Incidence, timing and risk factors of venous thromboembolic events in patients with pancreatic cancer

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Thrombosis Research 207 (2021) 134–139

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Incidence, timing and risk factors of venous thromboembolic events in patients with pancreatic cancer

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ARTICLE INFO

Keywords:
Pancreatic cancer
Venous thromboembolism
Bleeding
Survival

ABSTRACT

Introduction: Pancreatic cancer is associated with a high risk of venous thromboembolism (VTE). However, comprehensive data on incidence, timing and relevant determinants of VTE in this particular population are scarce. Current study assesses incidence, timing and predictors of VTE in pancreatic cancer through different phases of disease.

Methods: All pancreatic cancer patients treated in our tertiary referral center between 2013 through 2017 were studied. Occurrence of VTE was evaluated from diagnosis through end of follow-up or death. Relevant determinants of VTE were identified in logistic regression models. Hazard ratios were calculated to evaluate impact of VTE on overall survival.

Results: In total, 361 patients were followed for a median period of 43 months; 64 were diagnosed with VTE (18%). Most were tumor related thrombosis (59%), incidental (75%) and occurred after anti-cancer treatment had been stopped (80%), only 1.6% occurred during remission phase. Stage IV pancreatic cancer was a predictor for VTE (hazard ratio (HR) 2.46, 95% confidence interval (CI) 0.9–6.8). Biliary drainage (HR 0.52, 95%CI 0.28–0.98) and tumor resection (HR 0.45, 95%CI 0.45–1.83) were protective factors. VTE was not associated with worse survival (HR 1.3; 95% CI 0.97–1.74).

Conclusions: VTE in pancreatic cancer is disease-stage dependent, with 80% occurring in advanced phases of disease when patients no longer receive active treatment. We speculate that this is the main reason for the absence of a survival effect of VTE in our cohort. These practice-based findings should be taken into account when considering wide-spread introduction of primary thromboprophylaxis in patients with pancreatic cancer.

1. Introduction

Venous thromboembolism (VTE) is a common medical condition, with a yearly incidence of 1 to 2 per 1000 people among the general population [1]. VTE mostly encompasses deep vein thrombosis (DVT) of the extremities and pulmonary embolism (PE), although it may also occur in the visceral and cerebral veins. VTEs are associated with worse overall survival and quality of life, especially in the setting of cancer [2–9]. In cancer patients being treated with chemotherapy, VTE has even been shown to be the second leading cause of death after cancer itself [10]. Because of the major impact of VTE on the prognosis of patients with cancer, it has been argued that some cancer patients may benefit from thromboprophylaxis in the ambulatory setting, with several recent trials showing a clear lower incidence of VTE in cancer patients at high risk of VTE treated with prophylactic doses of oral FXa inhibitors compared to placebo [11,12].

Pancreatic cancer is considered among the most prothrombotic malignancies. The reported 25% VTE incidence peaks during chemotherapy [13]. According to current recommended risk stratification systems, patients with pancreatic cancer are by definition at intermediate to high risk of VTE, making them candidates for prophylactic anticoagulation [11,12,14]. However, in the available trials, the lower incidence of VTE achieved with pharmacological thromboprophylaxis was not associated with an overall survival benefit. Moreover,

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https://doi.org/10.1016/j.thromres.2021.08.002
Received 21 May 2021; Received in revised form 25 July 2021; Accepted 4 August 2021
Available online 8 August 2021

anticoagulation resulted in excess major bleeding compared to placebo. Notably, these studies focused on patients without particular risk factors for bleeding rather than all-comers. To fully appreciate the potential impact of widespread introduction of prophylactic anticoagulation in clinical practice circumstances, and its potential effect on survival, detailed information on the incidence, location of VTE and (treatment) phase of disease and bleeding events in the course of pancreatic cancer is necessary.

Therefore, we set out to evaluate the incidence, location of VTE and (treatment) phase of disease and bleeding events in patients with pancreatic cancer across all stages of disease. Further, predictive factors of VTE and the impact of VTE on survival was evaluated.

2. Methods

2.1. Patients and data acquisition

Consecutive pancreatic cancer patients referred to the Leiden University Medical Centre, a tertiary referral centre from the Netherlands, between 2013 and 2017 were evaluated. Patients were referred from surrounding hospitals if at initial screening there was a chance of surgery in the future. Patients were included if the diagnosis was either confirmed by pre- or postoperative pathology or, in cases without available histology, pancreatic cancer was ranked highest in the differential diagnosis based on radiology and biomarker tests [15]. All patients were treated in accordance with the 'National multidisciplinary guideline on pancreatic and periampullary carcinoma' by the Dutch Pancreatic Cancer Group [16]. In the studied cohort, patients who underwent pancreatic resection surgery routinely received thromboprophylaxis for a total duration of 6 weeks postoperatively [17]. All other patients only received thromboprophylaxis during hospital admissions, but not during (ambulant) chemotherapy.

Patients were excluded if the primary treatment occurred in other hospitals. Patient without follow-up data were also excluded. We reviewed the medical charts of all patients to collect demographics, treatment characteristics and clinical outcomes. Cause of death was determined by reviewing autopsy reports and medical charts. Two independent investigators (RGHS & AH) performed data collection from the medical charts. In case of dispute, a third independent investigator was consulted (JVG). VTEs and bleedings were independently adjudicated by a vascular medicine specialist (FAK) and a hepatopancreaticobiliary surgeon (JSDM). This study was approved by the Medical Ethics Committee of the Leiden University Medical Centre (LUMC), who waived the need for informed consent due to its retrospective design.

2.2. Aims and outcomes

The aims of this study were to evaluate the incidence of VTE and bleedings in pancreatic cancer patients in different phases of the disease and their effect on overall survival. Primary outcome was the incidence of objectively diagnosed VTE and bleeding complications overall and in each disease stage. Secondary outcomes were impact of VTE on overall survival and determinants of VTE.

2.3. Definitions

VTE was defined as any venous blood clot classified in five groups: 1) conventional VTE consisted of deep vein thrombosis (DVT) of the leg or acute pulmonary embolism (PE) [18], 2) local postoperative/surgery-related: VTE in portal, superior mesenteric or splenic veins diagnosed within 6 weeks after surgery, 3) tumor-related thrombosis, i.e. tumor thrombus (directly related to intravascular tumor expansion), 4) central line-related thrombosis, i.e. originated at site of central venous catheter (CVC), 5) other types of VTE, e.g. cerebral vein thrombosis. Both symptomatic and incidental VTE were included. We predefined five disease phases: 1) Post-surgery (from surgery to six weeks post-operatively), 2) Adjuvant chemotherapy phase (from start to two weeks after the last administration), 3) Remission phase (i.e. no detectable disease, from start of first imaging test confirming successful surgery), 4) Palliative chemotherapy phase (from start of chemotherapy until two weeks after the last administration in patients with irresectable or metastatic disease), 5) advanced disease phase (locally advanced, recurrent or metastatic disease without active anti-cancer treatment or after discontinuation of anti-cancer treatment, or terminal phase of life). In case of overlap in different phases of disease, the chronologically first phase was taken into account.

Bleeding events were classified into two main groups: Post-Pancreatectomy Haemorrhage (PPH) and bleeding events. Patients who underwent resection and developed bleeding within six weeks postoperatively were defined as PPH. PPH was graded from A to C depending on timing, severity and site of bleeding and classified in accordance with the International Study Group of Pancreatic Surgery criteria. PPH grade B and C were classified as clinically relevant [19]. Bleeding events were classified as: 1) 'major bleeding', as fatal bleeding; symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular resulting in vision changes, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome; bleeding causing a fall in hemoglobin level of 2-g/dL or more; and/or bleeding leading to transfusion of two or more units of whole blood or red cells. 2) 'clinically relevant non-major bleeding' defined as any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria:

i. requiring medical intervention by a healthcare professional
ii. leading to hospitalization or increased level of care
iii. prompting a face to face (i.e., not just a telephone or electronic communication) evaluation

All bleeding events were scored according to the criteria proposed by the International Society on Thrombosis and Haemostasis [20].

2.4. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA). Categorical variables were reported as frequency (N) and percentage (%). Continuous variables were reported as mean and standard deviation or median and interquartile range (IQR). For categorical variables, odds ratios were calculated with corresponding 95% confidence interval. For continuous variables, the mean difference was calculated with corresponding 95% confidence interval. Statistical comparisons were performed with χ^2 test or Fisher's exact test for categorical variables and Student's *t*-test or the Wilcoxon rank sum test for continuous variables.

Incidences were calculated for the primary outcome of both VTE and bleedings. If multiple types of VTE occurred in one individual patient, only the first was accounted for in all analyses. Absolute incidences of VTE were calculated for the different phases of disease. Uni- and multivariate logistic regression analyses were performed using a competing risk model to identify independent predictors of VTE (competing risk: death). A *p*-value of <0.10 was used as threshold for covariates inserted in multivariate analysis. Kaplan Meier analysis was used to compare overall survival in patients with and without VTE. Statistical significance for survival was determined using the log-rank test. All tests used in the analysis were two-sided. Statistical significance was defined as $P < 0.05$.

Table 1
Baseline and treatment characteristics.

		Total		VTE			
				No		Yes	
		N	%	N	%	N	%
Number of patients		361	100	297	82	64	18
Male sex		188	52	159	54	29	45
Age	Median (IQR)	68 (60–74)		67 (61–74)		64 (56–72)	
BMI	Median (IQR)	24 (22–27)		24 (21–27)		24 (22–28)	
ASA	I-II	280	78	233	79	47	73
	III-IV	81	22	64	22	17	27
Diabetes mellitus		99	27	87	29	12	19
Biliary drainage		140	39	125	42	15	23
Tumor location	Pancreas head	261	72	226	76	35	55
	Pancreas body	59	16	41	14	18	28
	Pancreas tail	41	11	30	10	11	17
Clinical stage	I	62	17	55	19	7	11
	II	152	42	128	43	24	38
	III	61	17	52	18	9	14
	IV	86	24	62	21	24	38
Neoadjuvant chemotherapy	Yes	17	4.7	15	5.1	2	3.1
Tumor resection		153	42	131	44	22	34
Adjuvant chemotherapy		100	65	86	29	14	21
Palliative chemotherapy		87	32	72	24	15	23

IQR = inter quartile range; N = number of patients; VTE = venous thromboembolism; BMI = body mass index; ASA = American Society Anasthesiologists score.

Table 2
Details of VTE and bleeding events.

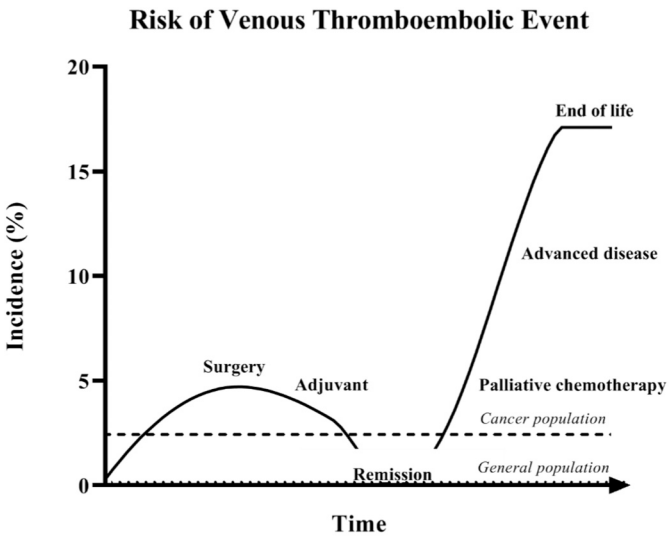
	Total cohort		No tumor resection		Tumor resection	
	N = 361	%	N = 208	%	***N*** = 153	%
VTE	64	18	42	20	22	14
Incidental	48	75	36	86	12	55
Symptomatic	16	25	6	14	10	46
VTE subgroup:						
Classic VTE	15	23	10	24	5	23
Tumor related thrombosis	38	59	31	74	7	32
Postoperative VTE	7	11	–	–	7	32
CVC related VTE	3	4.7	1	2.4	2	9.1
Other VTE	1	1.6	–	–	1	4.5
Other bleeding	36	10				
Major	18	50	9	45	9	56
CR-non-major	18	50	11	55	7	44
Post-pancreatectomy hemorrhage					22	14
A	–	–	–	–	5	23
B	–	–	–	–	10	46
C	–	–	–	–	7	32

VTE = venous thromboembolism; CVC = central venous catheter; N = number of patients; CR = clinically relevant;

3. Results

3.1. Baseline patient and treatment characteristics

A total of 361 patients with pancreatic cancer were studied (Table 1). Their mean age was 68 years (SD: 9.8) and 48% were female. Most patients had tumor stage I ($n = 152$, 42%) or stage IV ($n = 86$, 24%). The majority of patients had a tumor located in the pancreatic head ($n = 261$, 72%). One-hundred-fifty-three patients underwent surgical resection (42%). All other patients ($n = 208$) were diagnosed with an advanced stage of cancer, either locally advanced or metastatic. Eleven per cent (17 out of 153) received neoadjuvant chemotherapy in the form of either FOLFIRINOX ($n = 6$) or gemcitabine combined with radiotherapy ($n = 11$) in the PREOPANC trial, and 65% received adjuvant chemotherapy after tumor resection ($n = 100$ out of 153), mostly a gemcitabine-based regimen ($n = 93$). Lastly, 87 patients received palliative chemotherapy (32%).



	Total cohort	VTE	Incidence
	N	N	% (95% CI)
Surgery related	153	7	4.6 (1.9-9.2)
Adjuvant therapy	95	3	3.2 (0.7-9.0)
Remission	125	1	0.8 (0.02-4.4)
Palliative chemotherapy	85	2	2.4 (0.3-8.2)
Advanced disease	298	51	17.1 (13.0-21.9)
Cancer population	-	-	2.0
General population	-	-	0.104

VTE=venous thromboembolism; N= number of patients; CI=confidence interval

Fig. 1. Details of VTE in different disease phases.

3.2. Primary outcomes

The median follow up was 43 months (IQR 32–53); 299 out of 361 (83%) patients died during follow up. In total, 64 (18%) patients were diagnosed with VTE. In total, 42 VTEs occurred in the 'no tumor resection' group (incidence 20%, 95%) and 22 in the 'tumor resection' group (incidence 14% Table 2). In both groups, most VTEs were incidental: 36/42 (86%) and 12/22 (55%), respectively. Out of the five VTE subgroups, most VTEs ($n = 38/64$, 59%) were classified as directly tumor-related thrombosis, whereas 15 were 'conventional' (15/64, 23%; Table 2). The absolute VTE incidence was the highest in the 'advanced disease' phase with no active therapy, where 51 of 298 patients in the advanced disease phase were diagnosed with VTE (incidence 17%, Fig. 1). Only 1 of 125 patients developed a VTE during the remission phase, leading to the lowest incidence of 0.8%. This patient did not develop cancer recurrence during a 41-month follow-up period. The incidence during adjuvant or palliative chemotherapy ranged between 2.4 and 3.2%, with wide confidence intervals.

In total, 36 out of 361 patients developed a bleeding event: major and CR-non-major bleedings both occurred in 18 patients (incidence 10%, Table 2). Eleven patients (30%) suffered a bleeding while receiving anticoagulation treatment, of which seven (64%) patients in prophylactic doses of low molecular weight heparin (LMWH) and two patients (18%) received therapeutic LMWH treatment for VTE. Twenty-two out of 153 operated patients developed PPH (incidence 14%). Of the 22

Table 3
Uni-and multivariate analysis for VTE.

		Univariate analysis		Multivariate analysis	
		HR*	95% CI	HR	95% CI
Age		0.98	0.95–1.00	0.98	0.95–1.00
Sex	Male		Reference		
	Female	1.33	0.82–2.18		
BMI (kg/m^2)		1.01	0.97–1.06		
Diabetes mellitus	No		Reference		
	Yes	0.59	0.32–1.11		
Tumor stage	I		Reference		Reference
	II	1.44	0.62–3.35	1.42	0.60–3.33
	III	1.37	0.51–3.67	1.17	0.37–3.67
	IV	2.78	1.20–6.46	2.46	0.90–6.8
Tumor location	Pancreas head		Reference		Reference
	Pancreas body	2.59	1.46–4.57	1.95	1.04–3.53
	Pancreas tail	2.09	1.11–4.29	1.42	0.68–2.96
Biliary drainage	No		Reference		Reference
	Yes	0.45	0.25–0.80	0.52	0.28–0.98
Tumor resection	No		Reference		Reference
	Yes	0.67	0.40–1.12	0.45	0.45–1.83

OR, odds ratio; CI, confidence interval; BMI, body mass index.
* $p < 0.10$ was the threshold for covariates inserted in the model for MVA.

PPHs, most were classified as type B PPH ($n = 10$, 46%).

3.3. Secondary outcomes

Univariate analyses identified age, tumor stage III and IV as well as a tumor located in pancreas body and tail as predictors for VTE (Table 3). Biliary drainage and tumor resection were associated with a lower risk of VTE. Multivariate analyses confirmed that tumor stage IV is a predictor of VTE (HR 2.46, 95% CI 0.9–6.8 compared to stage I), whereas biliary drainage (HR 0.52, 95% CI 0.28–0.98) and tumor resection (HR 0.45, 95% CI 0.45-1,83) remained independently associated with a lower risk of VTE.

After twelve months, 44% of the total cohort was still alive and at the end of follow-up 17%. Analysis of the total cohort showed no association between VTE and survival (HR 1.3; 95% CI 0.97–1.75).

4. Discussion

The current study provides a detailed overview of incidence and type of VTE during different phases of pancreatic cancer. The cumulative incidence of VTE in the total cohort was 18%, with a comparable incidence between patients selected for surgery and those who were deemed inoperable. Notably, we observed that 75% of VTEs were incidental. Further, only 23% was conventional DVT or PE and 80% occurred in the advanced disease phase after all anti-cancer treatment had been stopped. Overall survival was poor and not effected by VTE status. Tumor stage IV was a predictor for the development of VTE (HR 2.46, 95% CI 0.9–6.8 compared to stage I), whereas biliary drainage and tumor resection were independently associated with a lower risk on VTE, because both of these factors imply a lower tumor stage. The incidence of VTE found in the current study is in accordance with available literature, where an incidence between 5 and 41% has been reported [21–30]. The low incidence of VTE, reported by Oh and colleagues may be explained by the Asian ethnicity of the patients, whereas the reported incidence of 41% by Epstein and colleagues, may be partly explained by the inclusion of arterial thrombosis [25,28]. Most studies report conventional DVT or PE and some report on abdominal vein thrombosis as well. The proportion of abdominal vein thrombosis is higher in the current study compared to literature, with a reported incidence of 30–50% versus 60% in our cohort [31–34]. Menapace and colleagues described that all abdominal vein thrombosis were incidental and did not impair survival, a finding confirmed by our study [31]. Frere and colleagues reviewed 731 pancreatic cancer patients, of which 152 patients developed a VTE. In total, 45 out of 152 patients developed an abdominal vein thrombosis (29.6%). Similar to our study they found that tumor location (body versus head) and tumor stage (locally advanced and metastatic disease) were independent predictors for the development of VTE. Another interesting finding Frere et al. described was the significantly impaired survival in patients with VTE (HR 2.02; 95% CI 1.57–2.60; $P < 0.001$) [33]. In the current study no association between VTE and survival (HR 1.3; 95% CI 0.97–1.74) was found.

Efforts to lower the incidence of VTE by administrating thromboprophylaxis to patients with advanced pancreatic cancer have been studied by Maraveyas and colleagues [35]. They performed a randomized controlled trial evaluating pancreatic cancer patients who received gemcitabine either with or without dalteparin thromboprophylaxis for a period of 12 weeks and found a decrease of VTE incidence from 23% to 3.4% ($P = 0.002$) at the cost of a higher incidence of bleeding events in the dalteparin group [35]. As discussed in the systematic review and meta-analysis by Frere et al., multiple randomized controlled trials have been performed thus far to determine whether primary thromboprophylaxis could prevent VTE in pancreatic cancer patients in ambulatory setting. They conclude that there is evidence that thromboprophylaxis could provide clinical benefit for patients during chemotherapy, but additional trials are necessary to determine the exact type of anticoagulant as well as dosage, duration etc. [36] This conclusion is supported by the review of Mulder et al. discussing international guidelines for thromboprophylaxis in cancer patients [37]. However, in the current study, most VTEs (51 out of 64, 80%) occurred in the advanced phase of disease in which patients no longer received any medical treatment. Therefore, wide application of the guidance document of the Scientific and Standardization Committee of the ISTH for primary thromboprophylaxis in ambulatory cancer patients will not prevent the majority of VTEs in patients with pancreatic cancer [14]. Additionally, bleeding events need to be taken into consideration when administrating thromboprophylaxis. Dallos and colleagues showed an overview of all recent randomized controlled trials with thromboprophylaxis in pancreatic cancer patients [38]. Overall incidences of general bleeding events were between 0.4 and 4.4%, and not significantly different in patients using thromboprophylaxis versus placebo. The incidence of general bleeding events in the current study was 14% (22 out of 153), which were equally distributed over the 'tumor resection' and 'no tumor resection group'. Eleven out of 36 patients (30%) suffered a general bleeding event while receiving anticoagulation treatment. Hence, the rate of bleeding found in trial circumstances may largely underestimate the rate of bleeding in clinical practice, which has also major implications for the considerations on thromboprophylaxis. The incidence of PPH in this study was 10% (36 out of 361) and was in accordance with literature (3 to 16%) [17,39].

Studies report a significant association between VTE and impaired survival, but mostly in selected patient subgroups [40,41]. Kruger and colleagues for instance excluded all patients with metastatic disease and Epstein and colleagues only analysed patients who received chemotherapy [28,42]. Unfortunately, subgroup analysis for the different phases of disease was not possible in the current cohort due to the low number of events per subgroup. Another limitation is the retrospective nature of the present study, causing selection bias resulting in a relatively large group of operated patients. Additionally, cause of death was not adjudicated and diagnostic tests for VTE were only performed when considered indicated by the treating physician. Especially in the advanced disease phase it is likely that rates of VTE were underestimated since the threshold to refer patients with only a short life expectancy for radiological imaging is high. A strength of this study was that VTEs were adjudicated by independent experts and survival analysis was performed using a competing risk model. Also, we studied all-comers with pancreatic cancer [41]. On top of that, other studies mostly discuss VTE incidence in general [4,43,44], whereas we analysed the incidence in pre-defined subcategories and stages of the patient journey, revealing that most VTEs (38 out of 64, 59%) occurred in abdominal

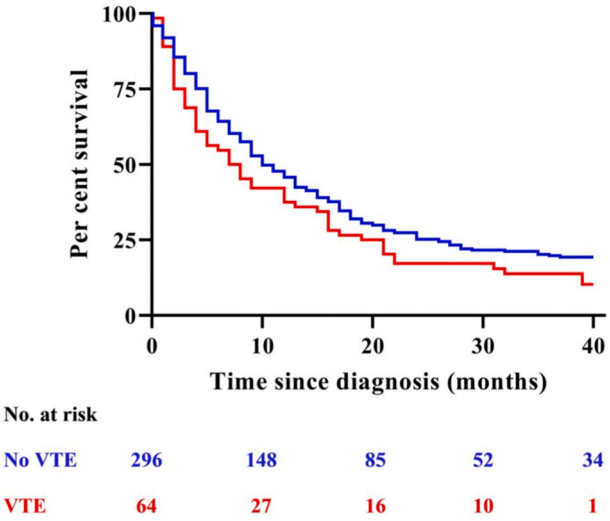


Fig. 2. Survival analysis for VTE in total cohort.

veins (tumor related thrombosis) and in the advanced phase of disease.

To conclude, VTE in pancreatic cancer patients is stage- and phase-dependent, with 80% occurring in the advanced phase of disease. Tumor location, age and stage are predictors for the development of VTE (Fig. 2).

To answer the question whether thromboprophylaxis is indicated in an ambulant setting, more randomized controlled trials are needed. However, given the fact that VTE did not seem to impair survival, most VTE occurred in the advanced phase of the disease and the incidence of bleeding was much higher than reported in the available randomized trials, the best strategy remains to be determined: broad introduction of primary thromboprophylaxis in ambulatory pancreatic cancer patients who receive chemotherapy versus treating thrombo-embolic events on diagnosis taking into account the patients prognosis without treatment.

Sources of support

This work was supported by ZonMW (project number: 50-53125-98-031 R.G. Hanna-Sawires) and a Bas Mulder Award (grant UL2015-7665) from the Alpe d'HuZes foundation Dutch Cancer Society (J.V. Groen & J. S.D. Mieog).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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