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Visceral Thrombosis in Pancreas Ductal Adenocarcinoma: Incidence, Management and Implications

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Abstract

Background: Visceral or splanchnic thrombosis, defined as thrombi within the hepato-portal venous system including; portal (PV), mesenteric (MV) and splenic vein (SV), as well as thrombi in renal (RV) or gonadal veins (GV). There are limited data to evaluate the prognostic significance, incidence and clinical management of VT in patients with pancreatic ductal adenocarcinoma (PDAC).

Methods: We conducted an analysis of N= 95 patients treated at Memorial Sloan Kettering Cancer Center with PDAC who had a visceral thrombosis.

Results: N= 154 Visceral thrombosis events (VTE) were identified in N= 95 patients (N=51, 54% woman). N=36 (37%) patients had locally advanced disease and N=59 (62%) patients had metastatic disease. Systemic therapies received: FOLFIRINOX (N=66, 60%) and GC/PTX (N=27,28%). All VTE events were incidentally detected. Overall survival of cohort was 12.3 months (10.2–14.4). VT Incidence in cohort: PVT (45%), MV (26%),SV(17%) and GV(8%). Time to develop first VTE 4.3m (3–5.6) and time to death from VTE development was 1.87m (0.8–2.8). N= 45 pts (47%) developed a second VTE. Sixty percent had Khorana risk score (>3). N= 39 (39%) were treated with short-term anticoagulation (AC) (<1m) (Low Molecular Weight Heparin (LMWH), N=34). Forty-five (46%) patients were treated with long-term AC (>1m) (LMWH N=32, N=23 were transitioned to an oral anticoagulant). N=22 (23%) patients were not treated with AC. N=8 (8%) patients had a bleeding complication from AC. PVT had the shortest OS with 3.6 m (2.3–4.8)

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Conclusions: In PDAC, VTE can frequently present as an incidental finding on routine abdominal imaging. The most common location is PV followed by MV and SV. We observed that AC is under-utilized in this setting despite a low bleeding complication rate. PV was associated with the least overall survival of the VTs. Future large prospective studies should explore the role of AC and value in this setting.

MicroAbstract

This was a cohort analysis evaluating patients with pancreatic adenocarcinoma who presented with or developed visceral thrombosis, including; portal, mesenteric and splenic vein, as well as thrombi in renal or gonadal veins. Among the 95 patients analyzed, a total of 154 visceral thrombosis events (VTE) occurred. VTE presented frequently as an incidental finding on routine abdominal imaging. The most common location was PV followed by MV and SV. Patients who received systemic anticoagulation had a low bleeding complication rate.

Keywords

Mesenteric vein thrombosis; Pancreas adenocarcinoma; Portal vein Thrombosis; Splenic Vein Thrombosis; Visceral thrombosis; Splanchnic Vein thrombosis

Introduction

Pancreatic ductal adenocarcinoma is one of the most common malignancies associated with thromboses.(1,2) Recent literature reports indicate an incidence between 17%–36%(1,3–7). This high risk is potentiated by the pancreatic cancer cell, which intrinsically, promotes tumor growth and angiogenesis by increasing platelet activation and expression of procoagulant factors, including tissue factor and thrombin.(8) Usually, thrombi can originate in any of the venous vasculatures; although is frequently observed in the deep venous system (DVT), the pulmonary vasculature (PE) and the venous portal system located in the abdominal cavity. Although, when thrombi develop in the portal venous system different terminology can also be used, such as; “splanchnic”, “abdominal” or “visceral” thrombosis. (9–13)

Typically, these visceral thromboses (VT) are observed in the main veins e.g. portal (18%), splenic (14%) and/or mesenteric vein system (13%); while the renal vein (1%) and gonadal vein (1%) can also be affected as well.(14) In the general population, VT is an infrequent event, in which most incidents occurred in patients with concomitant comorbidities. From a large international registry with unselected patients diagnosed with VT, Ageno et al. (15) observed a high incidence in patients with hepatic cirrhosis (27.8%), genetic hypercoagulable mutations (20.1%) and/or solid tumors(22.7%,136/609).In which, 8%(12/136) of patients were diagnosed with pancreatic cancer.

Conversely, when examining the cancer literature, the incidence of VTE appears to be much higher in an oncologic population with reported incidence of 22.9%(31/89) in PDAC (14). Evidence demonstrates that this high incidence is associated in part with a rise of incidental detection of VT with computed tomography (CT) scan for diagnosis and staging of pancreatic cancer(16). These incidental findings of VT have led to an increased interest in

the clinical significance of VT and interest in defining paradigms. While there is some evidence that points towards a decreased survival in PDAC (9,13), evidence is limited. There are no standard guidelines for management of VT in patients with PDAC.

We therefore conducted this retrospective cohort study to determine the impact of VT in patients with PDAC. We examined the time to develop first VT, the implications of VT in future thromboses and survival outcomes. In addition, we evaluated the role of systemic anticoagulation (AC), the type of AC utilized and duration of AC for each patient. The intent of the study reported herein is to extend knowledge of VT in PDAC and elucidate treatment paradigms.

Methods

Setting and Study design

The Institutional Review Board and Privacy board at Memorial Sloan Kettering Cancer Center (MSKCC) reviewed this single center retrospective cohort study. Patients who underwent imaging and received care at MSKCC, diagnosed between January 1, 2013 and December 31, 2015 with pathologic confirmation of PDAC who developed a VT (MV, PV, SV, RV, GV) either at presentation or which developed during the disease course, comprised the study population.

Search strategy and selection criteria

An institutional database (DARWIN) was used to retrospectively obtain medical records from patients diagnosed with pancreatic cancer that were identified either by using the *International Classifications of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)* with the following code: C259 pancreas ca, C250 pancreas ca-head, C251 pancreas ca-body, C252 pancreas ca-tail, C258 pancreas ca-overlapping lesion. The ICD-10 only has a specific code for PVT (I81 *portal vein thrombosis*), therefore, we included patients that had any of the following ICD-10 Codes, along with their pancreatic cancer diagnosis: I82.3 *other venous embolism and thrombosis of renal vein*, I82.891 *chronic venous embolism and thrombosis of other specified veins*, I82.890 *Acute venous embolism and thrombosis of other specified veins*, I82.91 *other venous embolism and thrombosis of unspecified site* and K55.0 *acute vascular disorders of intestine*.

Data extraction

A.M.H. performed electronic medical record review and data abstraction, and data was stored in a secure drive. Imaging reports were reviewed by accessing the institutional imaging. All reports were manually revised by a radiologist author (M.R), who reviewed the CT scans of abdomen/pelvis to corroborate the correct date of diagnosis and location of the visceral thrombi (PV, MV, SV, GV, RV). Detailed demographic and clinical information was extracted, including, date of cancer diagnosis, presenting symptoms, AJCC stage at presentation, performance status (ECOG) at presentation, sites of metastases at presentation, primary tumor location, treatment modalities (surgery, systemic therapy), types of systemic therapy received, lines of treatments, interval between diagnosis of pancreatic cancer and occurrence of thrombosis, presenting symptom of VT, method of diagnosis of VT, ECOG at

diagnosis of first VT, laboratory variables required to calculate Khorana score (cell blood count, comprehensive metabolic panel, coagulation studies), type and duration of systemic anticoagulation, complications of therapies and survival outcomes. (Tables 1–5).

Statistical methods

Baseline patients' characteristics, clinical findings at diagnosis of VT and laboratory evaluation at the time of VT diagnosis were summarized in Tables 1. Overall survival (OS) was calculated from date of diagnosis to date of death. Median overall survival and 95% CI were estimated using Kaplan-Meier methods. All p values were based on 2-tailed statistical analysis and $p < .05$ was considered to indicate statistical significance. All analyses were performed with SPSS version 24 (SPSS Inc.)

RESULTS

Demographic and Clinical Characteristics

One thousand four hundred and eighty-four patients with PDAC were identified from January 1, 2013 and December 31, 2015. The subset analyzed cohort ($N = 95$) was later identified with one of the ICD diagnoses previously described. These patients with PDAC had developed any type of VT either at presentation or during the disease course. Figure 1 illustrates the flow of patients that composed the analyzed cohort. Descriptive characteristics of the study cohort are summarized in Table 1. Forty-six percent ($N = 44$) were male, median age of PDAC diagnosis was 60.5 (range 38–86) years. Sixty-two percent ($N = 59$) presented with metastatic PDAC, 16% ($N = 15$) had locally advanced pancreas (stage III), and 22% ($N = 21$) had resectable disease at presentation (stage I–IIB). Primary pancreatic tumor was located in the head 53% ($N = 51$), body 17% ($N = 16$) and tail 16% ($N = 15$). Surgery was performed in 10% ($N = 9$) of patients, 6% ($N = 6$) had a Whipple procedure, 3% ($N = 3$) had other type of surgery (e.g. Appleby procedure, distal pancreatectomy) and 90% ($N = 86$) patients had unresectable disease.

For all 95 patients complete follow up data was available, three patients remain alive by March, 2017.. The median overall survival after first VT diagnosed was 4.3 months with a range of 3 to 5.6 months, and the time from diagnosis to VT development for the whole cohort was approximately 1.9 months with a range of 0.8 to 2.8 months. Principal organs with metastatic disease at first VT were; liver only 68% ($N = 66$), liver and lung 22% ($N = 21$), 21% ($N = 19$) patients had peritoneal carcinomatosis and 47% ($N = 45$) patients had radiographic ascites. Thirteen patients (13%) had a prior thromboembolic event (arterial and/or venous) prior to VT diagnosis.

Cancer Treatment

The total cohort of patients received at least one systemic chemotherapy regimen. As shown in table 1, Sixty percent ($N = 57$) of patients received FOLFIRINOX (folinic acid, 5-FU, irinotecan, oxaliplatin) or FOLFOX (folinic acid, 5FU) and gemcitabine in combination or alone ($N = 37$) represented about 40% of the total treatments administered. Eighteen percent ($N = 17$) received an investigational drug. The majority of patients in the cohort received at least three lines of systemic chemotherapy during their disease course.

Presenting Symptoms and diagnostic methods

Within this cohort, key findings are summarized in Table 2. All visceral thromboses were diagnosed by computerized tomography (CT). The primary clinical manifestations prompting a CT scan were; routine follow up imaging in 37% (N=36), abdominal pain and/or discomfort in 28% (N= 27), nausea and/or vomiting in 11% (N= 10) and fever workup in 10% (N= 9) patients. Assessment of performance status at first VT diagnosed was adjudicated as follows: ECOG 0 (20%, N=19), ECOG 1(60%,N=57) and 20% (N= 19) presented with performance status of ECOG 2.

Laboratory findings

Table 2, summarizes Khorana risk score stratification at the time of VT diagnosis for the total cohort. Eleven per cent (N= 11) had ascitic fluid analyzed, with a Serum Ascites Albumin Gradient (SAAG) mean of 2.35. (17). Only two patients had hypercoagulable studies performed for lupus anticoagulant, factor V Leiden deficiency and prothrombin G20210 mutation.

Visceral thromboses

Table 3, represents the thrombi position respective to the major and minor vein branches of splanchnic vein system. The VT location in the cohort was observed as follow; PVT was found in 55% (N= 69), MVT 32% (N= 41), SVT 20% (N= 26), GVT 9.6% (N= 12), RVT 2.4% (N= 3) and HVT 1.6% (N= 2) patients respectively. Cavernous transformation of the PV was found in 12% (N= 12) and Budd-Chiari in 4% (N= 4). Thrombi were categorized by their radiographic appearance (MR). A bland thrombus was defined as a filling defect in an otherwise well-opacified vein which was found in 20% (N= 19) patients. Tumor thrombus was observed in 8% (N= 8), which may be differentiated from bland thrombus through the presence of a contiguous adjacent mass and enhancement of a filling defect. Thrombi secondary to tumor occluding the vein was observed in 9% (N= 9). However, in 62% (N= 59) patients, the radiographic characteristic of the thrombi was uncertain and etiology was not assessed. The mean VT events per patient were 1.6. Table 3 summarizes the VT as seen on CT scan imaging by order of subsequent VT. Twelve per cent (N= 12) developed a 3rd thrombosis and one patient developed a 4th thrombosis. Other observed thrombotic events were, deep vein thromboses (DVT) 14% (N= 14) and pulmonary embolism (PE) in 12% (N= 12) of patients.

Treatment modalities

We evaluated the cohort by the principal treatment modality as shown in Table 4. Our results indicate that 23% (N= 22) of patients did not received any type of systemic anticoagulation, while 76% (N= 73) received either; short term systemic anticoagulation (STAC) defined as <1 month, and/or, long term systemic anticoagulation (LTAC), defined as >1 month. Forty-one (N=39) patient received STAC, in which low molecular weight heparin (LMWH) was used in 36% (N= 34) of patients, followed by fondaparinux 3% (N= 3).

Conversely, 45% (N= 47) patients received LTAC, from these patients, 32% (N= 32) were treated with LMWH and 24% (N= 23) with next generation oral anticoagulants (NOAC)

(e.g. apixaban, dabigatran rivaroxaban). Seventeen patients were taking an antiplatelet therapy, either aspirin 5% (N= 5) and/or 12% (N= 11) clopidogrel.

Outcomes

Table 5 summarizes survival outcomes. Mean overall survival (OS) after cancer diagnosis was 12.3 months (range 10.2–14.4m) and after first VT diagnosed 4.33 months (range 3–5.57m). The median time from cancer diagnosis to first VT diagnosis was 1.87 months (range 0.8–2.8m). Eight percent (N= 8) had bleeding complications while on AC (e.g. gastrointestinal bleeding, hemorrhagic stroke, intraabdominal bleeding). Fifteen percent (N= 15) of patients died in the hospital from complications related other medical comorbidities (e.g. sepsis, G bleeding, renal failure). Three percent (N= 3) patients died as consequence of thrombosis during the hospital admission. Figure 2, shows Kaplan-Meier estimates of conditional survival in patients with different visceral thromboses. PVT was associated with reduced OS with 3.6m (95% CI 2.3–4.8), MVT with 7.4m (95% CI 1.56–13.4) and SVT with 5.7m (95% CI 0–13). RVT had the longest OS with 10m (95% CI 1.6–18.3).

Discussion

Visceral thromboses in PDAC usually is diagnosed during late stage disease.(8) In a recent retrospective study, Sogaard et al. (9) analyzed patients with diverse malignancies who developed VT and found that VT is a prognostic factor for short-term survival in patients with PDAC and the 3 month survival after diagnosis was 35% vs 53% without VT (95% CI, 0.8–2.9). Among the gastrointestinal malignancies, PDAC has the highest incidence of VT (5,18) particularly owing to the intrinsic pancreatic cancer cells characteristics (8,19–21) and its position bordering vein branches of the portal-splenic system which may also contribute as a local risk factor.(22).

Limited data on the natural behavior of VT has led to uncertainty in clinical management. (15,23–28). To our knowledge this is one of very few studies investigating the impact of visceral thromboses (PV, MV, SV, RV, GV, HV) in PDAC only, along with the radiologic methods employed to diagnose it, course of therapy and outcomes for VT. Prior studies have evaluated VT, where the studied cohort had varied malignancies and not strictly PDAC, and other vein thromboses e.g. DVT and PE were included in those analyzes.(9,13,15,29,30) We present detailed characteristics of a cohort of N=95 patients with PDAC who developed at least one VT. Median survival after diagnosis of first VT was 4.3m (range 3.–5.57m) and our results confirm the limited available evidence (9) that VT is a poor prognostic marker.

Notwithstanding, the heterogeneity of its clinical presentation, VT can present acutely or chronic in which symptoms are nonspecific and most diagnoses are noted incidentally(25). In this cohort the diagnosis of VT was predominantly made with contrast-enhanced CT which has a reported sensitivity rate reach at least 90%(31,32). Literature defines an incidental finding as findings that are unrelated to the clinical indication for which the imaging scan had been requested(16,33). In our cohort we found that all VTs were incidentally found in patients, which correlates with other similar study by Menapace et al. (14) who observed that from N= 47 of VT, 100% were incidentally found. However, in some

circumstances, the clinician will judiciously order a CT scan for the purpose of additional evaluation for patient symptomology as presented in table 2.

The cohort was risk stratified according to Khorana's risk score(34). Sixty percent of the patients (N= 36) were classified as high risk (>3 points) and 40% (N= 24) as intermediate risk. However, only N= 60 of the patients had BMI data available to correctly calculate score. This high risk in our cohort was expected as the score adjudicates +2 for pancreas malignancy alone and +1 score for each other score variable. However, on the original Khorana's model, laboratory data pre chemotherapy was used. In our cohort, laboratory data was abstracted at the time of the first VT. Two patients underwent hypercoagulable study testing for lupus anticoagulant, Factor V Leiden and prothrombin G20210, although not routinely done in patients with PDAC since the malignancy predisposes to thrombosis, in this circumstance one patient had a hereditary thrombophilia that presented as an upper extremity deep vein thrombosis and the other patient had systemic lupus. Particularly, we observed that 13%(N=13) patients had a prior thrombotic event (arterial and/or venous) which was secondary to other high risk co-morbidities predisposing to an embolic event such; as e.g. multiple sclerosis, peripheral vascular disease and immobility. This high risk population will perhaps benefit from a through hypercoagulable workup and diagnosis imagining studies to rule out concomitant VT.

The total observed VTE in our cohort were N= 154 events in N= 95 patients throughout the disease course, in which most patients developing a mean of 1.6 VTE. Conversely, we observed that most patients developed a subsequent VTE which was anticipated as most thrombi can extend to continuous vein branches. Our findings suggest a higher incidence of PVT and MVT which are consistent with prior studies (9,14), however our cohort included only patients with PDAC. As expected with disease progression, most VT were diagnosed in patients with metastatic disease (62% N= 59, AJCC stage IV), while only small percent (10%, N= 9) of patients that developed a VT was conceivably associated with a prior surgical resection. (N=9).

In regards to treatment, the key purposes of anticoagulation in VT is to prevent formation of portal hypertension and improve recanalization of the vessel (35–37). Present-day treatment is based on extrapolation from guidelines made by American College of Chest Physicians(38) in which anticoagulation in patients with symptomatic VT is supported (grade 1B for PVT, MVT and/or but not suggested if it is incidentally detected VT (PV, MV, SV and/or HV, grade 2C) and the European Association for the Study of the Liver (EASL) in which anticoagulation is considered in patients with a strong prothrombotic condition, or past history suggesting intestinal ischemia or recurrent thrombosis on follow-up (Grade B2, low quality evidence).

In our cohort, 76% (N= 73) patients were treated with systemic anticoagulation with a mean duration of 5 months. LMWH was the most frequent AC used, supported by the robust evidence demonstrating superior efficacy in the front line setting (39). Interestingly, we found a higher use of novel oral anticoagulants in 23/45 patients, explained by standard institutional guidelines, as emerging data supports these next generation oral anticoagulants, which may be an effective alternative treatment.(23,24,40–43). The observed median OS

after 1st VT was diagnosed is 4.3m (CI 3–5.6), which relates to a reduced survival that has been observed in current literature (9). Moreover, PVT was associated with the shortest OS with 3.6m (CI 2.3–4.8) of all VTs. These findings are consistent with other prior studies in which VTs in PDAC is a marker for poor prognosis, as evidenced by the reduced OS after diagnosis(9,13,14,29,44). We observed a low bleeding complication rate while on AC. This finding correlates with the largest to-date prospective study (solid cancer N=136/600)(15) in which AC appears to be safe and effective in VT.

The results of our study should be interpreted in the context of several limitations. First, the retrospective design. Second, our study was performed at a single center specialist institution with inherent referral and other biases. Several potential confounders including patient demographics, ECOG status, stage at diagnosis and comorbidities, along with other confounding variables from other unmeasured factors. Thirdly, VT diagnosis was based on radiologic documentation and the time point for adjudication of the development of VT varies as this was adjudicated in retrospect by diagnostic imaging. Fourthly, the survival benefit of AC can be affected by disease burden and chemotherapy regimen.

CONCLUSIONS

This present study suggests that VT is a common thrombotic event in advanced PDAC. Predominantly discovered on incidental CT scan imaging. PVT is the most frequent thrombosis followed by MVT and SVT. We found a low incidence of RV, GV and HV thromboses. VT is a marker for poor prognosis, as demonstrated by an OS of 4.3 months. Use of systemic AC to treat VT was a common practice as 75% of the cohort was treated. The clinical benefit of AC, requires further prospective investigation. The weight of the evidence favors anticoagulation in PDAC with visceral thromboses.

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Clinical Practice Points

- Thromboses within the abdominal cavity can be referred as visceral or splanchnic vein thromboses. It comprises the portal, mesenteric, splenic, hepatic, gonadal and renal veins predominantly.
- PDAC is commonly associated with VT and usually is diagnosed incidentally on CT imaging.
- PVT is the most common of all VT followed by MV, SV and with a low incidence GV, HV and RV.
- Patients diagnosed with a first VT tend to develop a subsequent VT event.
- Anticoagulation is used to prevent development of portal hypertension and facilitate vein recanalization.
- There is low risk of bleeding with systemic AC for VT.
- VT is a marker of reduced OS in PDAC, from all VT, PVT has the shortest OS.

Figure 1.

Study Design. N= number of patients, PVT= Portal vein thrombosis, MVT= Mesenteric Vein thrombosis, SVT= Splenic Vein Thrombosis, RVT=Renal Vein Thrombosis, GVT=Gonadal Vein Thrombosis

Figure 2.
Survival by type of VT
Kaplan-Meier estimates of conditional survival in patients with different visceral thromboses.

Table 1.**Baseline Demographic and Oncological Characteristics of Cohort**

	N=95	Percentage
Sex		
Male	44	46
Female	51	54
Age at diagnosis, mean (range)	62.9 (37–86)	
Ethnic Origin		
Caucasian	75	79
Asian	5	5
African- American	12	13
Hispanic	3	3
Smoking Status		
Never nonsmoker	8	8
Former smoker	32	34
Active smoker	55	58
Alcohol History		
Alcohol use	39	42
No Alcohol	56	58
Past Medical History		
Diabetes	27	28
Hypertension	45	47
Family History of Thrombosis	3	3
Patients with prior thromboembolic event(s)¹		
Prior Deep Vein Thrombosis History	11	12
Prior Pulmonary Embolism	6	8
Arterial Thrombosis History	2	1
Other Venous Thrombosis History ²	2	1
Year Diagnosed		
2013	38	40
2014	42	45
2015	15	15
Pancreatic primary tumor location		
Head	51	53
Body	16	17
Tail	15	16
Overlap (body and tail)	13	14
Surgery performed		
Whipple procedure	6	6
Other type of resection ³	3	3

	N=95	Percentage
AJCC Stage at cancer diagnosis		
IB	1	1
II A	8	8
II B	12	12
III	15	16
IV	59	62
Systemic Therapy For Locally Advanced/ Metastatic Disease		
Gemcitabine + Nab-Paclitaxel	27	28
FOLFIRINOX/FOLFOX (5-FU, Irinotecan, Oxaliplatin)	57	60
Patients treated with Investigational Drug⁴	17	18
No chemotherapy received	10	10
Lines of treatment received:		
One	95	100
Two	66	68
More than three	27	29

¹Total patients were N=13, N=5 patients had 1 thrombotic event.

²Stroke and upper extremity thrombosis secondary to catheter.

³Splenectomy (1), Gastrectomy (1), Distal pancreatectomy(1)

⁴Investigational Drugs: ADI-PEG 20, tarextumab (TRXT, OMP-59R5, anti-Notch2/3), GVAX, clivatuzumab (y90 + h-PAMA4 Fractionated radioimmunotherapy), nivolumab (IgG4 anti-PD-1 monoclonal antibody), ulocuplumab, veliparib (PARP inhibitor), pembrolizumab, mogamulizumb, tremelimumab

Table 2.**Clinical Findings at Diagnosis of First Visceral Thrombosis**

	N=95	Percentage
Imaging Study for Diagnosis		
Abdominal CT scan with IV contrast	95	100
Incidental CT scan Finding		
	95	100
Primary clinical symptom/illness ¹ prompting a CT scan test		
Abdominal pain/discomfort	27	28
Nausea +/- vomiting only	10	11
Infectious process (fever/sepsis) work up	9	10
Gastrointestinal symptom work up ²	12	13
ECOG at First Thrombosis Diagnosis		
0	19	20
1	57	60
2	17	18
3	2	2
Radiographic extent of disease at first thrombosis diagnosis ³		
Peritoneal carcinomatosis +/- ascites	61	65
Liver metastasis only	66	68
Liver + lung metastases	21	22
Liver + lung + bone metastases	8	9
No Metastatic disease	2	1
Khorana Risk Score Stratification ⁵ (0–6) Risk of VTE N=60 ⁴ % Score Frequency		
Low Risk (0)	0.3–0.8%	0 0 –
Intermediate Risk (1–2)	1.8–2.0%	24 40 2 (N= 24)
High Risk (>3)	6.7–7.1%	36 60 3 (N= 26), 4 (N= 9), 5 (N= 1)

¹ Primary symptom/illness documented in clinical history by clinician.

² Ascites evaluation (N= 3), Bleeding (N= 6), Jaundice evaluation (N= 3)

³ Extent of disease evaluated by CT scan reports at the time the VT was diagnosed

⁴ Only N=60 patients had body mass index (BMI) and N=35 patients were omitted from calculations.

⁵ Khorana Risk Score= Pancreas (+2), Platelet Count $350 \times 10^9/L$ (+1), Hemoglobin level $<10 \text{ g/dL}$ (+1), leukocyte count $11 \times 10^9/L$ (+1), BMI 35 kg/m^2 (+1). Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood*. 2008; 111:4902–7.

Table 3.

Anatomic Location, Etiology and Frequencies of Thrombi with Diagnostic Imaging

Total visceral Thrombotic Events During Disease Course ⁺		N=153	%(from total VTe)
Portal Vein Branch		N=69**	45
Main Vein		41	
Left Vein		24	
Right Vein		29	
Mesenteric Vein		N=41*	26
Superior vein		36	
Inferior vein		5	
Splenic Vein		N=26	17
Hepatic		N=2	1
Gonadal		N=12*	8
Right		5	
Left		9	
Renal Vein		N=3*	2
Right		3	
Left		0	
Cavernous Transformation		12	12
Budd–Chiari		4	4
Description of First Thrombi Diagnosed¹		%(from N=95)	
Bland thrombus ²		19	20
Tumor Thrombus ³		8	8
Tumor occluding vein ⁴		9	9
Unable to Assess ⁵		59	62
Patients with 2 thromboses on first CT scan		N=29	30
Synchronous thromboses with PDAC diagnosis		N=11	11
Mean VT events per patient (range)		1.6(1–4)	

Frequencies of Subsequent Visceral Thromboses by Radiographic Diagnosis									
Vein Location	1 st		2 nd		3 rd		4 th		Total
	Thrombosis		Thrombosis		Thrombosis		Thrombosis		Thrombosis
	N=95	%	N	%	N	%	N	%	N %
Portal Vein	60	63	6	6	3	3			69 70
Mesenteric Vein	16	15	23	21	2	2			41 42
Splenic Vein	10	10	9	9	7	6			26 27
Renal Vein	3	2		1					3 3
Gonadal Vein	5	4	6	3			1	1	12 12
Hepatic Vein	1	1	1	1					2 2
Total Subsequent			45	47	12	13	1	1	

Frequencies of Subsequent Visceral Thromboses by Radiographic Diagnosis										
Vein Location	1 st		2 nd		3 rd		4 th		Total	
	Thrombosis		Thrombosis		Thrombosis		Thrombosis		Thrombosis	
	N=95	%	N	%	N	%	N	%	N	%
Thromboses										
Other Thromboses										
DVT ⁶			9	8	3	3	2		14	14
PE ⁷			5	5	5	5	2		12	12

*: Counted as a single thrombosis site

***: Some patients had more than one portal vein branch thrombosed

+: Patients had more than one vein thrombosed.

1: As per radiologist CT scans interpretation

2: Defined as a filling defect in an otherwise well-opacified vein

3: Tumor thrombus can be differentiated from bland thrombus through the presence of a contiguous adjacent mass and enhancement of a filling defect.

4: Thrombi were secondary to tumor occluding vein

5: Radiographically not sufficient to specify thrombi etiology

6: Deep vein thrombosis (DVT)

7: pulmonary embolism (PE)

Table 4.

Type and Duration of Systemic Anticoagulation

	N=95	%
Patients who did not received any type of anticoagulation (AC)	22	23
Patients who received Systemic AC	73	76
Only Short Term AC	28	29
Only Long Term AC	34	36
Both Short and Long Term AC	11	12
Short Term AC used (<1 month), mean duration (6d)	N=39	41
LMWH	34	36
UH	1	1
Fondaparinux	3	3
No short-term anticoagulation used	56	59
Long term AC agent used (>1 month), mean duration (5m)	N=45	47
LMWH	32	32
NOAC	23	24
Fondaparinux	1	1
Warfarin	1	1
No Long-term anticoagulation used	50	53
Patients using Antiplatelet		
Aspirin	5	5
clopidrogel	11	12

LMWH= low molecular weight heparin

UH= unfractionated weight heparin

NOAC= novel oral anticoagulant (apixaban, dabigatran, rivaroxaban)

Table 5.

Survival Outcomes

	N=95	%
Median Overall Survival, months(m), (95%CI)		
After cancer diagnosis	12.3m (10.2–14.4)	
After 1 st thrombosis diagnosed	4.3m (3–5.6)	
Median months to develop first VT	1.9m (0.8–2.8)	
Bleeding complication while on systemic anticoagulation^I	8	8.4
Death from other cause during hospital admission	15	15
Death secondary to thromboses during a hospital admission	3	3
Time in months from PDAC diagnosis to 1st VT presentation, median 1.8m (range 0.8m–2.8m)		
0–2	55 (0.7)	58
3–5	16 (3.7)	17
6–8	5 (6.6)	5
9–11	6 (9.5)	6
>12	13 (17.2)	14
Time in months from diagnosis of 1st VT to death, median 4.3m (range 3m–5.57m)		
0–2	32(1.1)	34
3–5	20(4.2)	21
6–8	13(6.8)	14
9–11	6(10)	6
>12	17(15.6)	18
Patients still alive by 03/2017	N=3	7
Median OS by VT location (months), (95%CI)		
Portal vein	3.6 (2.3–4.8)	
Mesenteric vein	7.4(1.5–13.4)	
Splenic Vein	5.7(0–13)	
Renal Vein	10(1.6–18.3)	
Gonadal Vein	5.8 (4.2–7.4)	

^I. Gastrointestinal bleeding, hemorrhagic stroke, intraabdominal bleeding