Cancer and Venous Thromboembolism

- Objectives
  1. Epidemiology of thrombosis in patients with malignancy
  2. Anticancer agents and thrombosis
  3. Current treatment protocols at UHN
  4. Prevention of DVT
  5. Asymptomatic DVT
  6. Newer antithrombotic agents

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Epidemiology of Thrombosis in Patients with Malignancy

- 4-12% of pt with VTE have concomitant cancer, higher with idiopathic, often advanced ca
- Numerous articles suggest – hx, O/E, lab tests and basic imaging are sufficient and cost effective (~80%)
- In patients with malignancy – second leading cause of death
- Compared with non-cancer patients risk of symptomatic VTE, 6-7 x higher in cancer pt with similar risks
- Until recently incidence and time course unknown, small cohort studies incidence ~4% among various pt groups

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Chew HK, Arch Int Med, Feb 2006

- California Cancer registry, assessed incidence and timing of VTE within 1-2 years after after diagnosis in 12 different malignancies
- 1.6% pt developed VTE within 2 yr (12% at time of diagnosis, 88% subsequently)
- Metastatic disease at diagnosis strongest prediction of VTE (56% of concurrent) 5-20x higher than local disease
- Pancreatic > stomach > bladder > uterine > renal > lung
- After adjustment for age, race, stage at time of diagnosis: within 1 yr – VTE diagnosis significant predictor of death

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Blom et al, JAMA , Feb 2005

- Netherlands - 3220 consecutive pt with VTE
- 7x ↑ risk of VTE with malignancy
- Pt with hematologic malignancies highest risk > lung > GI
- Risk highest in first few months, those with mets
- Factor V Leiden 12x risk

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Determinants of Risk of VTE in Cancer

1. Tumour stage
2. Tumour type
3. Anticancer therapy
4. Surgery
5. Prothrombotic abnormalities

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1. Tumour stage
   - Chow et al - metastatic – strongest predictor of VTE (4-13 x higher than localized)
   - Blom et al – those with metastatic disease, odds ratio 20
2. Tumour type
   - all tumour associated with VTE, relative risk varies from study to study
   - Blom et al hematologic highest, lung ca, GI
   - others pancreatic, lymph, brain highest followed by liver, leukemia, GI, Gyn

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4. Surgery
   - 2x greater risk in cancer/non-cancer patients
   - Some studies up to 3-4% cystectomy, neurosurgery
5. Prothrombotic abnormalities
   - immobilization, age, hypercoag states
   - FVL had 12x risk in cancer verses non-cancer pt, same for prothrombin mutation

Recurrent clots
   - after discontinuing warfarin, 2x risk ↑of recurrence in cancer patients
   - cancer pt who have DVT – 3x ↑ risk of recurrence in first 12 months compared to those without
   - Prandoni (2002 – 6.8 % recurrence in non-cancer pt verses 21% in those with cancer)

Prognosis

- Developing VTE predicts worse prognosis
- 1 yr survival 12% in pt with cancer and VTE, compared to 36% without VTE (Danish Registry)
- Other studies more than 2 fold higher mortality

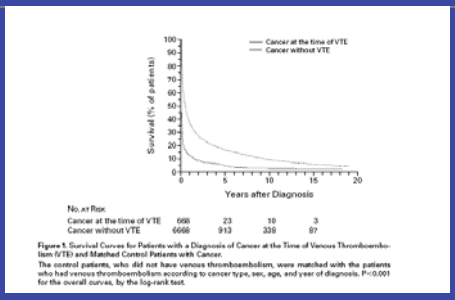

Figure 1. Survival Curves for Patients with a Diagnosis of Cancer at the Time of Venous Thromboembolism (VTE) and Matched Control Patients with Cancer.
The control patients, who did not have venous thromboembolism, were matched with the patients who had venous thromboembolism according to cancer type, sex, age, and year of diagnosis. P<0.001 for the overall curves, by the log-rank test.

Anticancer Agents and Thrombosis

- Chemotherapy well established as an independent risk factor for thrombosis and presently the most changing determinant
- Annual incidence ~11% of VTE in ca pt on chemo, climb as high as 20% depending on type (cancer pt 4x ↑ risk VTE, 6x when chemo)
- **Breast cancer**
  - Best evidence for role of chemo in VTE
  - DVT early breast ca – 1%, if adjuvant chemo 2-10%
  - Levine (Thromb Hemost 97)
    - stage II breast ca – CMFVP ± doxorubin + tamoxifen
    - 7% during chemo none while off. Stage IV disease 18%.
    - more recent Epirubin/Cyclo = 10%

Tamoxifen

- Women risk ↑ 2-3x N (similar to BCP/HRT)
- In early stage postsurgery 1.5 – 7 ↑ risk (post menopausal 3x higher than pre)
- When taken with chemo risk 3-8x ↑ than tamoxifen alone, 3-5x greater than chemo alone and 20x greater than no Rx
- Aromatase inhibitors
  - 1-2% incidence DTE, risk lower than tamoxifen

Thalidomide

- Monotherapy - ~5% risk, with dexamethasone 10-20% and with concurrent chemo – 20-40%
- Prophylactic LMWH may reduce risk, not low dose warfarin, ? role ASA
- Thalidomide analogues – Revlamid - ? thrombogenity appears ↑ with dexamethasone, several studies suggest ASA works – need for randomized

- Cisplatinum - germ cell tumors – 8.4%, lung cancer 17.6%, cervical cancer 16.7%
- L-asparaginase 4-14% in adults
- Bevacizomib colorectal 9% vs 19% (FU/LU)
  - other studies no ↑

EPO – definitely ↑ risk esp ↑ Hb

Radiation – theoretical but no reliable studies

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Treatment Protocol - UHN

- Cancer patients often ↑ risk of bleeding, VTE additional negative impact in quality of life, overall ↑ mortality compared to ca patient without VTE
- TGH Thrombosis Unit, cancer pt ~50% of new pt
- Symptomatic verses asymptomatic

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Risk of Recurrence

- Initial studies IV hep/LMWH, retrospective analysis of 3 months Rx → recurrence 27/100 pt years in cancer verses 9/100 pt years non-cancer, bleeding risk 6x ↑, 13/2 per 100 pt year
- Prandoni - cohort 842 pt - recurrence 20% / 7% (cancer/non-cancer), bleeding 12.5%/5%

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Initial Rx

- LMWH (outpatient) – standard initial Rx for all DVT/PE pt except renal failure/high bleeding risk (up to 80%)
  - some evidence twice daily LMWH better in cancer but no formal studies
  - no role for IVC filters in most pt

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Long Term Therapy

- Several previous studies – not specifically on cancer pt , no definite conclusion
- 2 more recent studies – changed dramatically the way we treat pt

Meyer et al. Arch Int Med 2002

- warfarin verses enoxaparin daily x3 months
- Warfarin – 21% major outcome events verses 10% LMWH
  - 6 deaths due to warfarin verses 0 in LMWH

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- Lee et al. NEJM, 2003 (Clot Study)
  - Fragmin verses warfarin x 6 months
  - 15.7% recurrent DVT in warfarin verses 8.0 on LMWH
  - major bleeding 3.6% warfarin, 5.6% LMWH (not significant)

Therefore LMHW – standard Rx for cancer pt

- reduces recurrence, no ↑ risk bleeding

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ACCP Guidelines

- 3-6 months of LMWH, grade 1A
- Consider therapy indefinitely or until cancer resolved (grade 1C)

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ASCO Guidelines (2007)

1. LMWH – preferred for initial 5-10 days
2. LMWH – for 6 months preferred over OA (INR 2-3)
3. After 6 months – continue Rx for those with metastatic disease or those on chemotherapy
4. IVC filter only for those with contraindication to anticoagulants or recurrent DVT despite adequate therapy
5. CNS malignancy – watch for bleeding
6. Elderly same as young

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TGH

- All cancer pt offered LMWH x6 months
- Monitor platelet count weekly x3 then monthly
- Dose reduction – for creatine clearance <30
- After 6 months, ? based on risk of bleeding verses recurrence
- No clinical trials – but definitely ↑ risk of recurrence
- Recurrence depends on presence of disease, chemo, level of mobility, if clot still present
- Recommend onging Rx for at least 6 months after chemo/radiation depending if any disease present. If no disease – suggest stop Rx. If disease still present – offer ongoing LMWH or oral anticoagulants
- ? Value of hypercoag workup

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Prevention of DVT

- ACCP Guidelines

1. Cancer & surgery – guidelines as relevant to surgery itself
2. Bedridden with acute illness – routine medical prophylaxis
3. Indwelling catheters, not use prophylactic LMWH (1B) or minidose warfarin (1B)
4. Chemo/hormone therapy – recommend against routine prophylaxis
5. Survival – recommend against routine use

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Prevention of DVT – cont'd

- ASCO Guidelines

1. Anticoagulants are not recommended to improve survival
2. Hospitalized pt should be given VTE prophylaxis
3. Surgical pt at least 7-10 days post-op prophylaxis
4. Routine prophylaxis not recommended, but thalidomide/lenolidomide with chemo or dex should receive LMWH or warfarin (INR 1.5)

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Asymptomatic DVT/PE

- At UHN asymptomatic DVT/PE up to 25% of patients seen in clinic
- Am J Roentgent, July 2007
  - 435 elective screening CT scans
  - prevalence of 6.8% unsuspected iliofemoral DVT, 1.2% unsuspected common iliac, 0.3% IVC DVT, 3.3% PE, overall 6.3%
  - more common in inpatients and RR 1.6 with advanced disease
  - other studies – unsuspected PE 1.5% routine CT chest with rates 2.6 – 3.4% in malignancies

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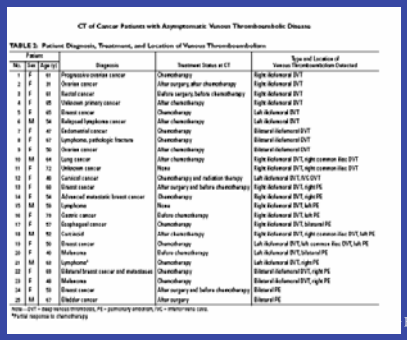


CT of Cancer Patients with Asymptomatic Venous Thromboembolic Disease

TABLE 2: Patient Diagnosis, Treatment, and Location of Venous Thromboembolism

Patient No.	Sex	Age (y)	Diagnosis	Treatment Status at CT	Type and Location of Venous Thromboembolism Detected
1	F	61	Progressive ovarian cancer	Chemotherapy	Right iliofemoral DVT
2	F	51	Ovarian cancer	After surgery, after chemotherapy	Right iliofemoral DVT
3	F	61	Rectal cancer	Before surgery, before chemotherapy	Right iliofemoral DVT
4	F	65	Unknown primary cancer	After chemotherapy	Right iliofemoral DVT
5	F	45	Breast cancer	Chemotherapy	Left iliofemoral DVT
6	M	56	Relapsed lymphoma cancer	After chemotherapy	Left iliofemoral DVT
7	F	47	Endometrial cancer	Chemotherapy	Bilateral iliofemoral DVT
8	F	57	Lymphoma, pathologic fracture	Chemotherapy	Bilateral iliofemoral DVT
9	F	76	Ovarian cancer	After chemotherapy	Bilateral iliofemoral DVT
10	M	64	Lung cancer	After chemotherapy	Right iliofemoral DVT, right common iliac DVT
11	F	72	Unknown cancer	None	Right iliofemoral DVT, right common iliac DVT
12	F	46	Cervical cancer	Chemotherapy and radiation therapy	Left iliofemoral DVT, IVC/SVC DVT
13	F	60	Breast cancer	After surgery and before chemotherapy	Right iliofemoral DVT, right PE
14	F	54	Advanced metastatic breast cancer	Chemotherapy	Right iliofemoral DVT, right PE
15	M	76	Lymphoma	None	Right iliofemoral DVT, left PE
16	F	79	Gastric cancer	Before chemotherapy	Right iliofemoral DVT, left PE
17	F	67	Esophageal cancer	Chemotherapy	Right iliofemoral DVT, bilateral PE
18	M	62	Carcinoid	After chemotherapy	Right iliofemoral DVT, right common iliac DVT, left PE
19	F	56	Breast cancer	Chemotherapy	Left iliofemoral DVT, left common iliac DVT, left PE
20	F	40	Melanoma	Before chemotherapy	Left iliofemoral DVT, bilateral PE
21	M	62	Lymphoma*	Chemotherapy	Left iliofemoral DVT, right PE
22	F	68	Bilateral breast cancer and metastases	Chemotherapy	Bilateral iliofemoral DVT, right PE
23	F	48	Melanoma	Chemotherapy	Bilateral iliofemoral DVT, right PE
24	F	76	Breast cancer	After surgery and before chemotherapy	Bilateral PE
25	M	67	Bladder cancer	After surgery	Bilateral PE

Note.—DVT = deep venous thrombosis, PE = pulmonary embolism, IVC = interior vena cava.
*Partial response to chemotherapy

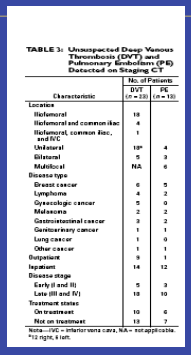


TABLE 3: Unsuspected Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) Detected on Staging CT

Characteristic	No. of Patients: DVT (n = 23)	PE (n = 10)
Location		
Iliofemoral	18	
Iliofemoral and common iliac	4	
Iliofemoral, common iliac, and IVC	1	
Unilateral	19*	4
Bilateral	5	3
Multifocal	NA	6
Disease type		
Breast cancer	6	5
Lymphoma	4	2
Gynecologic cancer	5	0
Melanoma	2	2
Gastrointestinal cancer	3	2
Genitourinary cancer	1	1
Lung cancer	1	0
Other cancer	1	1
Outpatient	9	1
Inpatient	14	12
Disease stage		
Early (I and II)	5	3
Late (III and IV)	18	10
Treatment status		
On treatment	10	6
Not on treatment	13	7

Note.—IVC = inferior vena cava, NA = not applicable.
*12 right, 4 left.

- JCO, Oct 2006
  - 59 pt unsuspected PE
  - up to 75% had symptoms – fatigue and SOB
  - 20% had previous VTE
  - no diff if chemo; central line or EPO

Asymptomatic PE

- ACCP Guidelines

1. Review CT scans to see if findings are convincing
2. Recommend same treatment as with symptomatic PE (1C)

- In Toronto variable approaches, especially to subsegmental PE's. (Options)
  1. Full dose treatment
  2. Dopplers – if negative, no treatment
  3. ? Role for prophylaxis

Newer Antithrombotic Agents

Present Medications
-Warfarin/LMWH

Newer Medications

Indirect AT-Mediated
-Fondaparinux (sc)
-Idraparinux(sc)
-Dabigatran Extilate (oral)

Direct(Factor Xa)
-Rivaroxaban

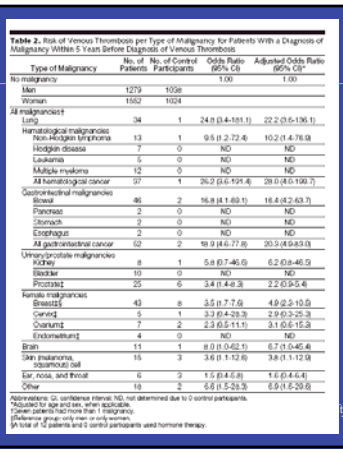
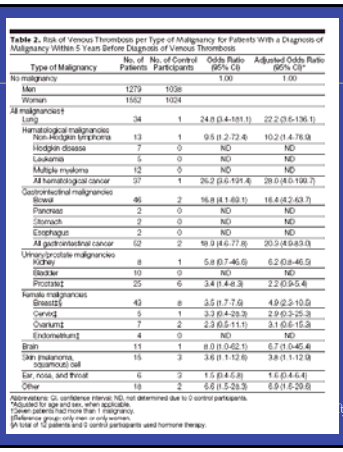


Table 2. Risk of Venous Thrombosis per Type of Malignancy for Patients With a Diagnosis of Malignancy Within 5 Years Before Diagnosis of Venous Thrombosis

Type of Malignancy	No. of Patients	No. of Control Participants	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
No malignancy			1.00	1.00
Men	1279	1038		
Women	1562	1024		
All malignancies†	34	1	24.8 (3.4–181.1)	22.2 (3.0–166.1)
Lung				
Hematological malignancies				
Non-Hodgkin lymphoma	13	1	9.5 (1.2–72.4)	10.2 (1.4–76.9)
Hodgkin disease	7	0	ND	ND
Leukemia	5	0	ND	ND
Multiple myeloma	12	0	ND	ND
All hematological cancer	37	1	26.2 (3.6–191.4)	28.0 (4.0–198.7)
Gastrointestinal malignancies				
Bowel	46	2	16.8 (4.1–69.1)	16.4 (4.2–63.7)
Pancreas	2	0	ND	ND
Stomach	2	0	ND	ND
Esophagus	2	0	ND	ND
All gastrointestinal cancer	52	2	18.9 (4.6–77.8)	20.9 (4.9–89.0)
Urinary/prostate malignancies				
Kidney	8	1	5.8 (0.7–46.6)	6.2 (0.8–46.5)
Bladder	10	0	ND	ND
Prostate‡	25	6	3.4 (1.4–8.3)	2.2 (0.9–5.4)
Female malignancies				
Breast‡	43	8	3.5 (1.7–7.6)	4.9 (2.2–10.8)
Cervix‡	5	1	3.3 (0.4–28.3)	2.9 (0.3–25.3)
Ovarium‡	7	2	2.3 (0.5–11.1)	3.1 (0.6–15.3)
Endometrium‡	4	0	ND	ND
Brain	11	1	8.0 (1.0–62.1)	6.7 (0.9–45.4)
Skin (melanoma, squamous) cell	15	3	3.6 (1.1–12.0)	3.8 (1.1–12.9)
Ear, nose, and throat	6	2	1.5 (0.4–5.8)	1.6 (0.4–6.4)
Other	18	2	5.6 (1.5–20.3)	6.9 (1.8–26.6)

Abbreviations: CI, confidence interval; ND, not determined due to 0 control participants.
*Adjusted for age and sex, when applicable.
†Seven patients had more than 1 malignancy.
‡Reference group: only men or only women.
§A total of 12 patients and 0 control participants used hormone therapy.



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All hematological cancer	37	1	26.2 (3.6–191.4)	28.0 (4.0–199.7)
Gastrointestinal malignancies				
Bowel	46	2	16.8 (4.1–69.1)	16.4 (4.2–63.7)
Pancreas	2	0	ND	ND
Stomach	2	0	ND	ND
Esophagus	2	0	ND	ND
All gastrointestinal cancer	62	2	18.9 (4.6–77.8)	20.3 (4.9–83.0)
Urinary/prostate malignancies				
Kidney	8	1	5.8 (0.7–46.6)	6.2 (0.8–46.5)
Bladder	10	0	ND	ND
Prostate‡	25	6	3.4 (1.4–8.3)	2.2 (0.9–5.4)
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Central Venous Catheters

- Initial small studies suggested coumadin 1 mg daily or LMWH prophylaxis reduced thrombosis
- Recent met analysis for cancer and central lines – low dose warfarin 6.34% verses 7.5%
- Cochrane Database Systemic Review 2007
  - LMWH trend to reducing DVT – not statistically significant
  - Warfarin not significant

Central line thrombosis – up to 37% venography, lower in ultrasound

- ? how long to treat
- Remove line or not ?
- Risk of embolization ?

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Cancer Survival and anticoagulants

- Theoretical evidence that anticoagulants exert negative impact on tumour angiogenesis by interfering with thrombin activity or tissue factor activation
- Met analysis of early studies – UFH/LMWH suggested survival benefit of LMWH independent of PE/bleeding
- FAMOUS study – J Clin Onc 2004
  - 385 pt – Fragmin 5000 unit/placebo x 1 yr
    - Placebo group 41%/18%/12%: 1, 2, 3 yr
    - Survival verses fragmin 46%/27%/21% - not significant
  - 2 further studies variable results

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Cancer Survival and anticoagulants – cont'd

- Recent lung cancer – J Thromb Hemost 2004
  - Chemo ± LMWH in small cell lung ca significant ↑ progression free and overall survival
- Cochrane Review – Sept 2007
  - LMWH – 8% reduction in 1 yr mortality, warfarin 3%, bleeding 1% in LMWH, higher in warfarin

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