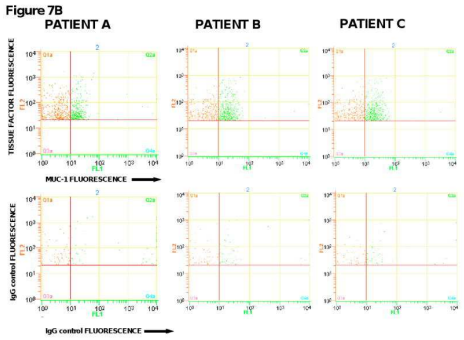
Histograms of tTF-MPs
detected in 4 cancer patients



Median number of TF-MPs in the cancer VTE (7.1x 10^4 micro-particles /µL) significantly greater than the idiopathic VTE ($P = 0.002$)

Pancreatectomy eliminated or nearly eliminated these microparticles



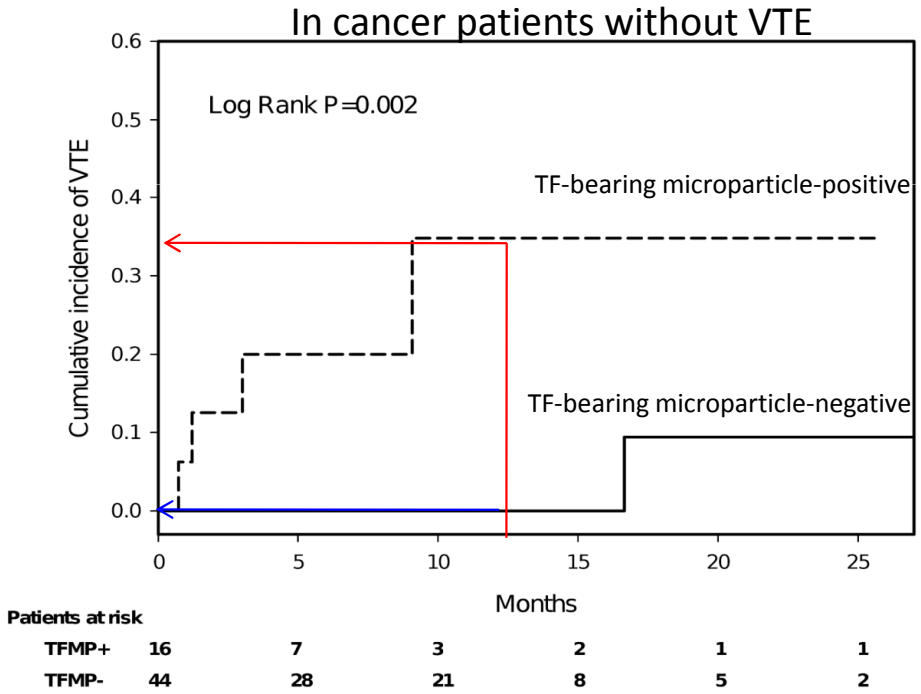


Clin Cancer Res. 2009; 15(22): 6830–6840

Circulating TF-MPs

- Elevated levels of TF-MPs are **associated with VTE**

  (adjusted OR, **3.72**; 95% CI, 1.18-11.76; P = 0.01)



Cumulative incidence of 1-year VTE: **35%** vs **0%**

Clin Cancer Res. 2009; 15(22): 6830–6840

www.oncotarget.com Oncotarget, 2018, Vol. 9, (No. 41), pp: 26453-26465

Research Paper

Biomarkers for the risk of thrombosis in pancreatic adenocarcinoma are related to cancer process

Dorothée Faille[1,2], Marie-Charlotte Bourrienne[1,2], Emmanuelle de Raucourt[2,3], Luc de Chaisemartin[4,5], Vanessa Granger[4,5], Romaric Lacroix[6,7], Laurence Panicot-Dubois[6], Pascal Hammel[8,9], Philippe Lévy[10], Philippe Ruszniewski[9,10], Nadine Ajzenberg[1,2] and Vinciane Rebours[9,10]

Table 5: Receiver operating characteristic (ROC) curve analysis for the performance of thrombin-antithrombin complexes (TAT), D-dimers, microvesicle-tissue factor (MV-TF) activity and CA 19-9 in predicting VTE

	AUC	Sensitivity (%)	95% CI	Specificity (%)	95% CI
TAT, ≥ 6.7 ng/mL	0.78	84.0	63.9–95.5	50.0	15.7–84.3
D-dimers, ≥ 2.16 µg/mL	0.76	85.7	67.3–96	57.1	18.4–90.1
MV-TF activity, ≥ 2.37 pg/mL	0.74	85.7	67.3–96	44.4	13.7–78.8
CA 19-9, ≥ 2153 U/mL	0.78	90.9	70.8–98.9	71.4	29.0–96.3

AUC: area under the curve

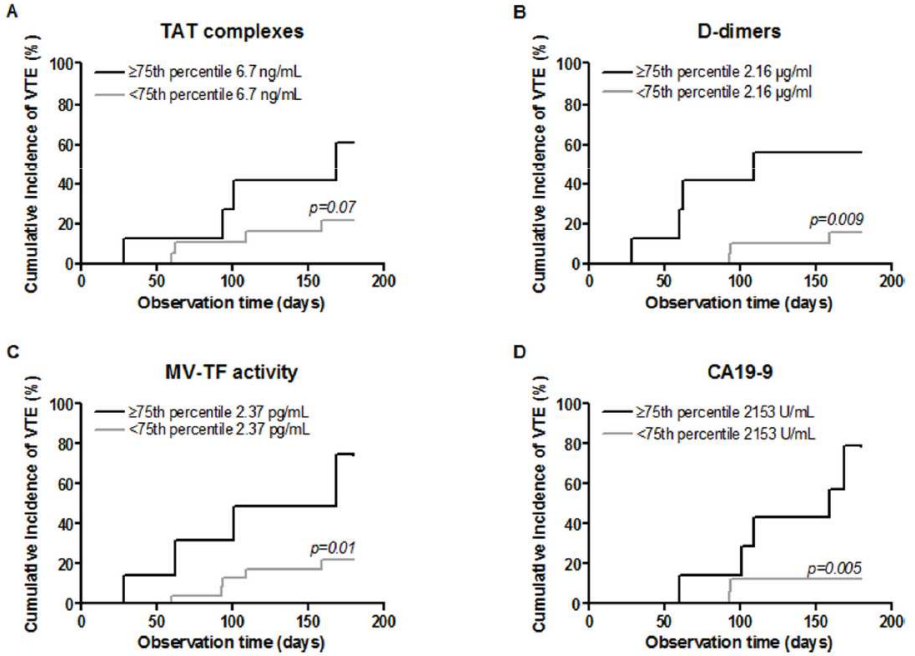


Figure 2: Cumulative incidence of VTE among cancer patients according to levels of D-dimers, MV-TF activity, TAT or CA-19-9 (<75th percentile or ≥75th percentile). *P*-values for log-rank test.

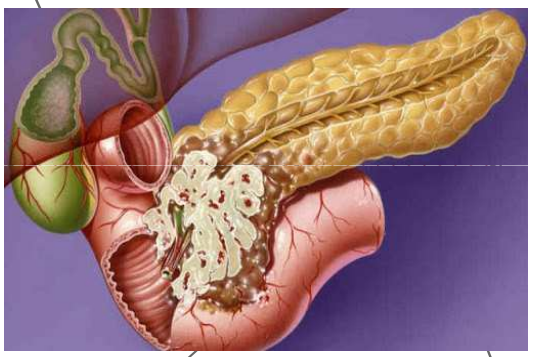
Identify the Thrombotic Burden for each PANCREATIC cancer patient

Cancer Related

- Site of Cancer HEAD, Isthmus vs body
- Histological Adeno vs Others
- Stage IV
- Molecular 90% KRAS mutated

Treatment Related

- Chemotherapy All Type
- Radiotherapy ?
- Central venous catheter
- Blood transfusion and Eritropoietin



Patient Related

- PS 2 , Female
- Medical comorbidities (≥3)
- Obesity and Cachettic
- AF
- Presence of varicose veins
- Prior VTE
- Hereditary Thrombophilia

Biomarkers

Hematologic (Plts, Lcytes, Hb…)

D-Dimers

TF

CA19.9

P-Selectin

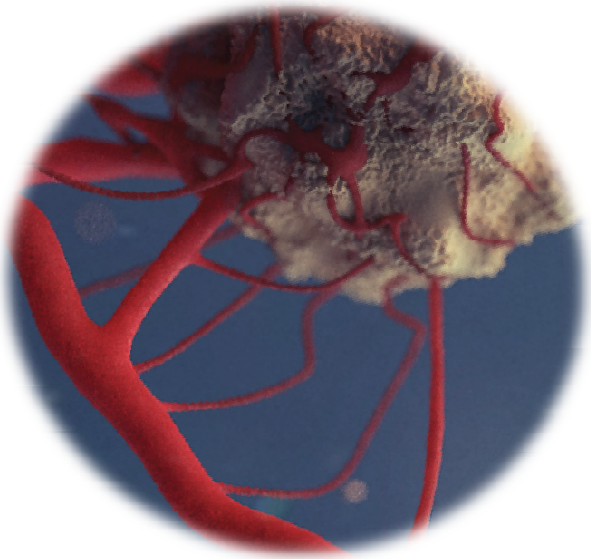
Thrombin Generation Potential

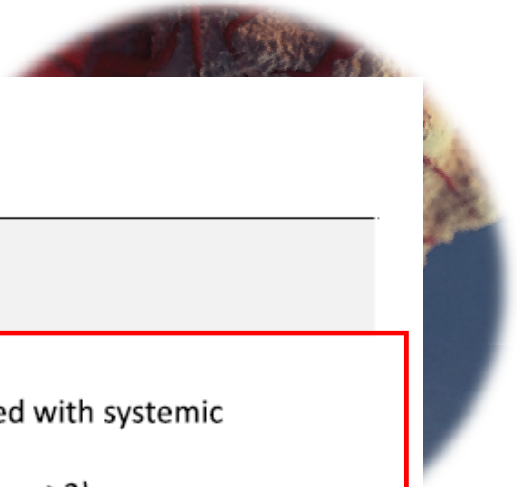
Microparticle-Tissue Factor activity

C Reactive Protein

Ay C, et al. Thromb Haemost. 2017;117: 219-230 Cancer-associated Venous Thromboembolism: Burden, Mechanisms, and Management

A chi e per quanto tempo si deve effettuare la profilassi nel tumore al pancreas?





Recommendations

ASCO 2019	• Routine pharmacologic thromboprophylaxis should not be offered • Khorana score ≥ 2 may be offered apixaban, rivaroxaban, or LMWH
ITAC 2022*	• LMWH, VKAs, or DOACs not recommended routinely • LMWH or DOACs (rivaroxaban or apixaban) in locally advanced or M+ ***pancreatic cancer*** treated with systemic anticancer therapy with low bleeding risk • DOACs (rivaroxaban or apixaban) recommended intermediate-to-high risk of VTE (*Khorana score ≥2)*
SSC of the ISTH	• DOACs suggested if **Khorana score ≥2**, no drug-drug interactions, and no high risk for bleeding (e.g. GI cancer) • LWMH, if concerns for safety of DOAC • If DOACs were to be used, iadministered for up to 6 months
ASH 2021	• Intermediate risk: DOAC (apixaban or rivaroxaban) - no LMWH • High risk: parenteral thromboprophylaxis (LMWH) DOAC (apixaban or rivaroxaban)
ESMO 2023	• For ambulatory pancreatic cancer patients on first-line systemic anticancer treatment , **LMWH** given at a higher dose (150/IU/kg dalteparin or 1 mg/kg enoxaparin) for a maximum of 3 months may be considered [II, C] • In ambulatory cancer patients starting systemic anticancer treatment who have a high thrombosis risk, **apixaban, rivaroxaban or LMWH** may be considered for primary thromboprophylaxis for a maximum of 6 months [I, B]

*International Initiative on Thrombosis and Cancer

Key NS, et al. J Clin Oncol 2019; Farge D, et al. Lancet Oncol 2022; Wang TF, et al. JTH 2019; Lyman G, et al. Blood Adv 2021; Falanga A, et al. Ann Oncol 2023

cancers

MDPI

Article

Primary Thromboprophylaxis in Ambulatory Pancreatic Cancer Patients Receiving Chemotherapy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Table 3. Thromboprophylaxis in ambulatory patients with PDAC treated with chemotherapy to prevent VTE.

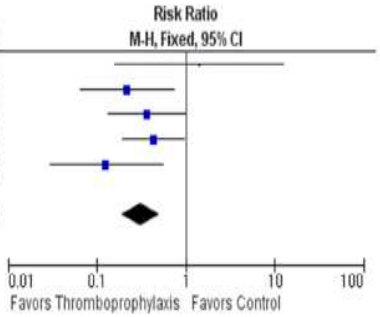
	LMWH				DOAC	
Study	CONKO-004 Pelzer et al. (2015) [97]	FRAGEM Maraveyas et al. (2012) [96]	PROTECHT Agnelli et al. (2009) [98]	SAVE-ONCO Agnelli et al. (2012) [99]	AVERT Carrier et al. (2019) [100,101]	CASSINI Vadhan-Raj et al. (2020) [102]
Cancer stage	LAPC or metastatic	LAPC, recurrent or metastatic	LAPC or metastatic	LAPC or metastatic	Newly diagnosed or progression, all cancer stages	All stages
No metastases (I/C)	26/22	52/41 LAPC: 31/26 Metastatic: 29/37	-	-	-	39/36 Stage I/II: 21/15 Stage III: 14/17 Stage IV: 61/65
Chemotherapy regimen	Gemcitabine or Gemcitabine+ 5-FU+Cisplatin	Gemcitabine	-	-	-	5-FU-based or gemcitabine-based or gemcitabine+ Capecitabine /5-FU
Study intervention (I)	Chemotherapy alone or chemotherapy plus enoxaparin 1 mg/kg once daily	Gemcitabine alone or gemcitabine plus dalteparin 200 IU/kg once daily for 4 weeks followed by 150 IU/kg once daily for 8 weeks	Nadroparin 3800 IU once daily or placebo	Semuloparin 20 mg once daily versus placebo	Apixaban 2.5 mg twice daily or placebo	Rivaroxaban 10 mg once daily or placebo
Duration intervention	3 months	12 weeks	Duration chemotherapy	Duration chemotherapy	180 days	180 days
Follow-up	3 months	100 days	Duration intervention plus 10 days	Duration intervention plus 3 days	210 days	180 days
VTE (I/C)	1.3% vs. 10.2% $p = 0.001$ NNT = 11	3% vs. 23% $p = 0.002$ NNT = 6	5.9% vs. 8.3% NNT = 42	2.4% vs. 10.9% NNT = 12	5% vs. 16% $p = 0.039$ NNT = 9	3.7% vs. 10.1% NNT = 15
MB (I/C)	4.5% vs. 3.4% NS NNH = 76	3.2% vs. 3.4% NS	-	-	5% vs. 3% NS NNH = 50	1.5% vs. 2.3% NS NNH = 125

PROTECHT, SAVE-ONCO, AVERT, and CASSINI included patients with cancer, including a subset of patients with pancreatic cancer. Only the outcome data of patients with pancreatic cancer are reported in this table. 5-FU: 5-fluorouracil; DOAC: direct oral anticoagulant; I/C: intervention/control; LAPC: locally advanced pancreatic cancer; LMWH: low-molecular weight heparin; MB: Major bleeding; NNH: number needed to harm; NNT: number needed to treat; NS: not statistically significant; PC: pancreatic cancer; VTE: venous thromboembolic event.

A. Risk ratio for venous thromboembolism (fixed effect)

Study or Subgroup	Thromboprophylaxis Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Agnelli 2009 PROTECHT	3	36	1	17	2.2%	1.42 [0.16, 12.64]
Agnelli 2012 SAVE-ONCO	3	126	14	128	22.7%	0.22 [0.06, 0.74]
Khorana 2019 CASSINI	5	135	14	138	22.7%	0.37 [0.14, 0.99]
Marayevas 2012 FRAGEM	7	59	17	62	27.2%	0.43 [0.19, 0.97]
Pelzer 2015 CONKO	2	160	15	152	25.2%	0.13 [0.03, 0.54]
Total (95% CI)		**516**		**497**	**100.0%**	**0.31 [0.19, 0.51]**
Total events	20		61			

Heterogeneity: Chi² = 4.36, df = 4 (P = 0.36); I² = 8%
Test for overall effect: Z = 4.60 (P < 0.00001)

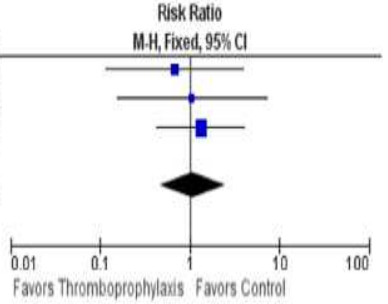


Primary thromboprophylaxis was associated to 69% risk reduction resulting in a NNT 11.9 to prevent One VTE, with no significant increas in major bleeding

A. Risk ratio for major bleeding (fixed effect)

Study or Subgroup	Thromboprophylaxis Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Khorana 2019 CASSINI	2	135	3	138	29.5%	0.68 [0.12, 4.01]
Marayevas 2012 FRAGEM	2	59	2	62	19.4%	1.05 [0.15, 7.22]
Pelzer 2015 CONKO	7	160	5	152	51.0%	1.33 [0.43, 4.10]
Total (95% CI)		**354**		**352**	**100.0%**	**1.08 [0.47, 2.52]**
Total events	11		10			

Heterogeneity: Chi² = 0.39, df = 2 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.19 (P = 0.85)



Cancer treatment induced thrombosis

Treatment Regimens	Thrombotic Risk[20,21,22]	Very common and common hematological implications	Very common and common GI Implications	P-gp	CYP3A4*
FOLFIRINOX – category 1 or modified FOLFIRINOX[6-9]	↑↑↑	Thrombocytopenia Anaemia	Diarrhoea / Stomatitis / Mucositis	-	Substrate
5-FU[7] + Leucovorin[6] + Oxaliplatin[9]	↑↑↑	Thrombocytopenia Anaemia	Diarrhoea / Stomatitis / Mucositis	-	-
If previous first-line FOLFIRINOX: FOLFIRI[6,7,8]	↑↑↑	Thrombocytopenia Anaemia	Diarrhoea	-	Substrate
Gemcitabine[10] + albumin-bound Paclitaxel[11]	↑↑	Thrombocytopenia Anaemia	Diarrhoea / Stomatitis / Colitis	-	-
Gemcitabine[10] + Capecitabine[16]	↑↑	Thrombocytopenia Anaemia	Diarrhoea / Stomatitis	-	-
(GTX regimen) Gemcitabine[10], Docetaxel[17], Capecitabine[16] – category 2B	↑↑	Thrombocytopenia Anaemia	Diarrhoea / Stomatitis	-	Substrate
Gemcitabine[10] + Cisplatin[12] (only for know BRCA1/2 or PALB2 mutation)	↑↑↑	Thrombocytopenia Anaemia	Diarrhoea / Stomatitis	-	-
Gemcitabine[10] + Erlotinib[13]	↑	Thrombocytopenia Anaemia	Diarrhoea / Stomatitis	Substrate	Substrate
Pembrolizumab[14] (only for MSI-H or dMMRtumors)	↑↑↑	Thrombocytopenia Anaemia	Diarrhoea / Colitis	-	-
Larotrectinib[18] (if NTRK gene fusion positive)	-	Anaemia	Nausea / Vomiting	Substrate	Substrate
Entrectinib[15] (if NTRK gene fusion positive)	-	Anaemia	Diarrhoea	-	Substrate
If previous platinum-based chemotherapy: Olaparib[19] (only for germline BRCA1/2 mutations)	↑	Thrombocytopenia Anaemia	Diarrhoea / Stomatitis	-	Substrate

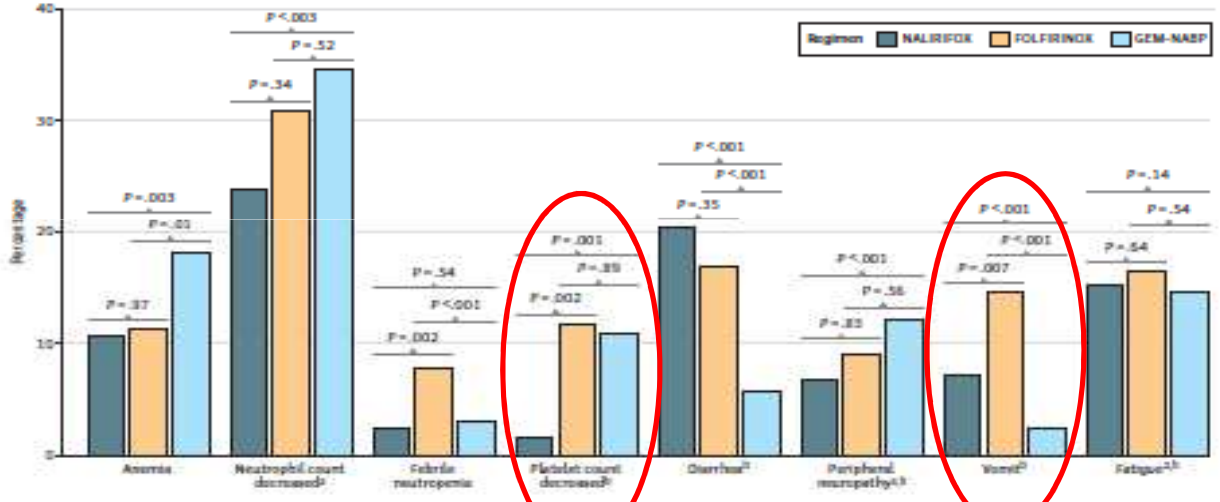
Modified Oppelt P, et al. Vasc Med 2015;20(2):153–61
cancer-associated thromboembolic disease in 2018-2019: First data from the TESEO prospective registry. Eur J Intern Med. 2020
Increased incidence of VTE with cancer immunotherapy. Med. 2021.
Long-term treatment of CAT : the choice of the optimal anticoagulant. J Thromb Haemost. 2017
Incidence, risk factors, and outcomes of venous and arterial thromboembolism in immune checkpoint inhibitor therapy. Blood. 2021.

NALIRIFOX, FOLFIRINOX, and Gemcitabine With Nab-Paclitaxel as First-Line Chemotherapy for Metastatic Pancreatic Cancer

A Systematic Review and Meta-Analysis

Federico Nichetti, MD; Simone Rota, MD; Paolo Ambrosini, MD; Chiara Pircher, MD; Eleonora Gusmaroli, MD; Michele Droz Dit Busset, MD; Sara Pusceddu, MD; Carlo Sposito, MD; Jorgelina Coppa, MD; Federica Morano, MD; Filippo Pietrantonio, MD; Maria Di Bartolomeo, MD; Luigi Mariani, MD, PhD; Vincenzo Mazzaferro, MD, PhD; Filippo de Braud, MD; Monica Niger, MD

Figure 3. Reporting Incidence of Grade 3 or Higher Toxic Effects According to the Pooled Treatment Regimens



P values of adjusted logistic regression models are plotted for each comparison. FOLFIRINOX indicates irinotecan, oxaliplatin, folinic acid, and fluorouracil; GEM-NABP, gemcitabine and nab-paclitaxel; NALIRIFOX, liposomal irinotecan, oxaliplatin, folinic acid, and fluorouracil.

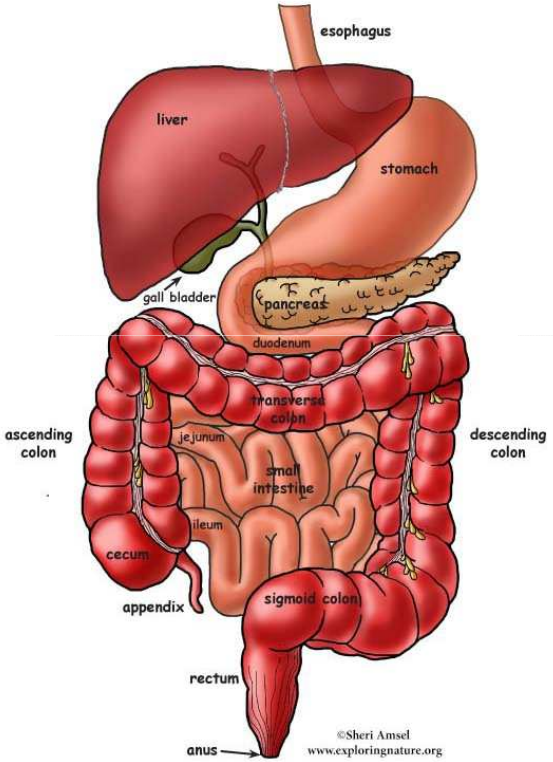
[a] Equivalent terms reported separately in original reports were pooled before the analysis, including *neutrophil count decreased* and *neutropenia*; *peripheral neuropathy* and *peripheral sensory neuropathy*; and *fatigue* and *asthenia*.

[b] The following toxic effects were not detailed in all trials: platelet count decreased and fatigue rates were not available in CanStarTIP[33] trial results; diarrhea rates were not available in HALO trial[34] results; peripheral neuropathy rates were not available in CanStarTIP,[33] HALO,[34] and AVENGERS00[32] trial results; vomit rates were not available in CanStarTIP, MPACT,[4] HALO,[34] and AVENGERS00[32] trial results.

Gastro-intestinal concerns can be challenging for the treatment of VTE in active cancer

Nausea, vomiting & inappetence and difficulty swallowing

- 50% of cancer patients will experience vomiting[2]
- Vomiting shortly after oral intake of medication raises concerns about re-dosing or omitting dosage[3]
- Swallowing difficulties and dysphagia occur in elderly and patients with tumors of the GI tract [1,4]

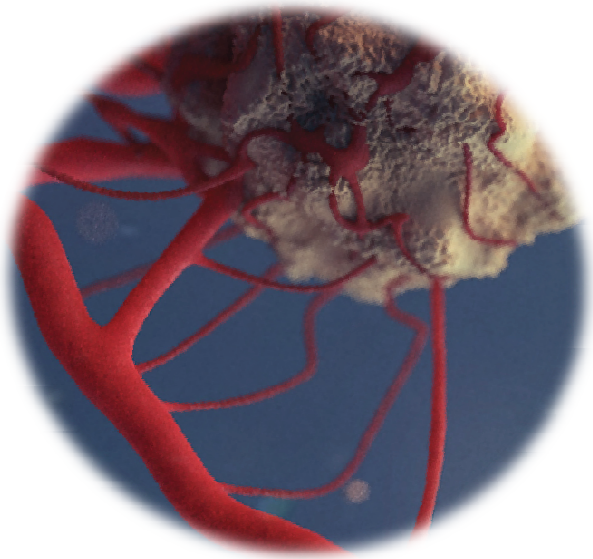


Gastrointestinal mucositis & diarrhea

- Inflammatory alterations of the intestinal mucosa may cause higher than normal absorption
- Diarrhea causes overall decreased bioavailability of oral medicines due to accelerated clearance
- Erosive lesions of colorectal cancer may increase the risk of GI bleeding

1. Elalamy I, Mahé I, Ageno W, Meyer G. J Thromb haemost 2017; 15(5):848-857.
2. Farge D, Bounameaux H, Brenner B, et al. Lancet Oncol 2016; 17(10): 452-466.
3.Voigtlaender M, Langer F. Hamostaseologie 2017; [Epub ahead of print]. doi: 10.5482/HAMO-16-09-0036
4. Sura L, Madhavan A, Carnaby G, Crary MA. Clinical interventions in aging. 2012;7:287.

Case report



Case report

Male, 75 y
Metastatic pancreatic adenocarcinoma (new diagnosis)
Previous VTE

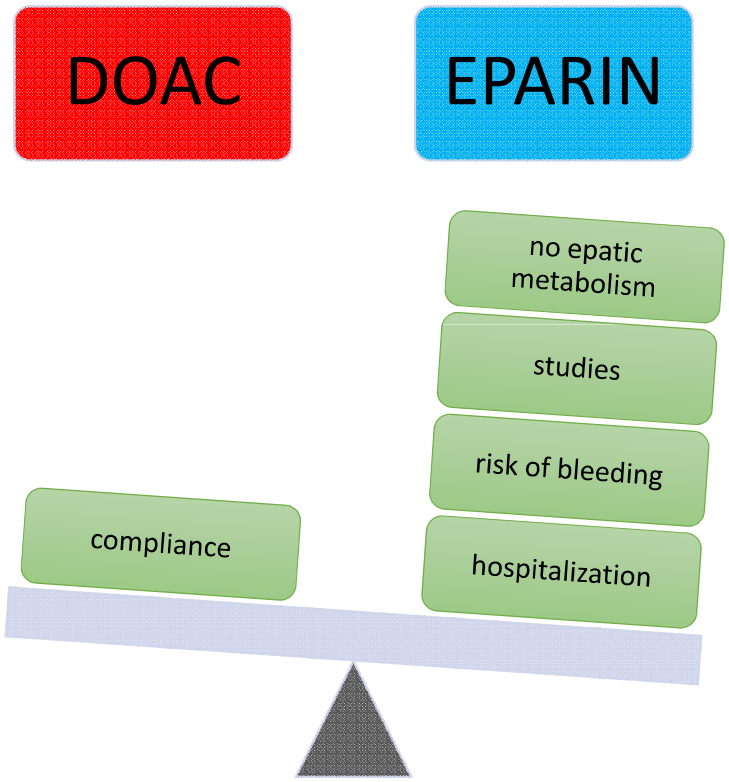
Khorana Score 2
ONKOTEV Score 4

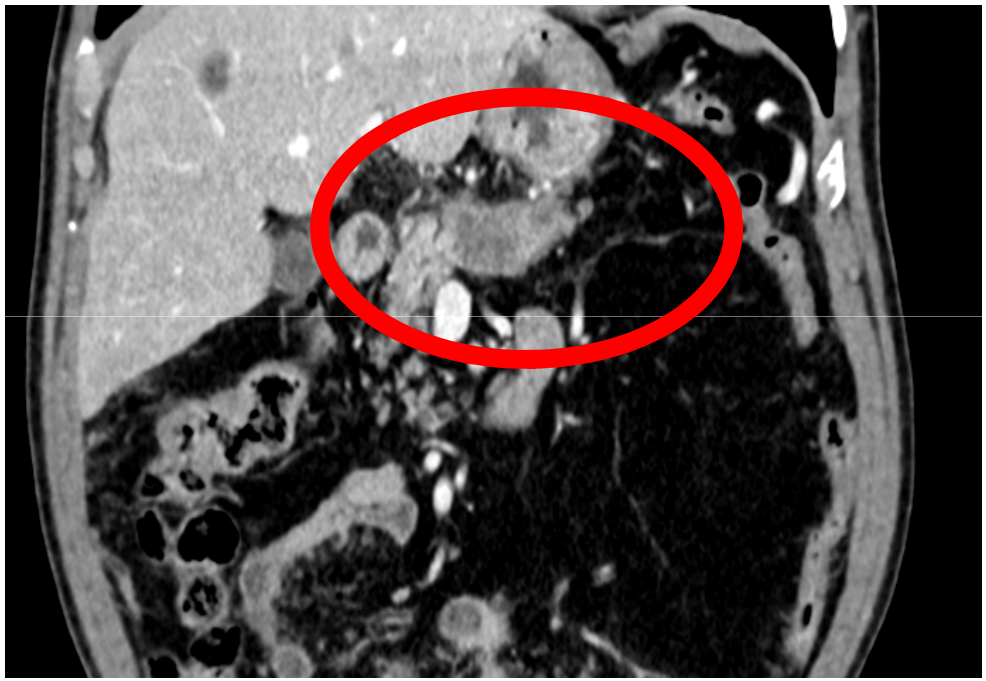
Concomitant drugs:
Plaunazide 20 mg + 12.5 mg
Esomeprazolo 20 mg Paroxetina 20 mg

ONKOTEV Score

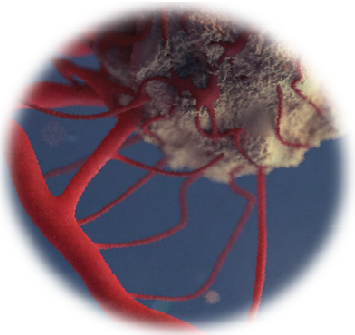
RISK FACTOR	SCORE
Khorana score ≥2	1
Previous venous thromboenbolism	1
Metastatic disease	1
Vascular / lymphatic macroscopic compression	1
Total ONKOTEV score	4

Case report


DOAC
EPARIN
no epatic metabolism
studies
risk of bleeding
hospitalization
compliance



Conclusions



- Lung cancer and Pancreatic cancer are considered HTB (High Thrombotic Burden) tumor type, with VTE being associated to increase morbidity and mortality and clinical benefit reduction limiting treatment opportunities

- VTE risk is a complex combination of multiple factors which are tumor, patient and treatment related, so even if RAMS MODEL exist for cancer type, other factor needs to be considered for the stratification of the risk in clinical practice (including physician expertise)

- At he same time, management Thrombosis in Lung and Pancreatic cancer patients needs a continuing assessment, and Anticoagulant choice should be personalized patient by patient