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High risk of venous thrombosis in patients with pancreatic cancer: A cohort study of 202 patients

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ARTICLE INFO

Article history:

Received 30 March 2005

Received in revised form 12 September 2005

Accepted 28 September 2005

Available online 29 November 2005

Keywords:

Pancreatic cancer

Venous thrombosis

Epidemiology

ABSTRACT

To estimate the risk of venous thrombosis associated with pancreatic malignancies we followed a cohort of patients with pancreatic cancer ($n = 202$). We calculated incidence rates of venous thrombosis and compared this with population rates using a Standardised Morbidity Ratio (SMR). The effects of location, histology and treatment were assessed by Cox-modelling. The incidence of venous thrombosis was 108.3/1000 patient-years (95% confidence interval (CI) 64.4–163.8), 58.6-fold increased (SMR 58.6, 95% CI 36.9–92.9). Patients with a tumour of the corpus/cauda had a 2-fold increased risk compared with those with a tumour of the caput. Patients treated with chemotherapy had a 4.8-fold increased risk (HR_{adj} 4.8, 95% CI 1.1–20.8), whereas radiotherapy did not increase the risk. In a postoperative period of 30 d, patients had a 4.5-fold increased risk of venous thrombosis (HR_{adj} 4.5, 95% CI 0.5–40.9). The risk was 1.9-fold increased in the presence of distant metastases (HR_{adj} 1.9, 95% CI 0.7–5.1). Anti-thrombotic prophylaxis seems warranted in the first month after surgery, during and after treatment with chemotherapy, and when distant metastases have been diagnosed.

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1. Introduction

Tumours of the pancreas are known to be associated with a high incidence of venous thrombosis. Sproul and colleagues conducted the first study reporting the relationship between pancreatic tumours and venous thrombosis in 1938 [1]. They described autopsy reports and found 60% (28 out of 47) of patients with pancreatic cancer had venous thrombosis in various locations, compared with 15–25% of patients with other malignancies. She concluded that pancreatic cancer often leads to venous thrombosis. Since this report, other studies have confirmed a correlation between pancreas carcinoma and venous thrombosis [2–4]. A high risk of venous thrombosis in patients with pancreatic cancer may result from the re-

lease of prothrombotic factors by the tumour, such as trypsin or mucin [5].

The relationship between pancreatic carcinoma and venous thrombosis is not unique. Lung cancer, prostate cancer, colon cancer and haematological cancer as well as pancreatic cancer are all associated with thrombosis, and are more often found in patients with idiopathic venous thrombosis than secondary venous thrombosis [6]. However, the incidence of symptomatic deep venous thrombosis and pulmonary embolism in patients with pancreatic cancer has not been measured accurately. For clinical practice an assessment of the magnitude of risk is important and, specifically, of the absolute risk, which is the basis of strategies for thromboprophylaxis.

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doi:10.1016/j.ejca.2005.09.013

This cohort study aims to estimate the absolute risk of venous thrombosis for patients with pancreatic cancer, and assess the effect of localisation, histological characteristics and treatment. We also compared the incidence of venous thrombosis with general population data.

2. Patients and methods

2.1. Patient selection

Between January 1990 and December 2000, 252 consecutive patients were admitted to the Leiden University Medical Centre (LUMC) with a tumour of the pancreas. Patients were identified from the oncology registration database of the hospital. This database was set up in 1970 and is staffed by specialised oncology data managers. It includes information on all patients diagnosed with and admitted for cancer in the LUMC. We excluded 27 patients because they only briefly visited the LUMC for diagnosis or therapy and 7 patients because they had a diagnosis of pancreatic cancer before 1990 or a primary diagnosis of pancreatic cancer that could not be confirmed. Sixteen medical records could not be traced. For the analysis we included 202 patients with a first diagnosis of pancreatic cancer established in the LUMC or with a first diagnosis within 2 months before referral to the LUMC. There were 115 men and 87 women in this patient group. Eighteen patients had a previous malignancy in their medical history, and for 2 of these it was unclear whether the pancreatic tumour was histologically different from the other malignancy.

2.2. Data collection

From the medical records, clinical characteristics, such as demographic data, use of anticoagulants, treatment (surgery, radiotherapy, chemotherapy) were recorded. In addition, tumour characteristics (the histological or cytological classification of the tumour, localisation and the extent of disease) were recorded. Thrombotic events, defined as deep venous thrombosis of the leg or arm or a pulmonary embolism after the first diagnosis of pancreatic cancer, were identified through the regional Anticoagulation Clinics. In the Netherlands, the anticoagulation clinics monitor all patients receiving treatment with oral anticoagulant therapy. We ascertained the occurrence of a venous thrombotic event since diagnosis of cancer from the records of the regional Anticoagulation Clinic and by consulting general practitioners.

Information on the date of death was obtained from the medical records, the registration offices of the municipalities where the patients lived or from their general practitioner. No information was available for 1 patient at the anticoagulation clinic or general practitioner, whereas the date of death was known. This resulted in a loss of a maximum of 0.4 person years.

2.3. Diagnosis

For 144 patients the diagnosis of pancreatic cancer was based on histological ($n = 102$) or cytological ($n = 42$) examination. In the 58 remaining cases, diagnosis was based on ultrasound or computer tomography imaging in addition to clinical symptoms.

2.4. Stage of disease

We used two stages for the classification of the extent of disease using the TNM-classification system. T indicates the size of the tumour, N indicates lymph node spread and M indicates the presence or absence of distant metastases. Any T, any N, M0 was classified as local tumour growth with or without lymph node spread and no distant metastases. The second group comprised patients with distant metastases (any T, any N, M+). In 14 cases, staging was not performed at diagnosis due to lack of therapeutic consequences. For the same reason, during the course of disease, the search for distant metastases was not always completed.

2.5. Therapy

Patients without distant metastases at diagnosis could be classified according to four different therapeutic approaches (Table 1):

- no further therapy;
- major surgery (pancreas tumour resection);
- explorative or palliative surgery (i.e., biliary digestive anastomosis or placing of stent);
- surgery with a combination of 5 weeks of radiotherapy and 5-fluorouracil in the first and fifth week of the radiotherapy (RT/5-FU). This therapy was given to patients who had a residual tumour mass of less than 5 cm after surgical therapy.

Patients with distant metastases at diagnosis were categorised as those without further surgical therapy and patients with explorative or palliative therapy (Table 1).

Radiotherapy was always given on the primary tumour area.

2.6. Statistical analysis

For each subject, person-years of follow-up were counted from the date of first contact until the date of a thrombotic event, the date of death, or the end of the study period (31st December 2000), whichever occurred first. A total of 176 person-years accrued. By dividing the number of cases of deep venous thrombosis or pulmonary embolism by the number of person-years we computed the incidence rates. An age- and sex-adjusted relative risk (Standardised Morbidity Ratio (SMR)) of venous thrombosis compared with the general population was calculated by comparing the observed sum of venous thrombotic events with the expected sum of events using the age- and sex-specific incidence rates of venous thrombosis of the leg and pulmonary embolism from the Dutch general population [7].

The effect of various factors on the occurrence of thrombosis was estimated by Cox proportional hazards models in which the hazard ratio can be seen as a relative risk. A time-dependent covariate for distant metastases (m) was added to the Cox-regression model, with $m = 0$ when no distant metastases were present and $m = 1$ from the moment distant metastases were diagnosed. For therapy we also used time-dependent covariates, with a variable t for chemotherapy. With $t = 1$ as ever

Table 1 – Stage of disease and therapeutic approaches

Distant metastases at diagnosis	Initial treatment (IT)	Median survival (years)	Venous thrombosis after IT (n)	Second treatment (ST)	Venous thrombosis after ST (n)
Absent (n = 81)	Major surgery, no residual tumour left (n = 21)	2.3	2 ^a	1 RT	
	Surgery, (2 major, 20 explorative/palliative) residual tumour ≤5 cm left (n = 22)	1.2		1 CT + RT	1
	Explorative ^c or palliative ^d surgery, primary tumour still in situ (n = 23)	0.7	2 ^b	RT/5-FU	
	No further therapy (n = 15)	0.3	0	1 CT + RT	1
				1 RT	
Present (n = 107)	Explorative or palliative surgery (n = 40)	0.5	3	6 CT	2
	No further surgery (n = 67)	0.3	8	3 RT/5-FU	
				4 CT	
Not determined (n = 14)	3 palliative surgery	0.5	0	3 RT	
	11 no further therapy				

CT, chemotherapy; RT, radiotherapy; 5-FU, 5-fluorouracil.
a 1 venous thrombosis in post-operative phase, 1 venous thrombosis before surgery.
b 1 venous thrombosis in postoperative phase.
c Only biopsy has been taken.
d Biliodigestive anastomosis.

having received chemotherapy starting from the moment the therapy started, and $t = 0$ as never having received chemotherapy or not yet having received chemotherapy. Similarly, for patients receiving radiotherapy (alone or in combination with 5-fluorouracil), with variable r defined as $r = 1$ as ever having received radiotherapy starting from the moment the therapy started, and $r = 0$ as never having received radiotherapy or not yet having received radiotherapy. Surgery plus 1 month post-operative also was a time-dependent covariate. This period of 1 month was chosen arbitrarily. Explorative operation or palliative surgery was not regarded as surgery in this model, because of its minor size compared with surgery for pancreas tumour resection. In the regression model we adjusted for age, sex and other possibly confounding variables.

3. Results

In this cohort of 202 patients the mean age at diagnosis was 64 years, with a median survival of 0.5 years from diagnosis until the end of the study or death. Twelve patients suffered from deep venous thrombosis of the leg, 4 patients had a pulmonary embolism and 2 patients had both. One patient developed arm thrombosis while having a central venous catheter. Six patients had a venous thrombosis in their medical history prior to cancer diagnosis. One of them had the thrombosis 1 month before the diagnosis of pancreatic cancer. The other 5 patients had venous thrombosis 4–19 years before the diagnosis of pancreatic cancer. None of the patients with a history of venous thrombosis had a venous thrombotic event after the diagnosis of pancreatic cancer. Eight patients used oral anticoagulant therapy for more than 2 months during the follow-up period for reasons other than venous thrombosis. None of these patients developed a venous thrombosis after the diagnosis of pancreatic cancer.

We observed 19 cases of venous thrombosis during the follow-up period, with an incidence rate of 108.3/1000 patient-

years, 95% CI 64.4–163.8 (overall cumulative incidence 94.1/1000, 95% CI 90.9–97.3). Fifteen out of 19 cases of venous thrombosis occurred in the first 6 months since diagnosis of the tumour (cumulative incidence 74.3/1000 (68.3–80.3)), 3 cases between 6 and 12 months, whereas 1 case occurred 4 years after diagnosis of the tumour. In the first 3 months following the diagnosis of cancer the incidence rate was 207.0/1000 patient-years (95% CI 92.0–367.8), and in the following 3 months it decreased to 91.9/1000 patient-years (95% CI 34.5–187.6). From 6 months until 1 year after cancer diagnosis the incidence rate was 34.7/1000 patient-years (95% CI 6.2–86.3).

Based on sex- and age-specific rates of venous thrombosis in the general population [7], only 0.31 cases of deep venous thrombosis of the leg or pulmonary embolism were expected. The 19 cases that were observed resulted in a 58-fold increased risk compared with the general population (SMR 58.6, 95% CI 36.9–92.9).

The localisation of the tumour in the pancreas could be determined in 194 cases. Tumours were most often located in the caput ($n = 149$), 21 tumours were located in the corpus and 23 in the cauda. One tumour was located in the peri-ampullary area. Tumours located in the corpus and cauda of the pancreas had a 2–3-fold increased risk of venous thrombosis compared with tumours in the caput of the pancreas (HR 1.9, 95% CI 0.5–6.7, and HR 2.9, 95% CI 1.0–8.5, respectively). Although tumours in the corpus and cauda were more often associated with distant metastases at diagnosis (70% versus 47%), after adjusting for distant metastasis, age and sex, these tumours still had an increased risk of venous thrombosis (HR 1.6, 95% CI 0.4–5.9 and HR 2.5, 95% CI 0.9–7.4, respectively). Of the 102 patients with a histological diagnosis, 41 had a mucinous adenocarcinoma and 47 a non-mucinous adenocarcinoma. Seven patients had a neuro-endocrine carcinoma and 7 were classified as 'other' tumour type. The distribution of the histological types of tumour was different between the various localisations. In the group of patients with a

histological verified diagnosis ($n = 102$) we found a mucinous adenocarcinoma in the corpus and cauda more often than in the caput of the pancreas (48% versus 37%). We found no difference in risk of venous thrombosis in mucinous adenocarcinoma compared with non-mucinous adenocarcinoma (HR_{adj} 1.0, 95% CI 0.2–4.6), adjusted for distant metastasis, age and sex.

A total of 107 patients (53%) had distant metastases at the time of diagnosis and another 23 (11%) were diagnosed with distant metastases in the follow-up period. For patients with distant metastases the risk of venous thrombosis was 2-fold increased (HR_{adj} 1.9, 95% CI 0.7–5.1, adjusted for age, sex, surgery and chemo- or radiotherapy) (Fig. 1). The cumulative incidence of venous thrombosis after detection of distant metastases was 87.3/1000 persons/6 months (95% CI 38.0–136.6). The incidence of venous thrombosis was 50.0/1000 persons/6 months (95% CI 2.2–97.8) in the absence of distant metastases.

Eleven out of 19 patients with a venous thrombosis died within 1 month after the venous thrombosis. These were patients who also had distant metastases at diagnosis. The median time for patients with distant metastasis to develop venous thrombosis was 92 d. Median survival after cancer diagnosis of patients with a venous thrombosis and distant metastases was 104 d. Patients with distant metastases who did not develop a venous thrombosis had a median survival of 116 d.

Twenty-three out of 81 patients without distant metastases had major surgery and 43 out of 81 had minor surgery (Table 1). Among 107 patients with distant metastases 40 had minor surgery. Three of the 14 patients in whom staging of the disease was not performed had minor surgery. One patient developed a pulmonary embolism within 2 weeks after major surgery resulting in a 4-fold increased

risk (HR_{adj} 4.5, 95% CI 0.5–40.9) for patients in the postoperative period of 30 d.

Twenty-six out of 81 patients without distant metastases received radiotherapy after surgery (Table 1); 22 had radiotherapy in combination with 5-FU and 2 had radiotherapy as well as other forms of chemotherapy. Six out of 107 patients with distant metastases received radiotherapy (3 in combination with 5-FU) and 10 of these 107 received chemotherapy. Radiotherapy with 5-FU was usually given shortly after surgery, while other forms of chemotherapy or radiotherapy were given 1–52 weeks after surgery. Two patients with a neuro-endocrine carcinoma had chemotherapy also before surgery. Chemotherapy was mostly given to patients with distant metastases (Table 1). No increased risk was found for patients after receiving radiotherapy (HR_{adj} 0.5, 95% CI 0.1–3.9, adjusted for age, sex and distant metastases). Three patients developed deep venous thrombosis of the leg within 3 months after discontinuation of their chemotherapy. We found a 4.8-fold increased risk for patients after receiving chemotherapy (HR_{adj} 4.8, 95% CI 1.1–20.8, adjusted for age, sex and distant metastases).

4. Discussion

This cohort study of patients with a first diagnosis of pancreas carcinoma shows that the risk of venous thrombosis is 60-fold increased compared with the general population, at a cumulative risk of nearly 10%. Cumulative incidence in the first half year since diagnosis of cancer was 74.3/1000 persons/6 months (95% CI 68.3–80.3), compared with the 39.1/1000 persons/6 months (95% CI 22.7–55.5) found earlier for lung cancer patients [8].

Patients with pancreatic cancer have always been assumed to have the highest incidence of venous thrombosis compared with patients with other cancers. This assumption began with the publication of a post-mortem study in 1938 [1]. However, in this report the localisation of the thrombosis was not stated and the conclusions were based on a relatively small number of patients with pancreatic cancer ($n = 47$). Since this study the relationship between pancreatic cancer and thrombotic events has been reviewed extensively and incidences varying from 5% to 60% have been found [2]. Many studies, however, included thrombi in veins contiguous with the tumour comprising about one-third of the thrombi found in these patients [2]. In agreement with our findings of 2 (1%) of 202 patients who died due to pulmonary embolism, others found 4 out of 541 (0.7%) cases with fatal pulmonary embolism [9].

In agreement with other studies of patients with pancreas tumours, we found that tumours of the corpus and cauda of the pancreas are associated with a higher incidence of venous thrombosis than tumours of the caput of the pancreas [1,2,5,10]. In our cohort, tumours of the corpus and cauda were more often mucinous adenocarcinomas, which might explain this higher incidence. Another reason for a higher incidence of venous thrombosis could be a larger tumour load. Tumours of the corpus and cauda are more often detected at a later stage due to the lack of symptoms and thus already have a larger volume than tumours of the caput of the pancreas [11].

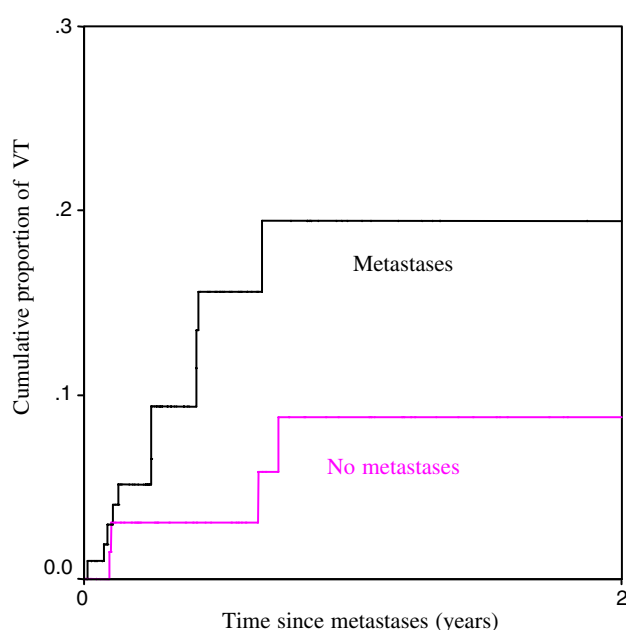


Fig. 1 – Risk of venous thrombosis in the presence of distant metastases compared with no distant metastases.

Almost 50% of the patients already had distant metastasis at the moment of diagnosis of the pancreas tumour. We saw a clear increase in the risk of venous thrombosis in the presence of distant metastasis.

In our study, there was a 4.8-fold increased risk of venous thrombosis after patients had been treated with chemotherapy. Surgery increased the risk 4-fold. The risk of venous thrombosis has previously been shown to be higher in cancer patients who receive chemotherapy [8,12,13] compared with those without chemotherapy. In addition, an increase in risk has been described before for radiotherapy [14] and surgery [15], but in our study there was no increase in risk during or after being treated with radiotherapy.

The underlying condition of the patient (e.g., immobilisation) could cause an overestimation of the effect of therapy or the presence of distant metastases on the risk of venous thrombosis. We limited this effect by including therapy and distant metastases as time-dependent variables in the Cox-model, so the effects of these variables are measured within the same individual and therefore the underlying condition of the patient in all likelihood would not alter the hazard ratio.

4.1. Clinical consequences

Only two patients with distant metastases died directly after a venous thrombotic event. It is unlikely that prophylactic anticoagulant treatment preventing venous thrombotic events would result in a gain in life expectancy for patients who already have distant metastasis. However, for patients with distant metastases prophylactic anticoagulant treatment may prevent serious co-morbidity and associated suffering. The incidence of bleeding so far described for cancer patients receiving anticoagulant treatment [16,17] is markedly lower than the incidence of venous thrombosis in patients with distant metastases.

For patients without distant metastasis, the incidence of venous thrombosis was much lower, and was similar to the reported incidence of bleeding during anticoagulant treatment [17]. Decisions about prophylactic anticoagulant treatment might well be guided by additional risk factors for venous thrombosis, i.e., surgery or chemotherapy treatment.

Conflict of interest statement

None declared.

Acknowledgements

We thank Mrs. M. van den Broeke for reviewing the medical records. This study was supported by the Dutch Cancer Foundation (RUL 99/1992).

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