ANTICOAGULAZIONE
Attualità cliniche e di laboratorio. Aspetti sociali

Ricercare oppure no il cancro nei pazienti con tromboembolismo venoso?

No, sì, a chi?

Dott.ssa S. Villalta - Treviso

Prof. Armand Trousseau

"The diagnosis in a patient with gastric pain and leg or arm phlegmasia alba dolens is the presence of cancer"

"I'm lost. A thrombosis developed overnight, which doesn't leave me any doubt of the nature of my disease"

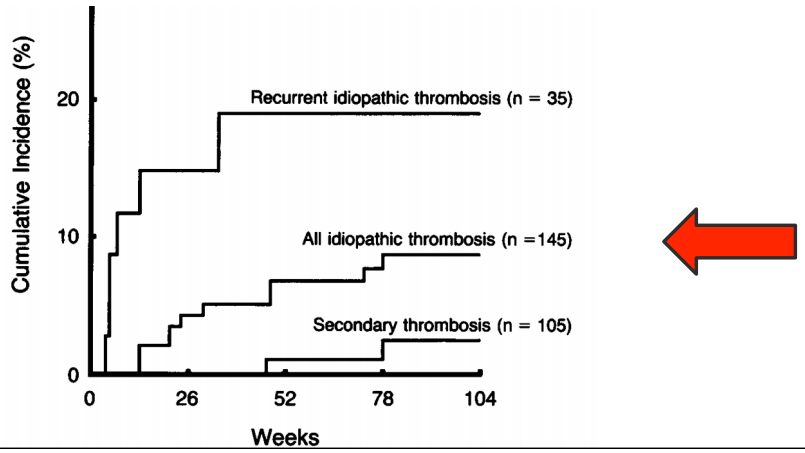
Agenda

- Aspetti epidemiologici
- Fattori di rischio
- Situazioni particolari
- Scores di rischio
- Analisi delle differenti strategie di screening - trial e metanalisi
- Cost-effectiveness delle diverse strategie impiegate
- Raccomandazioni delle linee guida
- Conclusioni

1128 THE NEW ENGLAND JOURNAL OF MEDICINE Oct. 15, 1992

DEEP-VEIN THROMBOSIS AND THE INCIDENCE OF SUBSEQUENT SYMPTOMATIC CANCER

PAOLO PRANDONI, M.D., PH.D., ANTHONIE W.A. LENSING, M.D., PH.D., HARRY R. BÜLLER, M.D., PH.D., ALBERTO COGO, M.D., MARTIN H. PRINS, M.D., ANNA M. CATTELAN, M.D., STEFANO CUPPINI, M.D., FRANCO NOVENTA, M.D., AND JAN W. TEN CATE, M.D., PH.D.



Prevalenza del cancro occulto nel TEV idiopatico

Table 1. Period Prevalence of Previously Undiagnosed Cancer in Patients with VTE

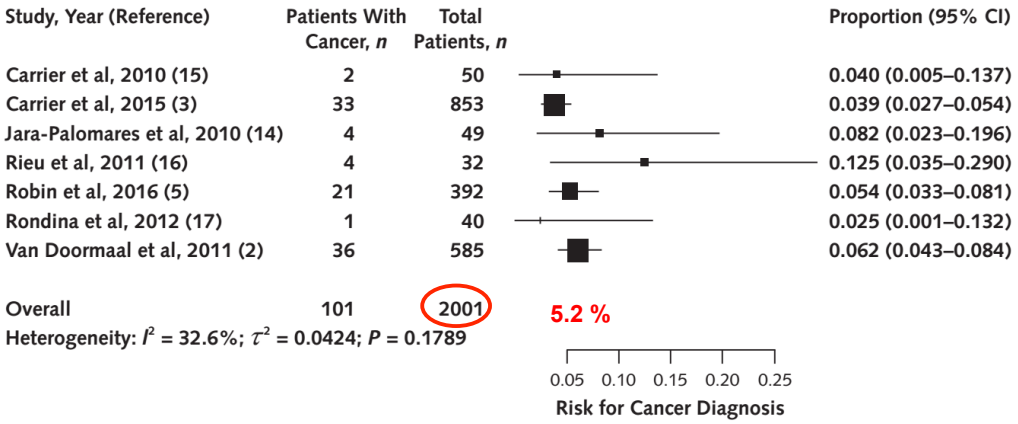
Ps 9516

Time Point and Type of VTE (Reference)	Period Prevalence of Previously Undiagnosed Cancer (95% CI), %
Baseline to 12 mo (0 to ≤12 mo)	
Overall (11–13, 17, 20–21, 23–29, 33–40, 43–44, 46)	6.3 (5.6–6.9)
Unprovoked (13, 17, 20–21, 23–24, 26–28, 35–36, 38–40, 43–44, 46)	10.0 (8.6–11.3)
Provoked (17, 21, 23–24, 27, 35, 38, 40, 44)	2.6 (1.6–3.6)

Carrier, Ann Intern Medicine 2008

Prevalenza del cancro occulto nel TEV idiopatico

2007→2016

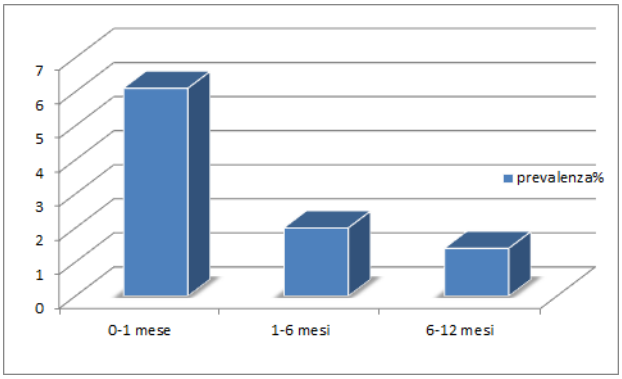


Cancer incidence non-VTE vs VTE: HR 2.26

van Es, An Intern Medicine 2017

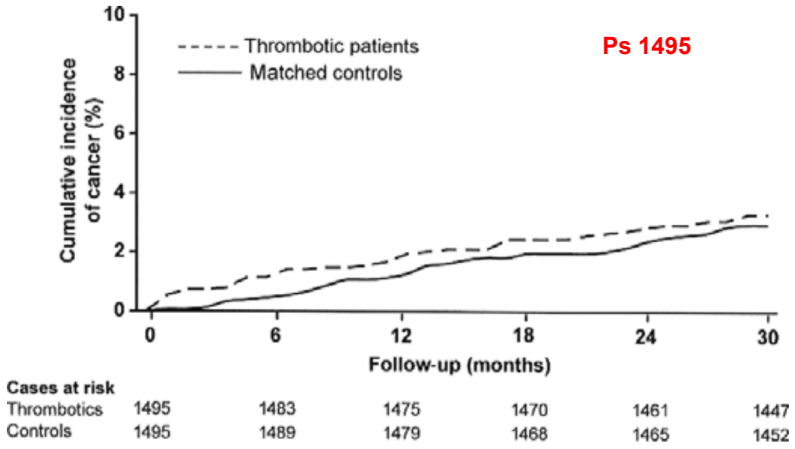
Sun, Journal of Thrombosis and Haemostasis, 2016

Andamento del rischio nel tempo



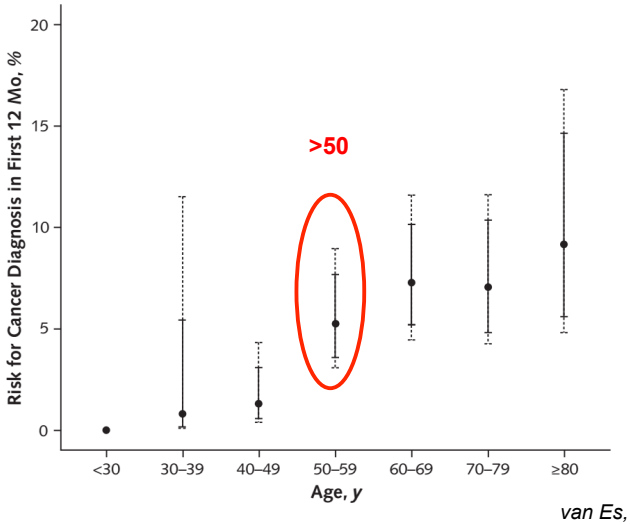
adapted from Carrier, Ann Intern Medicine 2008

Andamento del rischio nel tempo



Prandoni, J Thromb Haemost 2010

Fattori di rischio - età



van Es, Ann Intern Medicine 2017

Fattori di rischio - sesso

Controversie

- Robin: il genere maschile conferisce rischio maggiore. Negli uomini incidenza 8.7% vs 3.7% nelle donne dopo due anni di follow-up

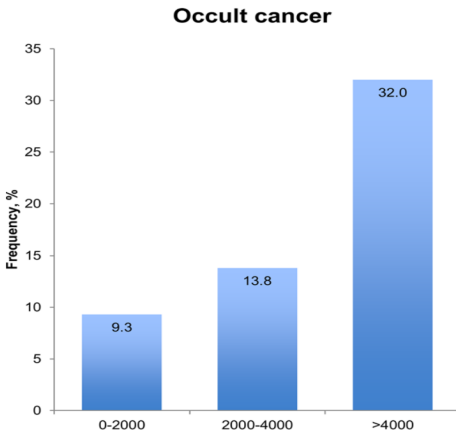
- Sun: non effettuata analisi specifica ma incidenze sovrapponibili. 2.47% annuo negli uomini Vs 1.97% nelle donne

- Jara Palomares: dai dati del registro RIETE la prevalenza fra i due sessi è simile (55% nei maschi vs 45% fra le femmine)

Robin, Thrombosis Research 2017
Sun, Journal of Thrombosis and Haemostasis, 2016
Jara-Palomares, Clin Appl Thromb Hemost. 2018

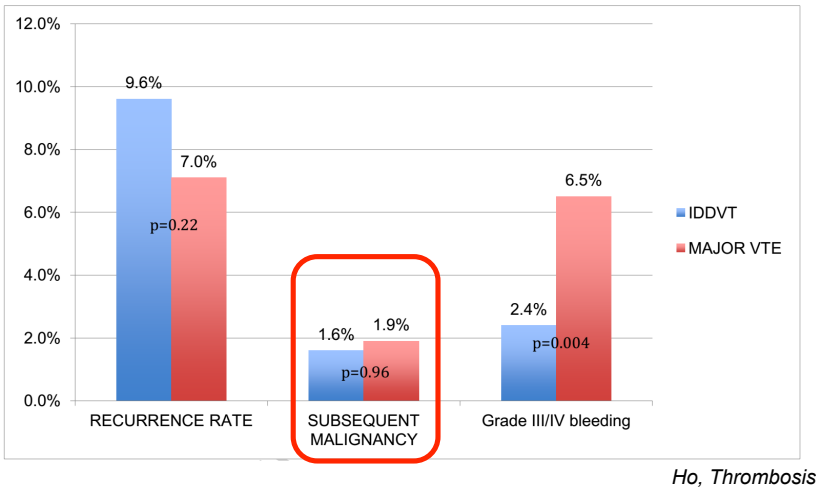
Fattori di rischio - GB e PLTs

	Risk of occult cancer (%)	P value
Gender		0.04
Male	8.7% (18/206)	
Female	3.8% (7/186)	
Age		0.01
≥ 50y	8.2% (24/291)	
< 50y	1% (1/101)	
Leukocytes count		0.004
≥ 10G/l	12.9% (12/93)	
< 10G/l	4.1% (12/290)	
Platelets count		0.03
≥ 350G/l	15.4% (6/39)	
< 350G/l	5.5% (19/347)	



Han, PLOS One 2016
Robin, Thrombosis research 2017

Situazioni particolari - trombosi venosa profonda distale



Ho, Thrombosis Research 2016

Situazioni particolari - trombosi venosa superficiale

Table 1 – Standardised cancer incidence ratios (SIRs) for all cancers for patients with venous thromboembolism during the first year of follow-up.

	Superficial thrombosis			Deep venous thrombosis			Pulmonary embolism			All venous thromboembolism		
	N	Observed no. of cancers	SIR (95%CI)	N	Observed no. of cancers	SIR (95%CI)	N	Observed no. of cancers	SIR (95% CI)	N	Observed no. of cancers	SIR (95% CI)
Total	7663	171	2.5 (2.1–2.9)	45,252	1236	2.7 (2.6–2.9)	24,332	717	3.3 (3.0–3.5)	77,247	2124	2.9 (2.8–3.0)
Female	4404	87	2.3 (1.8–2.8)	23,647	581	2.7 (2.5–2.9)	13,456	382	3.5 (3.1–3.8)	41,507	1050	2.9 (2.7–3.0)
Male	3259	84	2.7 (2.2–3.3)	21,605	655	2.8 (2.6–3.0)	10,876	335	3.1 (2.8–3.4)	35,740	1074	2.9 (2.7–3.1)
Age at thrombosis: <65	4905	66	3.0 (2.3–3.8)	25,322	399	3.5 (3.2–3.9)	10,400	258	5.5 (4.8–6.2)	40,627	704	3.9 (3.7–4.3)
Age at thrombosis: 65+	2758	105	2.2 (1.8–2.7)	19,930	837	2.5 (2.3–2.7)	13,932	459	2.7 (2.5–3.0)	36,620	1420	2.5 (2.4–2.7)

Sorensen, European Journal of Cancer, 2012

Incidence of Cancer after a Second Unprovoked Venous Thromboembolic Event

Prospective Cohort study **Ps 197**

Shéhérazade Rézig[1] Raphael Le Mao[1,2] Francis Couturaud[1,2,3] Karine Lacut[1,2] Aurélien Delluc[1,4]

What is known about this topic?

- VTE can be the first manifestation of cancer.
- The incidence of cancer after a second unprovoked VTE event is not clearly known.

What does this paper add?

- Cancer incidence after a second unprovoked VTE event occurring after anticoagulation discontinuation is similar to that after a first unprovoked VTE.
- Limited cancer screening might be reasonable after a second unprovoked VTE, except for patients who had their recurrent event less than 1 year after the first event, with bilateral DVT, past history of cancer and a VTE recurrence while on anticoagulation.

Rischio di recidiva 10 %

Rezig, Thrombosis and Haemostasis 2019

Sottopopolazioni a rischio - gravidanza

Table 2. SIRs of cancer among women with VTE during pregnancy and the postpartum period in Denmark, 1978-2013.

	All years		Within 6 months after VTE		Within 6-12 months after VTE		>12 months after VTE	
Cancer cases	**N**	**SIR (95% CI)**	**N**	**SIR (95% CI)**	**N**	**SIR (95% CI)**	**N**	**SIR (95% CI)**
All	250	1.01 (0.89-1.14)	4	1.77 (0.48-4.53)	3	1.24 (0.26-3.63)	243	1.00 (0.88-1.13)
VTE during pregnancy	64	1.24 (0.96-1.59)	0	—	3	3.27 (0.67-9.56)	61	1.23 (0.94-1.58)
Deep venous thrombosis	53	1.27 (0.95-1.66)	0	—	3	4.15 (0.86-12.12)	50	1.24 (0.92-1.63)
Superficial venous thrombosis	11	1.14 (0.57-2.03)	0	—	0	—	11	1.18 (0.59-2.11)
VTE in the postpartum period	186	0.94 (0.91-1.09)	4	2.86 (0.78-7.33)	0	—	182	0.94 (0.81-1.08)
Deep venous thrombosis	155	0.92 (0.78-1.08)	4	3.84 (1.05-9.84)	0	—	151	0.91 (0.77-1.06)
Superficial venous thrombosis	31	1.09 (0.74-1.54)	0	—	0	—	31	1.11 (0.76-1.58)

Tarp Hansen, Blood advances, 2017

Situazioni particolari - trombosi splancnica

Table 2. SIRs for cancer in 1191 patients with SVT, stratified by type of thrombosis

	Overall observed cancers and SIRs (95% CI)							
	Portal vein thrombosis		Hepatic vein thrombosis		Mesenteric vein thrombosis		Overall	
Cancer site								
Any	161	4.7 (4.0-5.5)	21	2.9 (1.8-4.4)	1	0.5 (0.0-2.5)	183	4.2 (3.6-4.9)
Liver	48	175 (129-232)	0	—	0	—	48	138 (101-182)
Myeloproliferative neoplasms	15	111 (62-184)	8	289 (125-570)	0	—	23	133 (85-200)
Pancreas	19	25 (15-40)	1	6.3 (0.2-35)	0	—	20	21 (13-32)

Soogard, Blood 2015

Situazioni particolari - malattia mieloproliferativa occulta

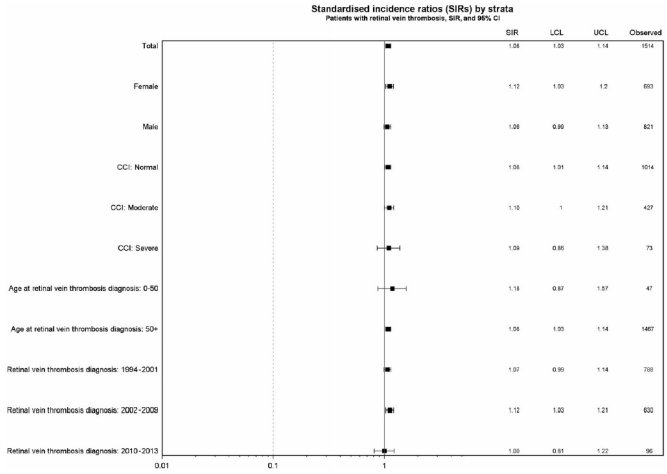
- Nel 25-65% delle trombosi splancniche il disordine mieloproliferativo è occulto, poichè non vi sono anomalie all'esame emocromocitometrico
- Importanza della diagnosi molecolare → JAK-2 e CALR

Sarid, IMAIJ 2013

ORIGINAL RESEARCH

WILEY Cancer Medicine Open Ac

Retinal vein thrombosis and risk of occult cancer: A nationwide cohort study



Tarp Hansen, Thrombosis and Haemostasis 2019

Scores di rischio - RIETE

	β	Odds ratio	95% CI Lower	95% CI Upper	*p*	**Points**
Underlying conditions						
Male gender	.378	1.46	1.19	1.79	<0.001	**+1**
Age >70 years	.642	1.90	1.55	2.33	<0.001	**+2**
Chronic lung disease	.338	1.40	1.07	1.84	.015	**+1**
Anaemia	.539	1.71	1.38	2.13	<0.001	**+2**
Platelets ≥350x10^6/mm^3	.334	1.40	1.03	1.90	.034	**+1**
Risk factors for VTE						
Postoperative	-.722	.49	.32	.73	<0.001	**-2**
Prior VTE	-.392	.68	.51	.89	.006	**-1**

ALTO rischio ≥ 3
BASSO rischio ≤2

Jara Palomares, Chest 2017

Scores di rischio - SOME

THROMBOSIS AND HEMOSTASIS

Risk factors predictive of occult cancer detection in patients with unprovoked venous thromboembolism

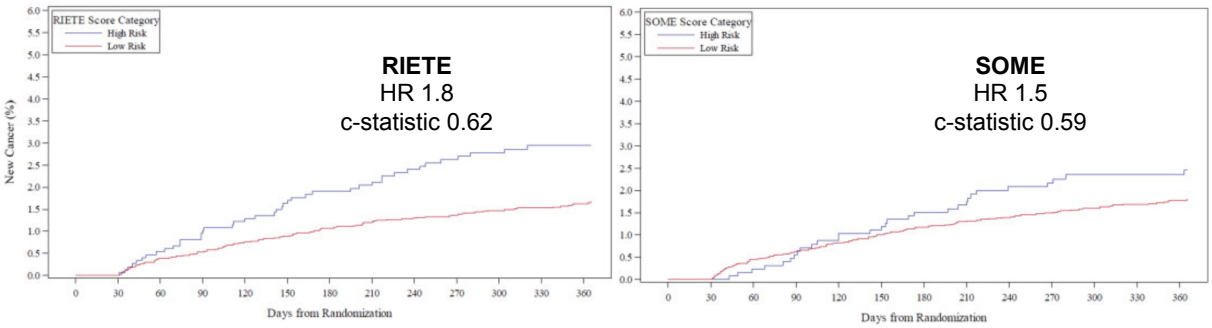
- Età > 60 anni +1
- Pregresso episodio di TEV provocato +1
- Tabagismo attivo +1

ALTO rischio ≥ 2
BASSO rischio ≤1

Ihaddadene, Blood 2016

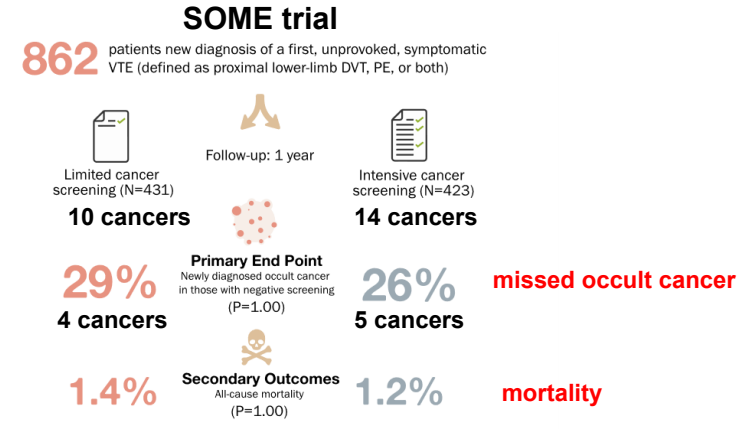
Scores di rischio - applicazione

Ps 854



Kraaijpoel, Thromb Haemost 2018

Strategie di screening



Carrier NEJM 2015

Strategie di screening

Extensive Computed Tomography versus Limited Screening for Detection of Occult Cancer in Unprovoked Venous Thromboembolism: A Multicenter, Controlled, Randomized Clinical Trial

Paolo Prandoni, MD, PhD[1] Enrico Bernardi, MD, PhD[2] Fabio Dalla Valle, MD[1] Adriana Visonà, MD[3] Pietro F. Tropeano, MD[4] Carlo Bova, MD[5] Eugenio Bucherini, MD[6] Md Shahidul Islam, MD, PhD[7,8] Andrea Piccioli, MD, PhD[1]

- **Nessuna differenza nel numero di casi diagnosticati**
- **Nessuna differenza nel numero di falsi negativi**
- **Non differenze di mortalità nei due gruppi**

Prandoni, Semin Thromb Hemost 2016

Strategie di screening

MVTEP study: limited versus PET/TC screening strategy

	Limited	Extensive	p
Cancer diagnosis at screening	2.0%	5.6%	0.065
Missed occult cancer after 24 m	4.7%	0.5%	0.02
Advanced cancer stage	54%	42%	0.7
Cancer related Mortality	2.5%	1%	/

Robin, Lancet Oncology 2015

Strategie di screening

Annals of Internal Medicine REVIEW

Screening for Occult Cancer in Patients With Unprovoked Venous Thromboembolism

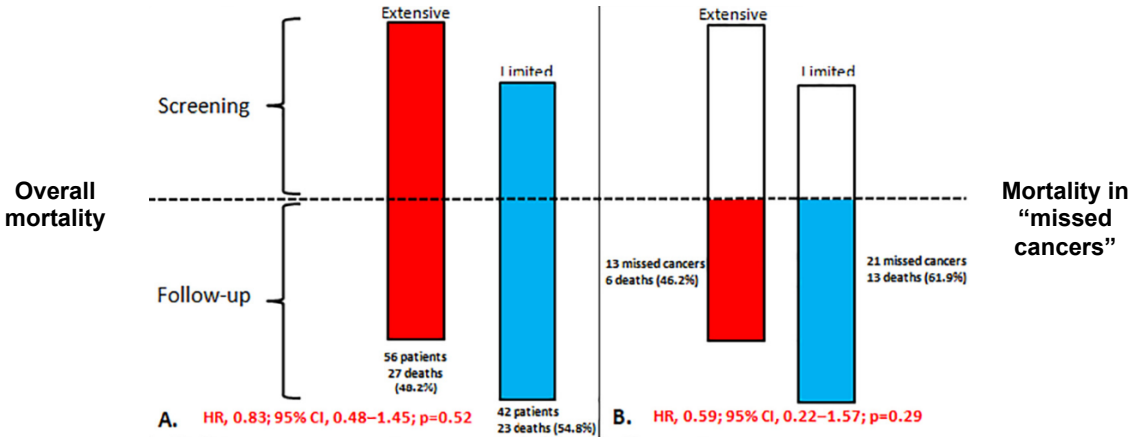
A Systematic Review and Meta-analysis of Individual Patient Data

- Lo screening estensivo porta alla diagnosi di cancro in un numero doppio di casi rispetto allo screening limitato
- Nessuna differenza statisticamente significativa nell'individuare il cancro nel suo stadio più precoce
- Non dati sulla mortalità

Robin, Lancet Oncology 2015

Strategie di screening - impatto sulla mortalità

Ps 1830



Robin, Thrombosis Research 2018

Cost-effectiveness

Cost effectiveness of the addition of a comprehensive CT scan to the abdomen and pelvis for the detection of cancer after unprovoked venous thromboembolism

Conclusions and relevance: The addition of a comprehensive CT scan of the abdomen/pelvis for the screening of occult cancer in patients with unprovoked VTE is not cost effective, as it is both more costly and not more effective in detecting occult cancer.

In patients with unprovoked VTE, does the addition of FDG PET/CT to a limited occult cancer screening strategy offer good value for money? A cost-effectiveness analysis from the publicly funded health care systems

Conclusion: Addition of a FDG PET/CT for occult cancer diagnosis was associated with better health outcomes

Coyle, Thrombosis Research 2017
Robin, Thrombosis Research 2018

Raccomandazioni dalle linee guida

1.5 Investigations for cancer

1.5.1 Offer all patients diagnosed with unprovoked DVT or PE who are not already known to have cancer the following investigations for cancer:

- a physical examination (guided by the patient's full history) **and**
- a chest X-ray **and**
- blood tests (full blood count, serum calcium and liver function tests) **and**
- urinalysis. **[2012]**

1.5.2 Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or PE who do not have signs or symptoms of cancer based on initial investigation (see recommendation 1.5.1). **[2012]**

NICE guidelines 2012

RECOMMENDATIONS AND GUIDELINES

Occult cancer screening in patients with venous thromboembolism: guidance from the SSC of the ISTH

A. DELLUC,* D. ANTIC,† R. LECUMBERRI,‡ C. AY,§ G. MEYER¶ and M. CARRIER**

Unprovoked

Recommendations

1 Patients with unprovoked VTE should undergo limited cancer screening, including a thorough medical history and physical examination, laboratory investigations (complete blood count, calcium, urinalysis, and liver function tests), and chest X-ray.
2 Age-specific and gender-specific cancer screening (colon, breast, cervix, and prostate) should also be performed according to national recommendations.

Recurrent unprovoked VTE

Recommendations

1 Patients with recurrent unprovoked VTE should undergo limited cancer screening (see above for details).
2 Age-specific and gender-specific cancer screening should also be performed according to national recommendations.
3 A lower threshold for cancer detection may be reasonable.

Delluc, Journal of Thrombosis and Haemostasis 2017

RECOMMENDATIONS AND GUIDELINES

Occult cancer screening in patients with venous thromboembolism: guidance from the SSC of the ISTH

A. DELLUC,* D. ANTIC,† R. LECUMBERRI,‡ C. AY,§ G. MEYER¶ and M. CARRIER**

Unusual site VTE

Recommendations

1 Patients with unusual site VTE should undergo limited cancer screening (see above for details).
2 Age-specific and gender-specific cancer screening should also be performed according to national recommendations.
3 In patients with splanchnic vein thrombosis or cerebral vein thrombosis, we suggest testing for underlying myeloproliferative disorder by the use of JAK 2V617F testing.
4 In patients with splanchnic vein thrombosis and aplasia or hemolytic anemia, and in patients with Budd–Chiari syndrome, we suggest testing for PNH.

Delluc, Journal of Thrombosis and Haemostasis 2017

Prospettive future

REVIEW ARTICLE

WILEY rpth | isth

Occult cancer detection in venous thromboembolism: the past, the present, and the future

Faizan Khan BSc[1,2] | Alvi Rahman BHSc[1] | Marc Carrier MD, MSc[2,3]

- Nuovi markers di malattia neoplastica, che identifichino le cellule tumorali circolanti.
- NCT02739867: Tumor-educated Platelets in Venous Thromboembolism

Delluc, Journal of Thrombosis and Haemostasis 2017

Conclusioni

- Nei pazienti con TEV apparentemente idiopatico, uno su venti è portatore di una neoplasia occulta
- Molteplici i predittori di rischio, il più importante è l'età
- Gli scores di rischio fino ad ora sviluppati non sono molto utili
- Le strategie estensive di screening, nonostante consentano di individuare un numero maggiore di neoplasie, e di farlo più precocemente, non portano ad un beneficio clinico netto
- Considerato il livello attuale delle conoscenze, non appare giustificato l'utilizzo sistematico di strategie estensive di screening