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Asymptomatic deep vein thrombosis and superficial vein thrombosis in ambulatory cancer patients: impact on short-term survival

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BACKGROUND: Asymptomatic venous thrombotic events (VTEs) are possible findings in ambulatory cancer patients. Data regarding the incidence and clinical impact of asymptomatic VTEs are conflicting. We therefore conducted a study to evaluate the occurrence of asymptomatic VTEs of the lower limbs in ambulatory cancer patients to further evaluate the association of these asymptomatic VTEs on survival during a 9-month follow-up period.

METHODS: In our prospective cohort, we included 150 consecutive ambulatory cancer patients who were free of any clinical symptoms for VTEs. Compression ultrasound to detect deep vein thrombosis (DVT) and superficial venous thrombosis (SVT) of the lower limbs was performed by a vascular specialist in all patients at baseline. In case of pathological findings the patients were treated with low molecular weight heparin (LMWH) because of current established guidelines. The occurrence of death was investigated during a 9-month follow-up period.

RESULTS: A total of 27 (18%) patients with VTEs were detected, which included 13 patients (8.7%) with a SVT and 16 patients (10.7%) showing a DVT. Two patients had both, a SVT and a DVT as well. During the 9-month follow-up period the occurrence of a VTE at baseline was associated with a 2.4-fold increased risk for death (HR 2.4 (1.2–5.3); $P = 0.03$).

CONCLUSION: Asymptomatic VTEs of the lower limbs in ambulatory cancer patients are frequently occurring concomitant features and are associated with poor survival during a 9-month follow-up period despite anticoagulation with LMWH.

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Venous thrombotic events (VTEs) are important and life-threatening complications for hospitalised cancer patients as well as for ambulatory cancer patients (Deitcher, 2003; Khorana *et al*, 2007). Symptomatic VTEs, namely deep vein thrombosis (DVT) and pulmonary embolism (PE), are frequently found and depend on cancer type and the administered type of chemotherapy. Recently, Menapace *et al* (2011) reported that symptomatic and asymptomatic VTEs occurred in more than one third of pancreatic cancer patients. Both were associated with an increased mortality rate (Menapace *et al*, 2011).

The impact of symptomatic VTEs on survival is discussed controversially in recent literature. In some studies VTE was a significant predictor of death (Lee *et al*, 2010; Sandhu *et al*, 2010), in other studies no adverse impact on survival has been demonstrated (Shah *et al*, 2010).

Asymptomatic VTEs are possible findings especially accidentally diagnosed in computed tomography (CT) scans performed for the purpose of staging of cancer patients. In one recent study, which included a wide range of different cancer types, the prevalence of incidental VTEs was described with 2.5% (Douma *et al*, 2010). Impact on survival of these asymptomatic VTEs was not investigated in this study. In most studies performed in this field the coexistence of venous thrombosis of the superficial venous system (SVT) is not investigated, although anticoagulation should be initiated as well, and progression of the thrombotic event and further involvement of the deep veins might occur.

A drawback of most studies published in the field of asymptomatic VTEs in cancer patients is the retrospective study design as well as the close association to CT scans mainly performed for staging purpose. We therefore conducted a prospective cohort study in ambulatory cancer patients evaluating the occurrence of VTEs of the lower limbs by using compression ultrasound (CUS). We further investigated a possible association of asymptomatic VTEs of the lower limbs with the survival of the patients during a 9-month follow-up period. As SVT are frequently found in cancer patients we also evaluated the superficial veins of the lower limbs of the patients included with CUS. A VTE event was therefore defined in our study as either a DVT or a SVT of the lower limbs.

MATERIALS AND METHODS

Study population

We included 150 consecutive patients at the outpatient clinic of the Division of Oncology at the Medical University of Graz, Austria.

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All patients were completely asymptomatic with regard to a potential VTE. None of the patients had asymptomatic PE confirmed by CT scan performed for staging purpose, neither did the patients included in our study show any signs of a DVT event, as defined by swelling, tender or pain of the lower limbs in the weeks before inclusion in the study. Further exclusion criteria were a positive history for VTE or any anticoagulant treatment given. Our study was approved by the local ethics committee (EK 24–160).

Diagnosis of asymptomatic VTE of the lower limbs

Compression ultrasound was performed by two experienced vascular specialists in all patients at baseline. To evaluate possible venous thrombosis in the pelvic veins, a duplex Doppler sonography of the common femoral vein was performed after a Valsalva manoeuvre. The flow velocity during respiratory manoeuvre was revealed. Afterwards, CUS was performed including the common femoral vein, the superficial femoral vein, the popliteal vein, the calf veins and the superficial lower limb veins in steps of 10 mm on both legs. Lack of vein compressibility was taken as diagnostic of DVT or SVT.

Treatment of asymptomatic VTE of the lower limbs

In case of diagnosis of a venous thrombosis anticoagulant treatment with low molecular weight heparin (LMWH) was initiated according to current guidelines (Kearon *et al*, 2012).

As for patients with asymptomatic DVT the same anticoagulant treatment is recommended, as in symptomatic DVT patients LMWH was given in a therapeutic dosage for 4 weeks. After 4 weeks the dosage was changed to 75% of the therapeutic dosage given once daily. Anticoagulant therapy was given for at least 3 months and as long as cancer was active or chemotherapy was given.

In symptomatic SVT treatment with LMWH in prophylactic dosage is recommended in current guidelines. In SVT recommendations concerning treatment of asymptomatic patients are not outlined in the current guidelines. However, as progression of venous thrombosis to the deep venous systems is highly probable due to the thrombophilic situation in cancer patients, we decided to treat patients with asymptomatic SVT with LMWH. Treatment with LMWH in prophylactic dosage was therefore given for at least 4 weeks and as long as cancer was active or chemotherapy was given.

Follow-up visits

In case of detection of a VTE further follow-up visits were scheduled at the outpatient clinic of the Division of Angiology every 3 months for evaluation of risk and benefit of the LMWH therapy. Major bleeding events, defined in accordance to recent recommendations, were evaluated during each visit (Schulman and Kearon, 2005).

Patients with negative CUS had follow-up visits according to the management of their underlying malignant disease at the outpatient clinic of the Division of Oncology. Clinical symptoms for VTE were evaluated during these follow-up visits. In case of typical symptoms further evaluation for a VTE event was scheduled.

We choose a follow-up period of 9 months in our patients to evaluate short-term survival.

Statistical analysis

Clinical characteristics of subjects were analysed using descriptive statistics. For comparison of groups χ^2 test for categorical values and *t*-test for continuous variables were used. Continuous variables were described as median and its 25th and 75th percentile, categorical variables were described by absolute numbers and percentages. Kaplan–Meier analyses were performed to evaluate differences in survival between patients with and without asymptomatic thrombosis of the lower limbs. Log-Rank Tests were used to test, whether differences among groups were statistically significant.

Hazard ratios were calculated by a proportional hazards model using multivariable Cox regression analyzes. The multivariable Cox regression analyses included age, sex, stage of cancer (palliative *vs* curative), tumour entity (pancreatic cancer *vs* non-pancreatic cancer), chemotherapy, surgery and radiotherapy. The last three factors (chemotherapy, surgery and radiotherapy) were assumed to be thrombophilic during therapy and also 6 weeks afterwards. The statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) for windows.

RESULTS

Characteristics of the study population

In our prospective study the most frequently included tumour entities were colorectal and anal cancer (32.7%), breast cancer (22.7%) and pancreatic cancer (21.3%). Chemotherapy was applied to 124 (82.7%) patients. The majority of patients included had a palliative cancer stage (109 patients; 72.7%). Clinical characteristics of the patients included in our study are detailed in Table 1.

We found asymptomatic VTEs in 18% of our patients (27 patients). We were able to detect a total of 13 (8.7%) asymptomatic SVT all located in the saphenous system, and 16 (10.7%) asymptomatic DVT events. In two patients included in our study we detected both, a thrombotic event in the superficial venous system as well as in the deep venous system. From the 16 detected DVT events, 7 events were located proximal and 9 events were isolated distal DVT events (Table 1). None of our patients showed clinical signs of symptomatic PE.

Table 1 Baseline characteristics of all patients

Baseline characteristics	Value
Median age, years (25th–75th percentile)	65 (56–71)
Sex, n (%)	
Female	69 (46)
Male	81 (54)
Chemotherapy at time of CUS, *n* (%)	124 (82.7)
Palliative setting, *n*(%)	109 (72.7)
Primary malignancy, n *(%)*	
Colorectal and anal	49 (32.7)
Breast	34 (22.7)
Pancreatic	32 (21.3)
Lung	7 (4.7)
Gastroesophageal	7 (4.7)
Prostate	5 (3.3)
Bladder and renal	5 (3.3)
Hepatobiliary	4 (2.7)
Sarcoma	3 (2.0)
Head and neck	2 (1.3)
Miscellaneous	2 (1.3)
Asymptomatic venous thrombotic event of the lower limbs, n *(%)*	
Patients with asymptomatic venous thrombotic events	27 (18.0)
Deep vein thrombosis	16 (10.7)
Proximal DVT	7 (4.7)
Distal DVT	9 (6)
Superficial venous thrombosis	13 (8.7)

Abbreviations: CUS = compression ultrasound; DVT = deep vein thrombosis.

Table 2 Baseline characteristics and differences between groups of patients with asymptomatic venous thrombotic events and patients without venous thrombotic events of the lower limbs

Clinical characteristics	Patients with venous thrombosis	Patients without venous thrombosis	*P*
Median age, years (25th–75th percentile)	66 (57–74)	62 (55–70)	0.1
Sex, n (%)			
Female	8 (29.6)	61 (49.6)	0.09
Male	19 (70.4)	62 (50.4)	
Chemotherapy at time of CUS, *n* (%)	24 (88.9)	103 (84.4)	0.8
Palliative setting, *n* (%)	22 (81.5)	87 (70.7)	0.3
Primary malignancy, n *(%)*			
Pancreatic	8 (29.6)	24 (19.5)	0.3
Colorectal and anal	7 (25.9)	42 (34.1)	0.4
Breast	5 (18.5)	29 (23.6)	0.6
Bladder and renal	2 (7.4)	3 (2.4)	0.1
Gastroesophageal	2 (7.4)	5 (4.1)	0.2
Hepatobiliary	1 (3.7)	3 (2.4)	0.4
Head and neck	1 (3.7)	1 (0.8)	0.1
Miscellaneous	1 (3.7)	1 (0.8)	0.1

Abbreviation: CUS = compression ultrasound.

In patients with asymptomatic VTEs the main tumour entity was pancreatic cancer (29.6%), colorectal and anal cancer (25.9%), and breast cancer (18.5%). Chemotherapy was applied in 88.9% of patients. Details concerning patients with asymptomatic VTEs are shown in Table 2. Differences in clinical characteristics of patients with and without VTEs were compared and we were not able to find statistical significant differences between these two groups. Details are lined out in Table 2.

Follow-up period

During the follow-up period no major bleeding events occurred in the patients treated with LMWH. In case of follow-up at the Division of Oncology (negative CUS at baseline) only in two patients suspected symptomatic DVT events were recorded. Both events were not confirmed by CUS.

Survival analyses

In the 9-month follow-up period 9 of 27 patients with asymptomatic VTEs at baseline died. Of 123 patients included in our study without VTEs 14 patients died in the same follow-up period. Using Log-rank test the difference between the groups was statistically significant ($P = 0.001$). Kaplan–Meier curve is shown in Figure 1. In a multivariable Cox regression analyzes including age, sex, stage of cancer (palliative *vs* curative), tumour entity (pancreatic cancer *vs* non-pancreatic cancer), chemotherapy, surgery and radiotherapy any VTEs at baseline was associated with a 2.4-fold risk to die during the 9-month follow-up period (95% CI 1.2–5.3; $P = 0.03$, Table 3).

DISCUSSION

Venous thrombotic events is a common complication associated with malignancy (Khorana *et al*, 2007). In recent literature various reasons for this fact are described. Increased microparticle tissue factor activity in cancer patients with VTE (Manly *et al*, 2010) have been described as well, as an increase in circulating tumour cells (Mego *et al*, 2009) or a high platelet count (Simanek *et al*, 2010) as a potential cause for the coincidence of VTE and cancer.

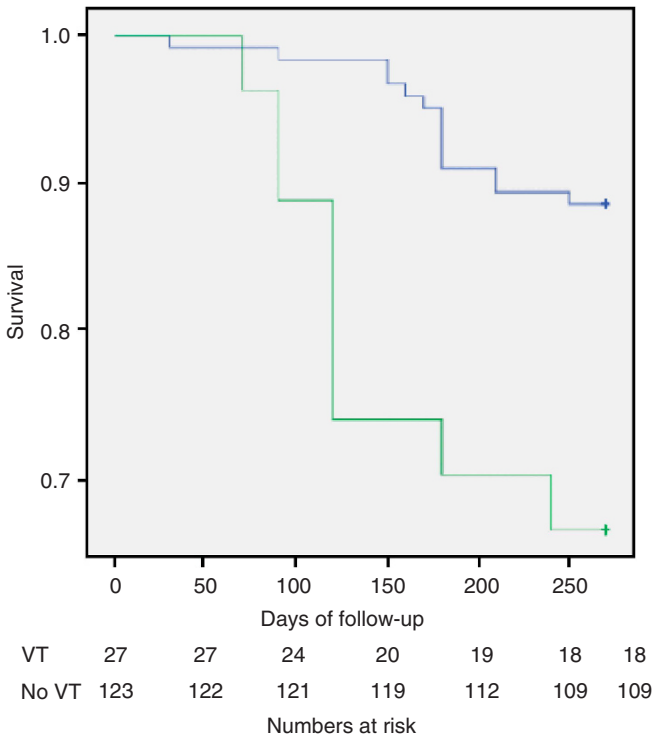

Figure 1 Kaplan–Meier estimates of the risk of death in patients with and without asymptomatic venous thrombotic event (VT). The difference between these two groups reached statistical significance (log-rank test, $P = 0.001$); green line: survival of patients with VT; blue line: survival of patients without VT (No VT).

Table 3 Multivariable Cox proportional hazards model for survival during a 9-month follow-up period

Parameter	HR	95% CI	*P*
Venous thrombosis	2.4	1.2–5.3	0.03
Sex	1.8	0.8–4.2	0.2
Age	1.0	0.9–1.0	0.8
Chemotherapy	1.7	0.4–7.5	0.5
Surgery	2.0	0.6–7.2	0.2
Radiotherapy	1.5	0.5–6.3	0.3
Palliative setting	1.5	0.4–5.1	0.6
Pancreatic cancer	2.5	1.1–5.4	0.02

Abbreviations: CI = confidence interval; HR = hazard ratio.

Owing to laboratory findings in combination with clinical parameters Khorana *et al* (2008) were able to define cancer patients at highest risk for VTE. This score was improved by adding further biomarkers—soluable P-selectin and D-Dimer–by Ay *et al* (2010). However, patients included for validation in these scoring systems were patients with symptomatic VTEs.

The impact of these symptomatic VTEs on survival has previously been described (Lee *et al*, 2010; Sandhu *et al*, 2010). In addition, in recent literature the clinical meaning of asymptomatic VTEs is also discussed. Owing to CT scans performed as a staging procedure asymptomatic PE events are found in some patients. In a recent study of Di Nisio *et al* (2010) incidental VTE was found in 5.3% including more than 1900 cancer patients. The authors concluded that incidental VTE was a common finding in patients with solid tumours, especially in the first months of receiving chemotherapy (Di Nisio *et al*, 2010). Menapace *et al* (2011)

reported that both, symptomatic and incidental VTEs were associated with a higher mortality in a group of pancreatic cancer patients with a hazard ratio of 25 for DVT and 8.9 for PE. It is well known that especially pancreatic cancer patients are at high risk for DVT as we also confirmed in our cohort. In our group with asymptomatic VTEs nearly one third (29.6%) were pancreatic cancer patients. One might assume that this fact might influence the outcome in our cohort. However, we were able to show that an asymptomatic VTE event was associated with a 2.4-fold risk to die during the 9-month follow-up period. This was independent from the coexistence of pancreatic cancer as this parameter was included in our Cox model. We also found that pancreatic cancer itself was an independent predictor of death. The diagnosis of pancreatic cancer was associated with a 2.5-fold risk to die during the 9-month follow-up period.

Superficial venous thrombosis is frequently found in cancer patients and is often associated with DVT or PE. To the best of our knowledge the exact incidence of asymptomatic SVT in ambulatory cancer patients has not been described in literature so far. We know that a quarter of patients with SVT also have DVT found in CUS or symptomatic PE as reported by a recently published analysis of Decousus *et al* (2010). Anticoagulant therapy is indicated in these patients similar to DVT patients. Current guidelines recommend LMWH therapy in high-risk prophylaxis dosage (Kearon *et al*, 2012). Whether the diagnosis of a symptomatic SVT is closely associated with occult cancer is discussed controversially. Findings from the Calisto trial suggest that patients with a SVT are not at an elevated risk to develop cancer in the following 26 months (Prandoni *et al*, 2011). In contrast, Sorensen *et al* (2012) were able to show that occurrence of SVT as well as DVT and PE is a pre-clinical marker of prevalent cancer, particularly during the first year after SVT diagnosis. Up to now no data exist on the prognostic impact of asymptomatic SVT in cancer patients.

In our study, we were able to show that the occurrence of any asymptomatic VTE—SVT as well as DVT—is a frequent finding in ambulatory cancer patients and is associated with a negative outcome during a 9-month follow-up period. Even after adjustment for age, sex, stage of cancer, tumour entity, chemotherapy, surgery and radiotherapy an asymptomatic VTE of the lower limbs was associated with a 2.4-fold risk to die in the following 9 months. Most interesting was the finding that this occurred despite LMWH therapy. As a matter of fact a fatal PE as a reason for death in these patients is unlikely. We therefore hypothesise that the occurrence of an asymptomatic VTE seems to be an expression of an advanced stage or associated with a more aggressive biologic behaviour of the malignant disease.

Our study has some limitations, above all the small sample size. Owing to the given sample size, one further limitation of the study is the low number of events when separating superficial, distal/proximal deep venous thrombosis for outcome analysis. Therefore, larger prospective studies are needed to validate our findings and which are powered to detect differences in short-term survival between the above-mentioned subgroups of venous thrombosis. Furthermore, we did not measure recently published blood-based biomarkers, which were associated with symptomatic VTEs in cancer patients. However, our patients were completely asymptomatic regarding their events. Whether changes in laboratory parameters associated with symptomatic VTEs are also associated with asymptomatic events remains elusive and needs to be validated in large prospective studies. Another limitation is the fact that we performed only one CUS at study baseline. We were therefore not able to record asymptomatic VTEs during the follow-up period.

However, our study shows for the first time in a prospective manner that ambulatory cancer patients are at high risk to suffer a completely asymptomatic VTE of the lower limbs. These patients are at higher risk to die in the following 9 months despite LMWH therapy. The aetiology of these completely asymptomatic VTEs needs further investigation.

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Conflict of interest

The authors declare no conflict of interest.

Author Contributions

T Gary, K Belaj, K Steidl, F Hafner, H Froehlich, E Pilger, M Brodmann: designed study, included patients, evaluated data, wrote manuscript; M Pichler, F Eisner, H Stöger, H Samonigg: included patients, wrote manuscript.

REFERENCES

Ay C, Dunkler D, Marosi C, Chiriac AL, Vormittag R, Simanek R, Quehenberger P, Zielinski C, Pabinger I (2010) Prediction of venous thromboembolism in cancer patients. *Blood* **116**(24): 5377–5382

Decousus H, Quere I, Presles E, Becker F, Barrellier MT, Chanut M, Gillet JL, Guenneguez H, Leandri C, Mismetti P, Pichot O, Leizorovicz A (2010) Superficial venous thrombosis and venous thromboembolism: a large, prospective epidemiologic study. *Ann Intern Med* **152**(4): 218–224

Deitcher SR (2003) Cancer-related deep venous thrombosis: clinical importance, treatment challenges, and management strategies. *Semin Thromb Hemost* **29**(3): 247–258

Di Nisio M, Ferrante N, De Tursi M, Iacobelli S, Cuccurullo F, Buller HR, Feragalli B, Porreca E (2010) Incidental venous thromboembolism in ambulatory cancer patients receiving chemotherapy. *Thromb Haemost* **104**(5): 1049–1054

Douma RA, Kok MG, Verberne LM, Kamphuisen PW, Buller HR (2010) Incidental venous thromboembolism in cancer patients: prevalence and consequence. *Thromb Res* **125**(6): e306–e309

Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR (2012) Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* **141**(2 Suppl): e419S–e494S

Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH (2007) Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. *Cancer* **110**(10): 2339–2346

Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW (2008) Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood* **111**(10): 4902–4907

Lee KW, Bang SM, Kim S, Lee HJ, Shin DY, Koh Y, Lee YG Cha Y, Kim YJ, Kim JH, Park DJ, Kim HH, Oh D, Lee JS (2010) The incidence, risk factors and prognostic implications of venous thromboembolism in patients with gastric cancer. *J Thromb Haemost* **8**(3): 540–547

Manly DA, Wang J, Glover SL, Kasthuri R, Liebman HA, Key NS, Mackman N (2010) Increased microparticle tissue factor activity in cancer patients with venous thromboembolism. *Thromb Res* **125**(6): 511–512

Mego M, De Giorgi U, Broglio K, Dawood S, Valero V, Andreopoulou E, Handy B, Reuben JM, Cristofanilli M (2009) Circulating tumour cells are associated with increased risk of venous thromboembolism in metastatic breast cancer patients. *Br J Cancer* **101**(11): 1813–1816

Menapace LA, Peterson DR, Berry A, Sousou T, Khorana AA (2011) Symptomatic and incidental thromboembolism are both associated with mortality in pancreatic cancer. *Thromb Haemost* **106**(2): 371–378

Prandoni P, Casiglia E, Tikhonoff V, Leizorovicz A, Decousus H (2011) The risk of subsequent cancer and arterial cardiovascular events in patients with superficial vein thrombosis in the legs. *Blood* **118**(17): 4719–4722

Sandhu R, Pan CX, Wun T, Harvey D, Zhou H, White RH, Chew HK (2010) The incidence of venous thromboembolism and its effect on survival among patients with primary bladder cancer. *Cancer* **116**(11): 2596–2603

Schulman S, Kearon C (2005) Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* **3**(4): 692–694

Shah MA, Capanu M, Soff G, Asmis T, Kelsen DP (2010) Risk factors for developing a new venous thromboembolism in ambulatory patients with non-hematologic malignancies and impact on survival for gastroesophageal malignancies. *J Thromb Haemost* **8**(8): 1702–1709

Simanek R, Vormittag R, Ay C, Alguel G, Dunkler D, Schwarzinger I, Steger G, Jaeger U, Zielinski C, Pabinger I (2010) High platelet count associated with venous thromboembolism in cancer patients: results from the Vienna Cancer and Thrombosis Study (CATS). *J Thromb Haemost* **8**(1): 114–120

Sorensen HT, Svaerke C, Farkas DK, Christiansen CF, Pedersen L, Lash TL, Prandoni P, Baron JA (2012) Superficial and deep venous thrombosis, pulmonary embolism and subsequent risk of cancer. *Eur J Cancer* **48**(4): 586–593