Assessing Risk and Mortality of Venous Thromboembolism in Pancreatic Cancer Patients

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Abstract. *Background: Venous thromboembolism (VTE) is associated with cancer. Cancer patient with thromboembolism have poorer prognosis. This study assessed the risk and mortality in pancreatic cancer patients who develop VTE. Patients and Methods: A retrospective chart review was performed of 201 patients with pancreatic cancer. Results: VTE was observed in 58 (28.9%) patients, 37/58 had deep vein thrombosis (DVT), 11/58 pulmonary embolism (PE) and 10/58 had both. Twenty-six out of 107 patients with tumor of head of the pancreas developed VTE (24%), compared to half of the patients with body of the pancreas involvement (11-22). Stage IV was defined in 99 patients, 39/99 had VTE (39%). Median survival time was 14.95 months for patients without VTE compared to 13.04 months with VTE. Conclusion: Patients with body of the pancreas and stage IV tumors had increased risk of developing VTE. There was no survival difference between patients with VTE compared to those without.*

Pancreatic carcinoma is a lethal disease with an annual incidence rate almost identical to the mortality rate. Cancer of the exocrine pancreas is the fourth most common malignancy in the United States and most newly diagnosed individuals will die within a year (1). The median survival time is 6-10 months with locally advanced disease and 3-6 months in patients with metastases. Without any specific anticancer therapy the median overall survival is between 2 to 4 months (2). In addition to the poor overall prognosis, the course of the disease is often complicated by thromboembolic events. Lower-extremity deep venous thrombosis, thrombophlebitis migrans, and pulmonary embolism are among the well-known presentations in pancreatic cancer (2). The first report describing the relationship between pancreatic cancer and thrombosis was published in 1938, documenting a 60% prevalence of venous thrombosis in various locations upon autopsy compared with 15-25% in other malignancies (3) This makes pancreatic cancer the tumor entity with the highest venous thromboembolism (VTE) rates. Further studies have confirmed the association of pancreatic adenocarcinoma with VTE reporting prevalence rates of 5 to 60% (4-6). In a recent cohort study in 202 patients with pancreatic cancer (based on histological and cytological examinations or ultrasound and computed tomography), the incidence of VTE was 108.3 per 1,000 patient-years (10.8%) resulting in a 58.6-fold increase in relative risk as compared with an age- and sex-adjusted general population (7). Patients treated with chemotherapy have further a 4.8-fold increased risk for VTE (8). This study examined the incidence of VTE in resected and unresected pancreatic adenocarcinoma and cancer of unknown primary along with its association to gender and age. Relation to prognosis defined as survival time (time to hospice referral, death and follow-up) calculated according to person-month contribution to the study was evaluated. The relation of VTE risk to the cancer stage and location of the tumor was also evaluated.

Patients and Methods

Retrospective chart review of patients diagnosed with pancreatic and unknown primary cancers at Yale New Haven Hospital between July 2003 and December 2008 was conducted after approval by the IRB. A total of 208 patients were identified with a diagnosis of pancreatic adenocarcinoma and cancer of unknown primary according to the histopathologic studies. Patients with history of cancer other than pancreatic adenocarcinoma (including neuroendocrine tumors), on anticoagulation, who had recent surgery within 3 months, diagnosed with coagulation defects,

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Key Words: Assessment of risk and mortality, venous thromboembolism, pancreatic cancer.

Table I. *Demographic data of patients with pancreatic and unknown primary cancers.*

Gender (male:female)	201 (122:79)
Median age, years (range)	64 (32-86)
VTE	58
Diagnosis	
Pancreatic cancer	192
Cancer of unknown primary	9
Location	
Head	107
Body	22
Tail	29
Neck	5
Combined	29
Stage	
I	11
II	51
III	37
IV	102

Table II. *VTE results in relation to gender, stage, diagnosis and location.*

Gender (male:female)	58 (33:25)
Diagnosis	
Pancreatic cancer	57
Cancer of unknown primary	1
Location	
Head	26
Body	12
Tail	8
Neck	3
Combined	9
Stage	
I	0
II	8
III	11
IV	39

pregnant or on medications with procoagulant side-effects were excluded. Out of 208 patients, 201 were eligible for the study. Data including age, gender, diagnosis and VTE time, location and stage of the tumor and death time were recorded.

Statistical analysis. VTE is defined as a radiologic evidence of any deep vein thrombosis and pulmonary embolism. Its presence was assessed in patients with pancreatic and unknown primary cancer stratified into stages of the cancer according to the American Joint Committee on Cancer (AJCC) (www.cancerstaging.org). Location of the cancer was evaluated. Survival time was calculated and a comparison was made between cancer patients who had VTE and those who did not. All data were recorded in Microsoft Excel 2003-2007 (Microsoft Corporation; Seattle, WA, USA); all statistical analysis was performed using SAS (version 8.2; SAS Institute; Cary, NC, USA). We used the Fisher's exact test to test the association between stage and VTE, chi-quare test to test the association between location and VTE and log-rank test to test the survival experience of patients with and without VTE.

Results

The 201 eligible patients included 122 males and 79 females with a median age of 64 (range: 32 and 86). The final diagnoses included: pancreatic cancer (192 patients) and cancer of unknown primary (9 patients). Demographics data of the patients is summarized in Table I. The most common reason for exclusion was patients with prior anticoagulation treated for atrial fibrillation. Venous thromboembolism was diagnosed in 57 patients with pancreatic cancer and 1 patient with unknown primary cancer. The tumor was located in the head (107 patients), body (22 patients), tail (29 patients), neck of the pancreas (5 patients) and combined location (29 patients). VTE was identified in 12 (50.0%) patients having body of the pancreas location, 26 (24.3%) patients with head of the pancreas location, 3 (60.0%) in the neck, 8 (27.6%) in the tail and 9 (31.0%) having combined locations (Table II).

Survival time was also defined in patients with VTE according to the type of the VTE. There was no difference in survival among the different VTE types. The types were defined according to the location of the VTE; whether it was in the deep veins (63.80%), pulmonary artery (18.96%) or a combined VTE (deep vein and pulmonary artery) (17.25%) (Table III).

Stage of cancer was I in 11 patients (5.5%), II in 51 patients (25.4%), III in 37 patients (18.4%) and IV in 102 patients (50.7%). None of the patients having stage I disease developed VTE, 8 patients in stage II developed VTE, 11 in stage III and 40 in stage IV. Survival time was assessed according to VTE development compared to no VTE. For the group without VTE, the median survival time was 14.95 months with a 95% CI of (11.01, 19.97) and the mean survival time was 16.63 months (standard error: 1.29). For the group with VTE, the median survival time was 13.04 months with a 95% CI of (10.97, 19.03) and the mean survival time was 16.67 months (standard error: 1.69). There was no survival difference among patients with VTE *versus* those without VTE (p-value 0.908) as demonstrated by Figure 1.

Discussion

Cancer, especially gastroenterologic cancer and more specifically pancreatic cancer, is known to be associated with VTE. This study shows the highest number of VTE incidences to be in pancreatic cancers. Recognizing the limitations of a retrospective analysis, this is the only study

Table III. *Venous thromboembolism (VTE) type defined by deep vein thrombosis (DVT), pulmonary embolus (PE) and combined (DVT and PE) the VTE group. There was no difference in survival between different types of VTEs.*

VTE type	Frequency (%)
Combined	10 (17.25%)
DVT	37 (63.80%)
PE	11 (18.96%)

Table IV. *Incidence of VTE in pancreatic cancer in the literature.*

Author (reference)	Number of patients	Incidence of VTE
Cubilla and Fitzgerald 1978 (10)	380	14%
Pinzon *et al*. 1986 (11)	130	6.80%
Mao *et al*. 1995 (12)	154	19.00%
Blom *et al*. 2006 (13)	202	108.3/1000 patient-years
Mandalà *et al*. 2007 (14)	227	26%
Mitry *et al*. 2007 (15)	90	27%
Oh *et al*. 2008 (16)	75	5%
Epstein *et al*. 2010 (17)	6,870	19%

to show no difference in survival in pancreatic cancer patients who develop VTE *versus* those who do not. These results show a need to be selective in instituting anticoagulation in patients with pancreatic cancer.

The risk of VTE, although considerably elevated in patients with cancer, varies markedly between patients and even within the same patient at different time points during the course of malignancy. Many risk factors have been identified in the attempt to stratify patients at risk of developing VTE. A review by Khorana *et al*. reported clinical risk factors for cancer-associated VTE to include primary tumor site, stage, and period after diagnosis, presence and number of comorbidities, and treatment modalities including systemic chemotherapy, anti-angiogenic therapy, and hospitalization. Candidate predictive biomarkers include elevated platelet or leukocyte counts, tissue factor, soluble P-selectin, and D-dimer (9). In the current study population, there was an increased risk of VTE in patients with stage IV pancreatic cancer. The body of the pancreas location of the tumor tended toward being statistically significant in terms of VTE risk. There was no survival difference between patients who had VTE compared to those who never developed VTE. These results might be explained by missing data and the data from the follow-up time. Table IV summarizes the incidence of VTE in different studies.

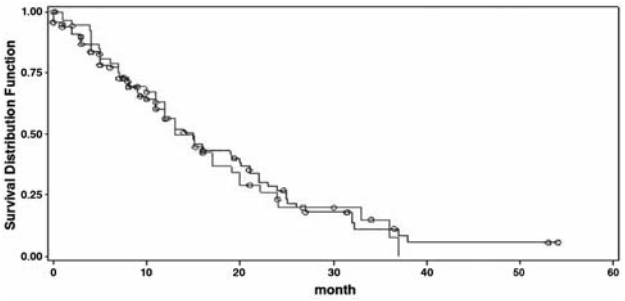

Figure 1. *Kaplan-Meier curve showing no difference between pancreatic cancer patients who had VTE during course of illness (gray) versus those who did not develop VTE (black). No survival difference is shown (p-value 0.9).*

In the current study, the incidence was 28.85%, which is higher than any previous studies.

Following the initial observation that cancer patients tend to develop venous thrombosis different anticoagulants have been tested to decrease the risk of VTE. Three major studies showed the superiority of low molecular weight heparins (LMWH) in terms of a favorable benefit risk ratio in this indication in comparison to oral anticoagulants (18-20). The incidence of bleeding so far described for cancer patients receiving oral anticoagulant treatment for VTE is markedly lower than the high incidence of recurrent venous thrombosis in these cancer patients (21).

The low incidence of malignancies in patients using long-term anticoagulant therapy raises the possibility of antineoplastic activities of these drugs. Also, dramatic tumor regression in some case reports and small studies has suggested the potential for anticancer activity of LMWH. LMWH therefore may be regarded not only as a suitable anticoagulant in cancer patients with VTE but also as an anti-cancer or anti-metastatic therapeutic principle. Recent guidelines of the American College of Chest Physicians (ACCP) recommend the use of LMWH for anticoagulation in patients with cancer-induced thrombosis (22). Icli *et al*. concluded that the addition of LMWH to the gemcitabine plus cisplatin combination significantly improved the response and survival in patients with advanced pancreatic cancer and the current schedule deserves to be tested in future clinical trials (23). This conclusion was further demonstrated by Riess *et al*. in a pivotal clinical trial, Prospective, Randomized trial Of Simultaneous Pancreatic cancer treatment with Enoxaparin (PROSPECT), elucidating the role of LMWH in advanced pancreatic cancer (2). In a recently published phase II study, El-Rayes *et al*. treated 47 patients with advanced or metastasized pancreatic cancer with a combination of gemcitabine, cisplatin and 5-FU. Excellent tumor response (26%) was achieved and the 1-year survival rate for patients with

metastases was 34% and the median overall survival 8.6 months (24). Although previous studies has shown that LMWH has an antineoplastic effect and a survival benefit, our study does not demonstrate the decline in survival demonstrates that more studies are needed to confirm our observation.

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Received 19 June 2010
Revised 13 July 2010
Accepted 26 July 2010