Paper III

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Occult cancer-related first venous thromboembolism is associated with an increased risk of recurrent venous thromboembolism

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Running title: VTE recurrence risk by cancer status at first VTE

Keywords: venous thromboembolism, cancer, occult cancer, recurrence

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Essentials

- Recurrence risk after an occult cancer-related incident venous thromboembolism (VTE) is unknown.
- We compared the risk of VTE recurrence in occult-, overt- and non-cancer related first VTE
- Patients with occult-cancer related first VTE had the highest risk of VTE recurrence.
- The high recurrence risk in occult cancer is likely due to the advanced cancers.

Abstract

Background: Although venous thromboembolism (VTE) is associated with a high recurrence rate, the absolute recurrence rates in cancer-related VTE, particularly in occult cancer, are not well known.

Objectives: We aimed to investigate the risk of VTE recurrence in patients with occult- and overt cancer-related VTE.

Methods: Incident VTE events among participants of the Tromsø 1-6 surveys occurring in the period 1994-2012 were included. Occult cancer was defined as cancer diagnosed within a year following a VTE, whereas overt cancer was defined as cancer diagnosed within the two years before a VTE.

Results: Among 733 patients with incident VTE, 110 had overt cancer and 40 had occult cancer. There were 95 recurrent VTE events during a median of 3.2 years of follow-up. The one-year cumulative incidence of VTE recurrence was 38.6% in occult cancer, 15.5% in overt cancer, and 3.8% in non-cancer subjects. The one-year risk of recurrence was 12-fold (HR 12.4, 95% CI 5.9-26.3) higher in occult cancer, and 4-fold (HR 4.3, 95% CI 2.0-9.2) higher in overt cancer, when compared with non-cancer subjects. The occult cancers associated with VTE recurrence were typically located at pro-thrombotic sites (i.e. lung and gastrointestinal) and presented at advanced stages. The majority (69%) of recurrences in occult cancer occurred before or shortly after cancer diagnosis and were therefore not treatment-related.

Conclusion: Our findings suggest that the increased risk of recurrence in occult cancer is mainly due to the advanced cancers in these patients.

Keywords: cancer, cohort studies, epidemiology, recurrence, venous thromboembolism

Introduction

Cancer has been a well-established risk factor for venous thromboembolism (VTE) for almost two centuries [1]. Active cancer is associated with a four- to sevenfold increased risk of VTE [2-4], and VTE is a common, severe, and often fatal complication of cancer [5]. Clinical consequences of

VTE in cancer, such as risk of VTE recurrence, anticoagulant-related bleeding, and death, are more frequent and often more grave than in non-cancer patients [6-8].

VTE is a chronic disease that frequently recurs [9]. Active cancer is associated with a two- to nine-fold increased risk of VTE recurrence, and a threefold higher risk of death, compared to subjects without cancer [7, 8]. The risk of recurrence is present across all cancers, but it is highest in brain-, pancreatic-, lung-, gastrointestinal-, ovarian- and hematological cancers [10].

VTE can be the first manifestation of cancer, and up to 10% of patients with an unprovoked VTE are diagnosed with cancer within the first year [11]. There is an ongoing debate regarding limited versus extensive screening for cancer in patients with incident VTE. Although extensive screening may result in earlier detection of cancer, it is not apparent that it favors the prognosis [12]. Complications of VTE, such as recurrence, have not been widely studied in patients with a first VTE during the occult cancer period [13, 14]. It is unknown to what extent identification of an underlying cancer could prevent VTE recurrences, and consequently reduce morbidity and mortality in these patients. Currently, the risk of VTE recurrence is not taken into account when considering a cancer screening strategy in patients with an unprovoked VTE.

Previous studies have either investigated the risk of VTE recurrence in subjects with an occult cancer-related VTE during a limited occult cancer period (three months after VTE), or combined a short occult-cancer period with the overt cancer period and defined it as ‘active cancer’ (i.e. 3 months before and after a VTE) [13, 14]. Consequently, there is insufficient knowledge regarding the risk of VTE recurrence in patients with occult cancer, as past studies have mainly focused on overt malignancy. Therefore, we aimed to investigate the risk of VTE recurrence and mortality in VTE patients with overt and occult cancer in a large population-based cohort study.

Methods

Study Population

The source population comprised of subjects participating in the first to sixth surveys of the Tromsø Study (conducted in 1974, 1979-80, 1986-87, 1994-95, 2001-02 and 2007-08, respectively), a single-center, population-based cohort study. All or part of the inhabitants of the Tromsø municipality were invited to participate in the surveys. A detailed description of the Tromsø Study cohort is described elsewhere [15]. Participants who were still alive and living in the municipality of Tromsø on January 1, 1994 (n=33 885) were followed through December 31, 2012, and all potential cases of first VTE were identified by linking to the hospital discharge diagnosis registry, the autopsy registry, and the radiology procedure registry at the University Hospital of North Norway. The University Hospital of North Norway is the only hospital in the region, and serves as the exclusive provider of all diagnostic radiological procedures and VTE-related healthcare in the area. Trained personnel reviewed the medical records for each VTE case and extracted information for case-validation, which included information on clinical risk factors and laboratory markers, using standardized forms. A VTE event was only considered to be verified and recorded when presence of clinical signs and symptoms of deep vein thrombosis (DVT) or pulmonary embolism (PE) were combined with objective confirmation tests (by compression ultrasonography, venography, spiral computed tomography, perfusion-ventilation scan, pulmonary angiography, autopsy), and resulted in a VTE diagnosis that required treatment, as previously described [16]. In total, 733 subjects with a validated first, lifetime VTE event were identified as eligible for our study. Recurrent VTE events were identified and validated using the same criteria as described for first lifetime VTE events. Information on mortality was collected from the Norwegian Population Registry. The study was approved by the Regional Committee for Medical and Health Research Ethics in Northern Norway and all participants gave informed written consent.

Measurements

Information on comorbidities, clinical- and provoking factors at the time of, and 8 weeks preceding the VTE event, as well as the location of the thrombus were extracted by review of medical records using standardized forms. Body weight and height were measured in subjects without shoes, wearing light clothing. Body mass index (BMI) was calculated by the weight in kilograms (kg) divided by height in meters (m) squared (kg/m^2) [15].

Cancer Assessment

Information about the date of cancer diagnosis, location of the disease (ICD-7-codes 140-205) and cancer stage (localized disease or presence of regional/distant metastasis) was obtained from linkage to the Cancer Registry of Norway. The Cancer Registry of Norway performs national surveillance of cancer diagnoses in the Norwegian population. A recent evaluation of the data quality found that the completeness of the Cancer Registry of Norway was estimated at 98.8%, with 94% of the cases being histologically verified [17]. Subjects with non-melanoma skin cancers (ICD-7 codes: 191.0-191.9) were regarded as cancer-free subjects (n=5), due to the non-metastatic potential of the disease.

Definition of Active Cancer

Temporal proximity to cancer diagnosis is a strong predictor of VTE risk [18]. Previous studies have found that the risk of VTE is especially high in the first years following a cancer diagnosis and substantially declines thereafter [18, 19]. The risk of VTE is already increased in the year before a cancer diagnosis, with a 7-fold higher risk of VTE in the six months before cancer [11, 20, 21]. This observation is in accordance with evidence suggesting that VTE risk is closely related to the rate of cancer growth rather than the extent of cancer [22]. Hence, we defined the active cancer period as the time ranging from one year before a cancer diagnosis until two years after. An overt cancer-related VTE was defined as a VTE occurring within two years following a cancer diagnosis and,

conversely, an occult cancer-related VTE was defined as a VTE occurring within one year before a cancer diagnosis.

Statistical Analysis

Statistical analysis was carried out using STATA version 14.0 (Stata corporation, College station, Texas, USA). Crude incidence rates (IRs) were calculated and expressed as the number of events per 1000 person-years for each exposure category in the periods 0-1 year and 0-5 years after the first VTE. Cox proportional hazard regression models were used to calculate one-year and five-year hazard ratios (HR) with 95% confidence intervals (CIs) across categories of occult-, and overt cancer, using non-cancer subjects as the reference group. The proportional hazards assumption was evaluated using Schoenfeld residuals. The five-year cumulative incidences of VTE recurrence in occult-, overt and non-cancer subjects were displayed using a 1-Kaplan Meier (1-KM) plot. Moreover, the one-year cumulative survival following a cancer diagnosis was displayed according to cancer status at the time of the VTE using a regular KM plot. Finally, the Fine–Gray model was applied for sensitivity analysis to account for mortality as a competing event [23].

Results

Baseline characteristics at first VTE by categories of cancer are summarized in TABLE 1. Of the 733 patients with a first VTE event, 110 (15.0%) had overt cancer and 40 (5.5%) had occult cancer. The time to diagnosis of cancer following a VTE-event in patients with occult malignancy is displayed in FIGURE 1. Cancer was diagnosed in 5.5% of all VTE patients without overt cancer within the following year, of which 87.5% were diagnosed within six months of the incident VTE event.

There were 41 VTE recurrences in the first year following a VTE event, of which 20 (3.4%) occurred in non-cancer subjects, 10 (9.1%) in overt cancer and 11 (27.5%) in occult cancer. The cumulative incidence curves of recurrent VTE were particularly steep for the cancer groups, and the occult cancers in particular, during the first year (FIGURE 2). At one year, the cumulative incidence

was 3.8% in subjects without cancer, 15.5% in subjects with overt cancer-related VTE and 38.6% in subjects with occult cancer-related VTE. The one-year risk of VTE recurrence was 4.3-fold (95% CI 2.0-9.2) higher for overt cancer, and 12.4-fold (95% CI 5.9-26.3) higher for occult cancer than the non-cancer group (TABLE 2). There were 95 recurrent VTE events in the five-year follow-up period. The incidence of VTE recurrence remained highest in those with occult cancer-related incident VTE than in overt- or non-cancer throughout the entire five-year follow-up (FIGURE 2). The five-year VTE recurrence risk was 6-fold higher in those with occult cancer (HR 6.4, 95% CI 3.5-11.8) and two fold higher in those with overt cancer (HR 1.9, 95% CI 1.0-3.6) compared to those without cancer (TABLE 2). The majority of those with an incident VTE during the occult cancer period (7/13, 54%) had a recurrence before the date of cancer diagnosis, and 69% (9/13) experienced a recurrent event either before or within five days of the cancer diagnosis. Of the occult cancer subjects, the majority (59.5%) received warfarin rather than heparin, as the cancer was not yet detected at the time of the incident VTE. The majority of the subjects with overt cancer received LMWH (63.5%) over warfarin, and they were in general treated for a longer period. However, adjustment for planned duration of anticoagulation did not affect the risk estimates for recurrence (data not shown).

Kaplan-Meier cumulative survival estimates after cancer diagnosis in those who had a VTE in the occult and overt cancer period, respectively, are shown in FIGURE 3. The one-year cumulative survival after receiving a cancer diagnosis was 59.5% in subjects who developed a VTE during the overt cancer period, and 41.6% in subjects who developed an incident VTE during the occult cancer period. The rate of early mortality was particularly high in subjects who developed a VTE during the occult cancer period, as the absolute mortality in these patients were 32.5% (13/40), 45.0% (18/40) and 57.5% (23/40) at three, six and 12 months, respectively.

Competing risk by death is especially important to consider when early mortality is present. As recurrence risk is known to be over-estimated when the mortality rate is high, we explored the impact of competing risk by death on the risk estimates for VTE recurrence by applying the Fine-Gray model. As expected, the sub-distribution hazard ratios (SHR) were lower than the hazard ratios

obtained by the regular Cox model. For one-year VTE recurrence the SHR was 2.8 (95% CI 1.3-6.2) in subjects with overt cancer, and 9.6 (95% CI 4.5-20.5) in those with occult cancer, compared with those without cancer. The five-year VTE recurrence risk was also considerably lower when taking competing risk by death into account for overt cancer (SHR 1.0, 95% CI 0.6-1.9) and occult cancer (SHR 3.7, 95% CI 1.9-7.2).

Incident VTE events and recurrences by cancer site are shown in TABLE 3. Subjects who developed a VTE during the occult cancer period were most often diagnosed with lung (30.0%), gastrointestinal (17.5%) and hematological cancers (15.0%). Recurrent VTE events were most often seen in subjects with cancer at the similar sites: lung (36.0%), gynecological (16.0%), gastrointestinal (12.0%), and prostate (12.0%). Of those with a known cancer stage, 61% (17/28) of subjects with an occult cancer-related VTE presented with widespread metastases, while 43% (30/70) of subjects with an overt cancer-related VTE had distant spread at the time of cancer diagnosis. In subjects who developed a VTE during the occult cancer period, 8/12 (67%) of those with lung cancer presented with a widespread metastatic cancer, while all (4/4) of those with prostate cancer had only localized or regional metastasis at the time of diagnosis.

Discussion

In the present study, we investigated the risk of VTE recurrence in patients with occult and overt cancer-related incident VTE. VTE patients with occult cancer had a higher risk of recurrence than those with overt cancer and those without cancer. The risk estimates of recurrence were lowered when competing risk by death were taken into account, especially in the occult cancer-related VTEs, where the early mortality rate was high. The majority of the VTE recurrences in patients with occult cancer occurred before cancer was diagnosed and were therefore not treatment-related. Subjects with an occult cancer-related VTE were more often diagnosed with late-stage cancers at cancer sites typically associated with VTE. Thus, the higher recurrence risk in VTE patients with occult cancer was most likely explained by the advanced nature of the cancer itself.

Our findings are in line with previous studies. In the RIETE registry, patients with a VTE within three months before cancer diagnosis had a 5.4-fold higher incidence of three-month recurrence (11.4% vs. 2.1%), and 3.7-fold higher mortality rate (20% vs 5.4%), compared to VTE patients without cancer [14]. Furthermore, the one-year cumulative incidence rate of VTE recurrence was 26.7% in a population-based study where active cancer was defined as 92 days before or after the initial VTE event [13]. In comparison, the one-year cumulative incidence of VTE among subjects with active cancer, which included both occult and overt cancers, was 22.7% in our study. Previous studies have not compared subjects who experienced a first VTE during a prolonged occult cancer period (i.e. one year) to overt cancer and non-cancer patients. We found that the one-year cumulative incidence of recurrence was highest among those with first VTE related to occult cancer (38.6%) compared to overt (15.5%) and non-cancer subjects (3.8%). Subjects with occult cancer-related VTE had also the highest five-year risk of VTE recurrence.

The majority of VTE recurrences in patients with occult cancer-related VTE occurred before the date of cancer diagnosis (54%) or before or within five days after cancer was diagnosed (69%). Our findings suggest that VTE recurrences in occult cancer are not precipitated by cancer treatment-related risk factors like chemotherapy or surgery. Data from a cancer cohort [8] and the REITE Registry [24] reported that lung, gastrointestinal, genitourinary, pancreatic, and brain cancers were associated with the highest risk of VTE recurrence. Similarly, in our study, cancers of the lung, gastrointestinal and hematological sites, which have been previously noted as more pro-thrombotic cancers [25, 26], were most often diagnosed in patients with occult cancer and recurrent VTE. In addition, patients with incident VTE in the occult cancer period had more advanced cancer at the time of diagnosis. In those with occult cancer at the time of incident VTE (and a known cancer stage at the time of cancer diagnosis), 61% had distant metastases and 79% had either regional or distant metastases when cancer was diagnosed. Several studies have shown that the risk of VTE recurrence is higher in patients with metastatic disease [8, 24, 27]. Our findings suggest that pro-thrombotic properties and the severity and spread of the cancer itself, rather than treatment-related factors,

most probably are responsible for the majority of VTE recurrences in patients with first occult cancer-related VTE.

In the presence of competing risk by death, the cumulative incidence of VTE recurrence is dependent on both the hazard of recurrence and the hazard of dying, and consequently, VTE recurrence risks are often overestimated when the mortality rate is high [28-30]. The cumulative survival curves displayed high mortality rates in subjects with overt cancer-related VTE (41.6%) and especially in those with occult cancer-related VTE (59.5%) during the year following the cancer diagnosis. Accordingly, the one-year recurrence risk was markedly lower for both overt cancer (HR 4.3, SHR 2.9) and occult cancer (HR 12.4, SHR 9.6) when competing risk was taken into account. The difference between HR and SHR was even greater when looking at five-year risk of VTE recurrence in the overt and occult cancer groups, as the five-year survival in cancer, especially cancer complicated with VTE, is generally low [7]. Similarly, Chee and colleagues reported that the 10-year cumulative recurrence rate among patients with active cancer dropped from 52.2% to 28.6% when competing risk by death was taken into account [13].

Despite that cancer was diagnosed within a short time following the incident (86% diagnosed within 6 months) or recurrent (69% diagnosed with cancer before or within five days) VTE, early mortality among these patients was high. Nearly half (45%) of the patients with an occult cancer-related VTE died within six months after cancer diagnosis. It is likely to assume that screening for cancer at diagnosis of incident VTE would not reduce the morbidity and mortality associated with VTE recurrence since the recurrent events appear to be associated with advanced cancer stages with high early mortality that occur within a short time following the initial event. In fact, a randomized controlled trial assessing the efficacy of extensive screening for occult cancer in unprovoked incident VTE concluded that extensive screening did not reduce cancer-related mortality [12].

Coagulation activation and tumor progression are closely related. Tumor growth and aggressiveness rely largely on the capacity of cancer cells to promote the formation of new blood vessels and spread [31]. Various components of the hemostatic system contribute to this process

including thrombin, tissue factor (TF), FVIIa, FXa and fibrinogen [31]. Cell surface TF is thought to potentiate cancer progression through an enhancement of angiogenesis and by facilitating metastasis [32], and previous reports have proposed a role of TF in the development of cancer-associated VTE [33]. Increased TF expression has been reported in a number of cancers including those of the brain, pancreas, lung, colon/rectum, kidney and ovary [34]. Interestingly, cancers at these sites are known to be more prothrombotic, and tumor cells themselves are likely to be an important source of elevated levels of circulating TF. Moreover, increased TF expression in pancreatic cancer biopsies was shown to correlate with a greater incidence of VTE [35].

The main strengths of our study include the cohort study design and constitution of unselected and validated VTE events in the cohort. In addition, the linkage of our dataset to the Cancer Registry of Norway permitted us to address both overt and occult cancer. Although we had reasonably large numbers of subjects with VTE and cancer in our cohort, when the subjects were divided into overt and occult cancer groups, relatively small numbers remained in the sub-categories. Information regarding patient-characteristics was collected from medical records, and relied on the reporting by physicians, nurses and other health care professionals. However, the main exposures in this study are major clinical events for which a low degree of underreporting and misclassification would be expected. In addition, information on cancer treatment modalities was also not available in our study. However, the majority of the recurrences in the occult cancer group were not impacted by cancer-treatment as they occurred before the cancer was diagnosed.

In conclusion, we found that individuals with an incident VTE event during an occult cancer period had a substantially higher rate of VTE recurrence than those with overt cancer and those without cancer. Patients in the occult cancer group who experienced a VTE recurrence had a preponderance of prothrombotic and advanced cancers at diagnosis, suggesting that the recurrence risk can be attributed to tumor-related factors, such as tumor type and stage.

Author Contributions

O. V. Gran analyzed the data and drafted the manuscript. S. K. Brækkan and J. B. Hansen were involved in conception of the study, data collection and revision of the manuscript. B. Paulsen, H. Skille, F. R. Rosendaal were involved in interpretation of the results and critical revision of the manuscript. All authors read and approved the final version of the manuscript.

Authors state no conflicts of interests.

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Tables

TABLE 1: BASELINE CHARACTERISTICS OF PATIENTS WITH A FIRST EPISODE OF VTE. THE TROMSØ STUDY.

	No cancer (n=583)	Overt cancer (n=110)	Occult cancer (n=40)
Age (years)	66.3 ±15.0	65.9 ±13.0	69.7 ±11.2
Sex (% men)	48.4 (282)	50.9 (56)	52.5 (21)
BMI (kg/m^2)	25.8 ±4.1	25.0 ±3.7	24.2 ±3.0
Unprovoked VTE	53.1 (309)	3.6 (4)	50.0 (20)
Deep vein thrombosis	56.9 (332)	62.7 (69)	62.5 (25)
Pulmonary embolism	43.1 (251)	37.2 (41)	37.5 (15)
Comorbidities*	23.7 (138)	10.0 (11)	27.5 (11)
Pregnancy	0.1 (1)	0 (0)	0 (0)
Surgery	15.2 (94)	19.1 (21)	2.5 (1)
Trauma	10.3 (60)	1.8 (2)	5.0 (2)
Immobilization**	18.7 (109)	18.2 (20)	15.0 (6)
Long distance travel ¥	1.2 (7)	0 (0)	0 (0)
Planned type of anticoagulation			
Heparin	8.1 (45)	63.5 (66)	40.5 (15)
Warfarin	91.9 (509)	36.5 (38)	59.5 (22)
Missing information	5.0 (29)	4.5 (5)	7.5 (3)
Planned duration of anticoagulation			
0-3 months	19.6 (100)	22.2 (22)	8.6 (3)
3-6 months	46.6 (237)	28.3 (28)	47.7 (16)
6-12 months	23.8 (121)	22.2 (22)	31.4 (11)
>12 months	10.0 (51)	27.3 (27)	14.3 (5)
Missing information	12.7 (74)	10.0 (11)	12.5 (5)

Values are means ±SD, or percentage with numbers in parenthesis.

* Comorbidities: a myocardial infarction or a stroke within 12 months preceding VTE, COPD, myeloproliferative disorders, systemic lupus erythematosus (SLE), or chronic infection;
** bedrest (>3 days), wheelchair, crutches
¥ >4 hours within the previous 14 days

TABLE 2: INCIDENCE RATES AND HAZARD RATIOS FOR ONE AND FIVE YEAR VTE RECURRENCE ACCORDING TO CANCER STATUS AT THE TIME OF THE FIRST VTE. THE TROMSØ STUDY.

	EVENTS (n)	IR (95% CI)*	HR (95% CI)**	SHR (95% CI)**
ONE YEAR RECURRENCE				
NO CANCER	20	39.4 (25.4-61.0)	1.0	1.0
OVERT CANCER	10	188.6 (101.5-350.6)	4.3 (2.0-9.2)	2.9 (1.3-6.2)
OCCULT CANCER	11	501.8 (277.9-906.1)	12.4 (5.9-26.3)	9.6 (4.5-20.5)
FIVE YEAR RECURRENCE				
NO CANCER	69	36.0 (28.4-45.6)	1.0	1.0
OVERT CANCER	12	89.5 (52.0-154.1)	1.9 (1.0-3.6)	1.0 (0.5-1.9)
OCCULT CANCER	13	253.8 (147.4-437.1)	6.4 (3.5-11.8)	3.7 (1.9-7.2)

n: number, IR: incidence rate, HR: hazard ratio (Cox regression), SHR: subdistribution hazard ratio (competing risk for mortality regression), * per 1000 person years, ** adjusted for sex and age

TABLE 3: INCIDENT AND RECURRENT VTE EVENTS BY CANCER SITE. THE TROMSØ STUDY.

Cancer Site	Overt Cancer-related VTE % (n)	Occult Cancer-related VTE % (n)
Incident VTE	**(n=110)**	**(n=40)**
Colorectal	16.4 (18)	7.5 (3)
Upper GI	4.5 (5)	10.0 (4)
Pancreatic	7.3 (8)	2.5 (1)
Lung	19.1 (21)	30.0 (12)
Breast	3.6 (4)	0
Gynecological	11.8 (13)	7.5 (3)
Prostate	5.5 (6)	10.0 (4)
Urological	10.9 (12)	5.0 (2)
CNS	3.6 (4)	2.5 (1)
Hematological	9.1 (10)	15.0 (6)
Remaining Cancers*	8.2 (9)	10.0 (4)
Recurrent VTE	**(n=12)**	**(n=13)**
Colorectal	16.7 (2)	7.7 (1)
Upper GI	0	0
Pancreatic	8.3 (1)	0
Lung	25.0 (3)	46.2 (6)
Breast	0	0
Gynecological	25.0 (3)	7.7 (1)
Prostate	8.3 (1)	15.5 (2)
Urological	8.3 (1)	7.7 (1)
CNS	8.3 (1)	7.7 (1)
Hematological	0	7.7 (1)
Remaining Cancers*	0	0

GI: gastrointestinal, *remaining cancers: ear nose and throat cancers, melanoma, endocrine cancers, sarcoma, cancer of unknown origin

Figures:

FIGURE 1: TIME TO DIAGNOSIS OF CANCER FOLLOWING A FIRST VTE EVENT IN PATIENTS WITH AN OCCULT MALIGNANCY. THE TROMSØ STUDY.

FIGURE 2: FIVE-YEAR CUMULATIVE INCIDENCE OF RECURRENT VTE ACCORDING TO CANCER STATUS AT THE TIME OF THE FIRST VTE. THE TROMSØ STUDY.

FIGURE 3. ONE-YEAR CUMULATIVE SURVIVAL FOLLOWING A CANCER DIAGNOSIS IN PATIENTS WITH OVERT AND OCCULT CANCER-RELATED VTE. THE TROMSØ STUDY.