Risk factors of thrombosis in cancer : the role of microparticles

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5 Risk of venous thrombosis in patients with adeno-and squamous cell carcinoma of the upper gastro-intestinal tract

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submitted

Abstract

Background

Patients with malignancy are at increased risk for venous thrombosis and it is widely assumed that those with adenocarcinomas are at highest risk.

Patients and methods

To determine the incidence of venous thrombosis in patients with adenocarcinoma or squamous cell carcinoma of the upper-gastrointestinal tract we performed a cohort analysis and reviewed the medical records of 1000 consecutive patients diagnosed with upper-gastrointestinal cancer diagnosed between 1980 and 2000 in one academic centre. These were 535 esophageal carcinoma patients, of whom 216 (40%) had an adenocarcinomas and 319 (60%) a squamous cell carcinoma, and 465 patients with adenocarcinoma originating in the stomach.

Results

The mean age was the same for patients with cancer arising in the esophagus or stomach, those with squamous cell carcinoma and with adenocarcinomas; nor did the numbers of years at risk differ. There were 70 venous thrombotic events (incidence rate 3.9 per 100 person-years). In patients with esophageal cancer the incidence of thrombosis was 3.3 per 100 person-years, and in those with gastric cancer it was 4.5 per 100 person-years. The incidence of venous thrombosis in patients with adenocarcinoma (59/681, 4.8 per 100 person-years) was 2.6-fold increased (HR 2.63, 95% CI: 1.38-5.00) compared to the risk in patients with squamous cell carcinoma (11/319, 1.9 per 100 person-years). The survival was worse for patients who developed venous thrombosis (HR 2.13, 95% CI: 1.64-2.88) than other patients, irrespective of whether the tumor originated in the stomach or the esophagus.

Conclusions

The risk of venous thrombosis in upper-gastrointestinal cancer patients is 10 to 15-fold increased as compared to the general population. Patients with adenocarcinoma have a higher risk to develop thrombosis than patients with squamous cell carcinoma, whereas patients who develop thrombosis have a worse survival compared to those who do not.

Introduction

The association of thrombosis and cancer originates from the observations of Armand Trousseau, who in 1865 noted that patients who present with idiopathic venous thrombosis frequently had an occult malignancy (1). In the past years several investigators have confirmed the strong association between cancer and venous thrombosis. Hospital-based and national registries offer an opportunity to study the risk of venous thrombosis in large cohorts of cancer patients, which is essential in decisions on prophylactic anti-coagulant treatment. Two large population-based studies performed by Sorensen *et al*. (2) and Baron *et al*. (3) have demonstrated that the incidence of cancer is increased in the years following the diagnosis of venous thrombosis. The peak incidence of cancer in the first year after the diagnosis of venous thrombosis strongly suggests that these patients already had cancer during their episode of venous thrombosis.

Blom *et al*. (4) showed that the overall risk of venous thrombosis was 7-fold increased in patients with a malignancy versus persons without malignancy. Patients with hematological malignancies, followed by lung cancer and gastrointestinal cancer had the highest risk of venous thrombosis. Sallah *et al*. and Levitan and *al*. (5;6) showed that of the solid tumors, gastrointestinal tract cancer, kidney, brain and ovarian cancer were most strongly associated with venous thrombosis. Although the overall incidence of venous thrombosis has been shown to be increased in cancer patients, few data exist on the incidence for different histological types of cancer in one organ site. Although squamous cell carcinomas and adenocarcinomas both arise from epithelial cells, adenocarcinomas are presumed to carry a higher risk of thrombosis than squamous cell carcinomas.

To study the incidence of venous thrombosis in adenocarcinomas and squamous carcinomas arising in the same organ site, we performed a follow-up study in patients with upper gastro-intestinal cancer, *i.e*. gastric and esophageal carcinoma.

PAtients and methods

Patients

All patients who were treated between January 1980 and January 2001 in our hospital for upper gastro-intestinal cancer were identified from the Cancer Registry database of the Leiden University Medical Center (LUMC). This database contains information concerning

all patients diagnosed with cancer who are admitted to our hospital for treatment. The database has been set up in 1970 and has since been staffed by a specialized team of oncological data managers.

Data were collected from 1177 consecutive patients who presented with either a malignancy of the esophagus or stomach at the Leiden University Medical Center (Figure 1). In all patients, the malignancy was histologically confirmed. Of these 1177 patients, 568 patients had esophageal carcinoma and 609 patients had a malignancy of the stomach. Of the 568 patients with esophageal carcinoma, 24 cases were excluded because of incomplete records and 11 cases because they had a different malignant tumor type than adeno- or squamous cell carcinoma. Of the remaining 535 esophageal carcinoma patients, 216 (40%) had an adenocarcinoma and 319 (60%) had a squamous cell carcinoma (Figure 1). Of the 609 patients with gastric carcinoma, 4 were excluded because of incomplete records and 140 patients because of a different malignant tumor type (mainly lymphoma or sarcoma). The 465 remaining patients with gastric carcinomas all had an adenocarcinoma. Thus, a total of 1000 patients were included in the study.

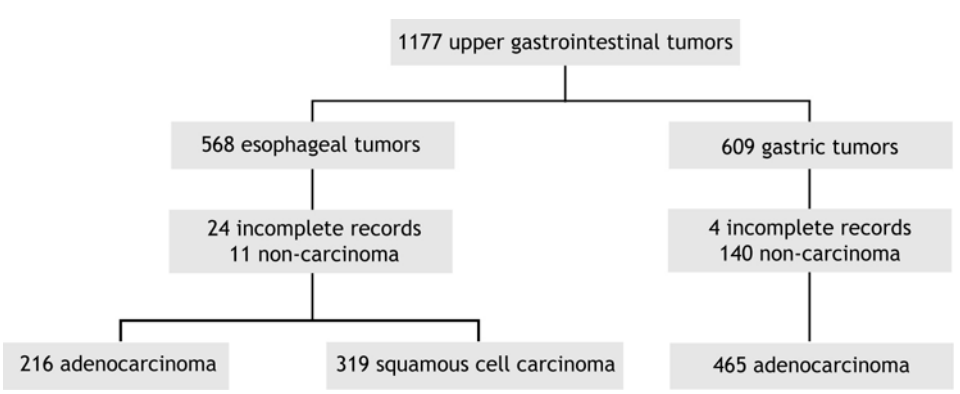

Figure 1

Patient and tumor characteristics were recorded from the medical records and information about the occurrence of venous thrombosis was collected from medical records or through the Leiden Anticoagulation Clinic. In all cases the diagnosis of venous thrombosis was confirmed by duplex ultrasonography or venography in case of deep vein leg thrombosis, high-probability ventilation-perfusion scans in case of pulmonary embolism and in some cases confirmation was also obtained by autopsy. We counted all venous thrombosis which occurred at the time of, or after the diagnosis of cancer was made.

Statistical analysis

We counted person-years of follow-up for each subject from the date of diagnosis of cancer until the date of a thrombotic event, the date of death, or the end of the study period (31 December 2006), whichever occurred first. A total of 1790 person-years accrued, with 4 patient lost to follow-up 3 or more years after their initial diagnosis of cancer. We computed the incidence rates by dividing the number of cases of venous thrombosis by the number of person-years, and cumulative incidences by dividing the number of thrombosis cases by the number of patients at start of follow-up. A Standardized Morbidity Ratio was calculated using the incidence rate of deep venous thrombosis of the leg and pulmonary embolism in the Dutch population of 1994 (7). We compared thrombosis incidence between various groups of patients with Cox modeling.

For the survival analysis of patients who developed a venous thrombosis after diagnosis of esophageal cancer we used a Cox proportional hazards model with the thrombotic event as a time-dependent covariate.

Results

Characteristics of the 1000 patients with upper-gastrointestinal tract carcinoma are shown in Table 1. Most of the patients were men and the mean age did not differ between squamous and adenocarcinoma patients, nor between patients divided into those with a tumor located in the esophagus versus stomach. The median survival of patients with a tumor arising in the esophagus respectively stomach was 9.7 respectively 9.0 months, with 143 (14.3%) patients alive after 3 years of follow-up.

We observed 70 cases of venous thrombosis with 1790 person-years of follow-up in all upper gastro-intestinal tract carcinoma patients, for an incidence rate of 3.9 per 100 person-years. Of the 70 patients who developed venous thrombosis, 26 patients had a pulmonary embolism and 11 patients died as a consequence of the thrombotic event. Five patients with a venous thrombosis developed their venous thrombosis within one month after surgery for their primary tumor. The median time from first admittance for upper-gastrointestinal tract carcinoma until development of the venous thrombosis was 2.0 months (range 0.0–150 months). The cumulative incidence of venous thrombosis was 7%: 5.6% after the first and 6.3% after the second year of follow-up.

When analysis was performed according to localization, we observed 28 venous thromboses, including 13 cases with pulmonary embolism in esophageal cancer patients (Table 2) in 857 person-years with an incidence rate of venous thrombosis of 3.3 per 100 person-years. The incidence of venous thrombosis in the first 6 months after the diagnosis of esophageal carcinoma was 9.3 per 100 person-years and 0 per 100 person-years in the next six months. In patients with gastric carcinoma, 42 events of venous thrombosis including 13 cases with pulmonary embolism were observed in 933 person-years with an incidence rate of venous thrombosis of 4.5 per 100 person-years. The incidence of venous thrombosis in the first 6 months after the diagnosis of gastric carcinoma was 17.2/100 person-years, which is 25-fold higher than in the subsequent time period.

Table 1. Patient's characteristics in 535 esophageal and 465 gastric carcinoma patients at the time of diagnosis.

Histology	**Patients with esophageal cancer**				**Patients with gastric cancer**	
	Squamous cell carcinoma *n* = 319		Adenocarcinoma *n* = 216		Adenocarcinoma *n* = 465	
	No	(%)	No	(%)	No	(%)
Sex						
Men	192	(60.2)	168	(77.8)	340	(73.1)
Female	127	(39.8)	48	(22.2)	125	(26.9)
Age (years)						
mean	65.6		68.2		65.4	
range	22-89		39-88		21-92	
Survival (months)						
median	9.6		9.5		8.8	
range	0.2-300		0.2-255		0.1-300	
Initial Treatment						
urgery	93	(29.2)	94	(43.5)	338	(72.7)
radiotherapy	214	(67.1)	120	(55.6)	31	(6.7)
chemotherapy‡	3	(0.9)	11	(5.1)	20	(4.3)
Distant Metastases						
yes	60	(18.8)	73	(33.8)	205	(44.1)
no	256	(80.3)	141	(65.3)	256	(55.0)
unknown	3	(0.9)	2	(0.9)	4	(0.9)

‡ Another 76 patients received chemotherapy later during the course of the disease; 39 patients with esophageal cancer (21 squamous cell and 18 with adenocarcinoma) and 37 patients with gastric adenocarcinoma.

The thrombotic risk in esophageal carcinoma was 10 times higher than in the Dutch population [SMR: 10.6 (6.8-14.4)], as 2.73 cases instead of the observed 28 were expected based on age- and sex-specific incidence rates from the general Dutch population. The thrombotic risk in gastric cancer patients was 15 times higher than expected (42 observed and 2.73 expected) in the Dutch population [SMR 15.2 (13.7-22.4)].

Table 2. Risk of thrombosis in patients with squamous and adenocarcinoma (esophagus and stomach) of the upper gastrointestinal tract and in patients with either sqamous or adenocarcinoma of the esophagus.

	VT‡ Yes	VT No	Total	HR	95% CI
All Patients					
Squamous cell carcinoma	11	308	319		
Adenocarcinoma	59*	622	681	2.63	1.38-5.00
Esophageal cancer patients					
Squamous cell carcinoma	11	308	319		
Adenocarcinoma	17‡	199	216	2.47	1.16-5.29

‡ Of the patients with a venous thromboembolism, 26 had a pulmonary embolism; 13 patients with esophageal cancer (7 squamous cell and 6 adenocarcinoma) and 13 patients with an adenocarcinoma of the stomach.
* Three patients with an adenocarcinoma had a second venous thrombosis (VT) during the course of their disease, 1 with esophageal cancer (‡) and 2 with gastric carcinoma.

Among the 319 patients with a squamous cell carcinoma we observed 11 (3.4%) cases with venous thrombosis, whereas in 681 patients with an adenocarcinoma we found 59 (8.7%) cases with venous thrombosis (Table 2). The incidence rate among the patients with a squamous cell carcinoma was 1.9 per 100 person-years. Incidence rates among patients with an adenocarcinoma were 4.8 per 100 person-years of follow-up. The hazard of venous thromboses was 2.6-fold increased in patients with adenocarcinoma versus patients with squamous cell carcinoma (HR 2.63, 95% CI: 1.38-5.00, Table 2.).

Among 110 patients who received chemotherapy, 15 (13.6%) developed thrombosis, versus 55 (6.2%) out of 890 who did not receive chemotherapy (HR 2.40 95% CI 1.30-4.41). This difference was restricted to those with gastric cancer, amongst whom 11 of 57 with chemotherapy developed venous thrombosis, versus 31 out of 408 who did not. There was no difference in venous thrombosis in patients with or without radiotherapy (data not shown).

We analyzed survival in the 1000 cancer patients using as predictor variables age, sex, metastatic disease, esophageal or gastric carcinoma, squamous or adenocarcinoma, surgery, radiotherapy and chemotherapy. In the Cox regression model, risk of death was increased 2.1-fold in those who had experienced thrombosis (95% CI 1.64-2.88), adjusted for histological type of cancer, metastatic disease, surgery, radiotherapy and chemotherapy, and localization.

Discussion

This study shows a high risk of venous thrombosis in patients with upper gastro-intestinal tract cancer, with an annualized risk 3.9 %, and a cumulative incidence at one year of 5.6%. Patients with an adenocarcinoma of the upper gastrointestinal tract had a 2.6-fold higher risk of thrombosis than patients with a squamous cell carcinoma in the same organ site. Development of venous thrombosis also negatively affected survival.

Although many studies have shown an increased risk of thrombosis in malignancies (6) with in particular a high estimated relative risk in patients with an adenocarcinoma (8), estimations of the incidence for different types of cancer have rarely been made. In a previous study we showed an increased risk of venous thrombosis in patients with adenocarcinoma of the lung versus squamous lung tumors (9). In that study we also found reduced survival in those with thrombosis (9).

The mechanism of the thrombogenicity of adenocarcinomas may be the increased expression and shedding of aberrant mucins (10;11) which may bind to P- and L-selectins on platelets and leucocytes. This leads to platelet activation and aggregation and initiation of blood coagulation as suggested by the work of Wahrenbrock *et al*. (12). Another explanation may be that in the blood of adenocarcinoma patients circulating microparticles –of which some possibly arise from the tumor cells themselves- may express active tissue factor, the primary initiator of the coagulation cascade, and thus contribute to the coagulopathy observed in such patients (13).

Among the postulated mechanism for anti-cancer therapy-related venous thrombosis are the release of procoagulants and cytokines by chemotherapy-damaged tumor cells (14), or vascular endothelium damage by chemotherapy or radiotherapy (15;16) . In accordance with our previous findings in lung carcinoma patients (9), we found an increased risk of thrombosis during chemotherapy in the patients with an adenocarcinoma arising from the

stomach, but not in patients with a carcinomas arising from the esophagus. The latter may be explained by the small group of esophageal cancer patients (< 10 %) who were treated with chemotherapy, for in another study an increased risk during chemotherapy was shown for patients with a squamous cell carcinoma (17).

This study supports the widespread believe that patients with adenocarcinoma have a higher risk as compared to squamous cell carcinoma, and there are strengths but also limitations to the study. The large sample size and the single centre study are strong points of this study. However, the incidence of venous thrombosis may even have been underestimated by us as the diagnosis of a fatal pulmonary embolism may well have been missed at the time of death. Autopsy was only performed in a small number of patients and would have provided more precise information about the true incidence of pulmonary embolism

In conclusion, patients with an adenocarcinoma are more likely to develop thrombosis than patients with squamous cell carcinoma in the upper gastrointestinal tract. In recent years, adenocarcinomas are more frequently diagnosed than squamous cell carcinomas in the upper gastrointestinal tract. The incidence of thrombosis may thus increase due to this rise in incidence of adenocarcinoma in the upper gastro-intestinal tract and the more widely applied intensified treatment consisting of a combination of chemotherapy and radiotherapy. For this reason, the use of thrombosis prophylaxis should be reconsidered in those patients with the highest risk to develop venous thrombosis, and weighed against the risk of bleeding episodes in this group of patients.

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