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Visceral Thromboses (VT) in Pancreas Adenocarcinoma (PDAC): A Systematic Review

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Abstract

Background: Within gastrointestinal malignancies, primary liver (HCC) and pancreatic ductal adenocarcinoma (PDAC), are frequently associated with visceral thromboses (VT). Thrombus formation in the portal (PVT), mesenteric (MVT), or splenic vein (SVT) system leads to portal hypertension and intestinal ischemia. VT in PDAC may convey a risk of increased distal thrombosis and poses therapeutic uncertainty regarding the role of anticoagulation.

Rationale: An increasing number of reports describe VT associated with PDAC. It is possible that early diagnosis of these events may help reduce morbidity and speculatively improve oncologic outcomes.

Objectives: Perform a systematic review to study VT (portal, mesenteric and splenic vein thromboses) associated with PDAC and provide a comprehensive review.

Data source: PubMed, EMBASE, Web of Science, Scopus, and the Cochrane library.

Data extraction and assessment: Two blinded independent observers extracted and assessed the studies for diagnosis of PVT, MVT, SVT in PDAC. Studies were restricted to English literature published between 2007 and 2016.

Results: Eleven articles identified. Five case reports and 7 retrospective studies were found with a total of N=127 patients meeting the inclusion criteria. The mean age at diagnosis was 64 years.

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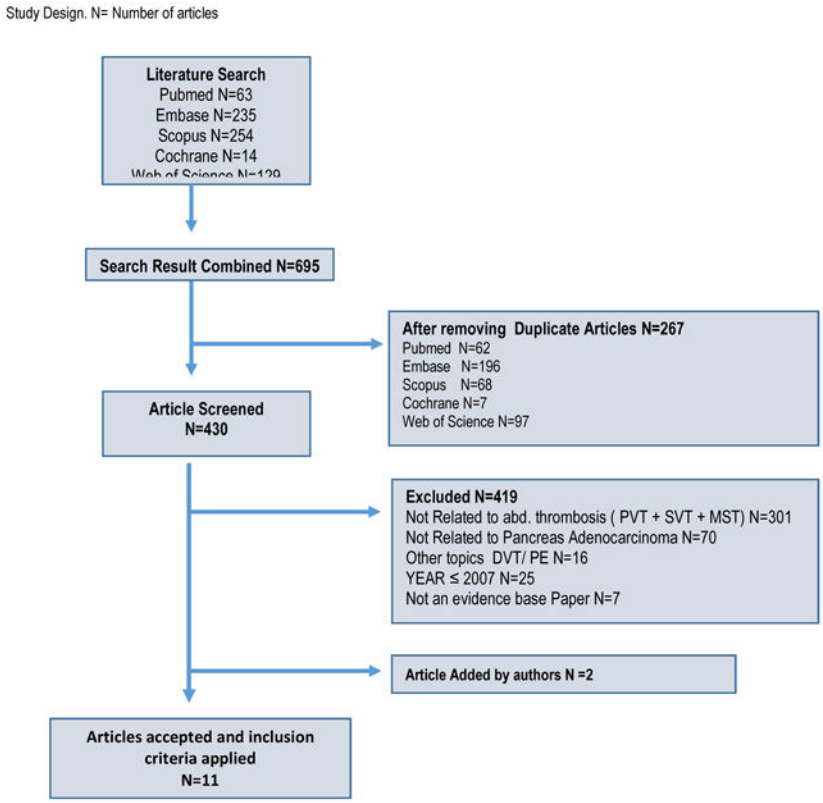
PVT found in 35% (N= 46), SVT 52% (N= 65), MVT 13% (N= 15). Mean follow up time 26 months. Only 3 of the selected articles studied the impact of anticoagulation in visceral thrombosis. All patients with non-visceral thrombosis (e.g. DVT, PE) were therapeutically treated, in contrast, only rare instances of patients with VT received treatment.

Conclusions: Visceral thrombosis in PDAC is a frequent finding at diagnosis or during disease progression. Evidence to guide treatment choices is limited and current management is based on inferred experience from non-oncologic settings. Anticoagulation appears to be safe in VT with most of the large studies recommending a careful assessment for patients with high risk of bleeding.

Graphical Abstract



Keywords

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

Background

The word splanchnic derives from the Greek "*splanchnikos*", from "*splanchna*", plural of viscera,(1) thus the term visceral or splanchnic vein thromboses are common adjectives in medical terminology to refer to thromboses in, near or pertaining to the viscera or intestines while visceral relates to the internal organs of the body. In this article we refer to visceral

thromboses as the involvement of the abdominal veins, Figure 1 (portal, splenic, mesenteric).

Pancreatic ductal adenocarcinoma (PDAC) is currently the fourth leading cause of cancer related death in the USA (2), and one of the most common malignancies associated with thrombotic events (3-6), with an estimated incidence of 36% in a large single-institution cohort of 690 patients with PDAC. (7)Retrospective analyses have found that the most common thrombotic complications include; deep vein thrombosis (dVTE) and pulmonary emboli (PE) both with almost equal incidence (46% vs 39%)(8), catheter-related thrombosis (15%) (9) and visceral thrombosis (VT) predominantly portal vein thrombosis (PVT) (7). With the advancement of diagnostic imaging (10-12), visceral vein thrombosis has become a well-defined entity that is commonly encountered in patients with prothrombotic disorders (28%), cirrhosis (13%) and malignancies such as PDAC and hepatocellular carcinoma. (13). In one study the prevalence of VT in PDAC was approximately 22.9%(14), and almost all were incidentally discovered on routine surveillance and restaging scans(14). With such incidental discoveries and given the lack of therapeutic guidelines for VT management, there are significant uncertainties related to the potential increased risk of complications, reduced survival, and inferior prognosis. (14, 15) In this systematic review we examine the most recent published literature on VT, specifically pertaining to PDAC and assess its clinical implications and prognosis.

Portal Venous System:

Portal Vein Thrombosis (PVT)

PVT is the formation of a thrombus that partially or completely occludes the portal vein, the latter which is formed by the confluence of the splenic vein and the superior mesenteric vein(16). The thrombus can arise in the trunk of the PV and can extend into the intrahepatic branches(17). PVT is the most well studied and described site of visceral thromboses; most notably, due to the increased incidence in patients with liver cirrhosis, inherited thrombophilic disorders and malignancies. The prevalence increases with the severity of cirrhosis, being approximately 1-16% in compensated cirrhosis (18) and 35% in patients with decompensated cirrhosis and HCC. (19,20)

PVT is commonly considered ‘acute’ if presentation is within 60 days or chronic if it has been present for >60 days. However, when chronic it may induce complications due to portal hypertension with worsening ascites, splenomegaly and variceal bleeding. (21)

PVT has been classified into four categories depending on the extent of thrombosis: Type I-limited to PV; Type II-extension into SMV but patent vessels; Type III-diffuse thrombosis of splanchnic venous system with large collaterals; Type IV-extensive splanchnic venous thrombosis but with only fine collaterals.(22). Chronic portal vein obstruction can lead to the development of multiple collateral vessels, known as cavernous transformation.(23)

The long-term sequel of portal vein thrombosis is portal hypertension which in pancreas adenocarcinoma patients has been shown to significantly contribute to ascites formation. A recent study found that 82% of patients with PDAC and ascites had a serum-ascites albumin

gradient ≥1.1. In that study the authors concluded that VT and tumor burden were possible causes of increased ascites formation in this population. (24)

Commonly with intra-abdominal diseases, thrombosis will originate in large veins at the site of compression and later progress peripherally to involve smaller vessels, while in contrast, thrombosis due to hematological disorders typically affects the smaller vessels and then progresses to larger trunks.(25)

Mesenteric Vein Thrombosis (MVT)

The mesenteric vein (MV) is anatomically divided into superior and inferior mesenteric veins, in which the former drains into the splenic vein.(16) MVT can be defined as ‘primary’ if not associated with any other disease; and ‘secondary’ if attributed to an acquired etiology (e.g. malignancy or thrombophilia). MVT typically is associated with nonspecific symptoms, may be difficult to diagnosis and has low awareness among clinicians (26). It can also be an uncommon cause of mesenteric ischemia in 5-15% of cases(27). Its prevalence has been reported to be 12%, according to a Swedish autopsy registry study in which 6 of 51 patients had an underlying pancreatic malignancy (28). Common presentations, include presentation with acute abdominal symptoms, particularly in patients with prior thrombotic episodes or documented coagulopathy(29). Currently, MVT is classified as ‘acute’, ‘sub-acute’ and ‘chronic’(30). The former accounts for 6-9% of all cases and typically presents with severe abdominal pain out of proportion to physical exam, whereas chronic MVT, accounts for 20-40% of the cases and is associated with vague and non-specific abdominal discomfort (31).

Splenic Vein Thrombosis (SVT)

Anatomically, the SV arises by the union of smaller vein branches from the stomach, pancreas and large intestine (via the inferior mesenteric vein)(16). It is associated with the posterior surface of the tail and body of the pancreas from the hilum of the spleen to its junction with the superior mesenteric vein, where it forms the portal vein(33). It was originally described as a cause of gastrointestinal bleeding (GIB) (32), but it was later observed to be a frequent thrombosis site owing to: its close vicinity to the pancreas (33), inflammation from pancreatitis (34), direct tumor invasion or compression (35) and as consequence of direct trauma and pseudocyst formation(33).

The foremost hazard of SVT is gastrointestinal bleeding to due to the generation of localized portal hypertension referred as “sinistral”(36) or left-sided” (37). Most of the currently available evidence is connected to pancreatitis-induced SVT(34,38-40). A meta-analysis by Butler et al, found that the overall incidence of SVT in the non-cancer setting was 14.1% and the overall rate of gastrointestinal bleeding was 12.3%. (39) In contrast SVT in PDAC has not been frequently studied and limited data exist. One retrospective study that evaluated SVT in PDAC, by Denadia et al. evaluated N= 70 patients who underwent surgery for pancreatic exocrine cancer. In the cohort, N=27 patients had SVT, and 46% (N=12) had resectable disease (Stage IA/IB, IIA) and 54% had locally advanced disease (IIB/III). PDAC was identified in 19 patients (70%). In this study the authors concluded that SVT was correlated with higher rates of intraoperative blood loss, pancreas-specific complications and

reduced long term survival rate (35). This highlights the significance of SVT in the preoperative evaluation of patients with PDAC as well as the potentially increased risk of associated intraoperative complications.

Radiographic Diagnosis

Computed tomography (CT) is the imaging modality of choice for the diagnosis of VT. To make a correct diagnosis, radiologists need to rely on radiographic features to distinguish between bland thrombi (secondary to a hematological disorder) versus tumor thrombus (malignant thrombi) (25), which often can be technically difficult to interpret as no parameter is entirely specific. Several radiographic criteria were proposed by Tublin et al. (41) to differentiate between benign and malignant thrombi (Fig 2-4) including; mural signs (e.g. halo sign, abnormal wall enhancement), vascular signs (e.g. venous filling defect, vein enlargement, venous engorgement) and extramural-nonvascular signs (e.g. mesenteric fat edema, bowel dilation).(25) The precise interpretation of the thrombus etiology has direct therapeutic implications for the oncologic patient.

Anticoagulation

The presence of thrombus within the visceral veins may represent a clinical challenge for treatment decisions, particularly in view of the concomitant cancer progression and the prothrombotic state that often accompanies PDAC (42,43). Consequently, this can theoretically lead to intestinal or splenic infarction and thus portend an increased risk of gastrointestinal bleeding with a potential risk of death(44-46). Hence the purpose of anticoagulation is not only thrombus dissolution and recanalization but also to prevent the progression to cavernous transformation of the portal vein and thus a reduced risk of portal hypertension.(23, 47,48).

Current therapeutic strategies follow the recommendations made by the American College of Chest Physicians 9ed (ACCP) (49) for venous thromboembolism, however, evidence from this guideline does not specifically address the use of anticoagulation in circumstances like VT. Use of anticoagulation is not standardized and questions about whether to anticoagulate or not pertain to the type of treatment and duration of therapy and the overall context of prognosis. These uncertainties and the lack of guidelines collectively contribute to challenging decision making in this setting. (50) Currently, most treatment algorithms regarding VT are extrapolated from studies based on patients with liver cirrhosis with/without HCC (13,18,19,51-53), owing to the increased incidence of VT in liver cirrhosis compared to PDAC.

If acute PV, MS or SV thromboses present in patients with malignancy, anticoagulation is generally recommended preferably with either low molecular weight or unfractionated heparin (54,55) given the strong evidence of greater efficacy and safety in contrast to oral vitamin K antagonists (VKA) (56). In the non-cancer setting the duration of treatment should be at least 3 months as per current guidelines by ACCP(49), with goals to halt thrombus extension, achieve vein recanalization, prevent portal hypertension and intestinal ischemia(26), the latter which can be potentially fatal. Currently, expert opinion

recommends at least 6 months of LMWH monotherapy.(57). Plessier et al. (46) found that recanalization occurred in one-third of patient receiving early anticoagulation and therefore supported early anticoagulation of patients with acute PVT, nonetheless, if SVT and ascites was detected on imaging, recanalization with anticoagulation was unlikely.

Role of Newer anticoagulants

Following the introduction of the newer oral anticoagulants (NOACs), e.g., dabigatran, apixaban, rivaroxaban, recent data has reported on their application in oncologic patients. (58-61) These novel anticoagulants are attractive to patients and clinicians due to the ease of oral administration and absence of laboratory monitoring(62) making them attractive alternatives to low molecular weight heparin (LMWH). Currently there are limited outcome data on these agents in the cancer setting and there is only one approved reversal agent, idarucizumab (63). Cancer patients pose several unique challenges to AC therapy, primary owed to disease progression that can affect organs (e.g. renal or liver) that can limit therapeutic choices(64) and secondary to anti-cancer therapies that have significant interactions with the CYP3A4 enzyme and/or p-glycoprotein transporter (65,66) which can modify pharmacological clearance resulting in an increased predisposition to bleeding complications.

NOACs have been well studied in acute vein thrombosis. A recent meta-analysis by Sardar et al (59) evaluated the results of six trials with a pooled analysis of 19,832 patients in which 1197 were cancer patients. The authors concluded that NOACs are effective in the prevention and treatment of DVT and did not cause excessive clinically relevant bleeding compared to LMWH for the treatment of acute VTE.

Presently, the use of NOACS in VT is based on expert recommendations. The international society on thrombosis and hemostasis, published in 2013 (65), recommended against the use of NOACs for the initial and long term treatment of cancer associated thrombosis and recommended investigating the efficacy and safety of NOACs in randomized controlled trials. Expert guidance for cancer associated thrombosis published by Khorana et al. (57) and Ageno et al. (67) recommended to consider long term anticoagulation for all patients with visceral thrombi, with treatment decisions to be made on a case-by-case basis by balancing risk factors for recurrence (e.g. underlying prothrombotic conditions) and the risk of bleeding.

Therefore, NOACs appear to be an attractive alternative to provide long-term anticoagulation for VT, however, presently limited evidence cannot recommend their use as standard of care owing to the limited evidence of their safety and efficacy.

METHODS

The primary objective of this systematic literature review was to identify the most recent available evidence pertaining to diagnosis, treatment and management of VT in pancreatic ductal adenocarcinoma. Our hypothesis being that currently there is limited published data pertaining to this topic and clinical management lacks appropriate recommendations. Therefore, we anticipate that this review will increase clinical awareness and encourage

further study of visceral thromboses in PDAC. This review followed the elements of the PICOS methodology, shown in table 1.

Searching Methods

Systematic literature searches were conducted (February 2, 2016) in five databases for references written in English-only with a population age of 19+ years. The searches were filtered to human-only research and include the date range of December 1, 2005 – February 2, 2016. The databases searched were: (1) MEDLINE (via PubMed), (2) Embase, (3) The Cochrane Library (Cochrane), (4) Web of Science (WoS), and (5) Scopus. For the following databases both controlled vocabulary and text words were used in the development of the search strategies: PubMed, Embase, Cochrane. All search results were combined in a bibliographic management tool (EndNote) and duplicates were eliminated both electronically and manually.

The search strategy had two major components that were linked together using the AND operator: (1) pancreatic cancer terms including adenocarcinoma, glandular tumor; (2) intra-abdominal thrombosis terms including portal vein thrombosis, venous thromboembolism, VTE, venous thrombosis, thrombotic events and thromboembolic events. Comprehensive searches were also conducted in two grey literature sources to incorporate this perspective to the final qualitative synthesis of the investigation: (a) *Grey Literature Report* and (b) *Open Grey*. For a complete list of MeSH and keyword terms used, please refer to the MEDLINE search strategy accompanying this paper.

Inclusion Criteria and Data extraction—Table 2, depicts the eligibility inclusion criteria. Data extraction was performed by one of the reviewers (AMH) blinded to the names of authors, institutions, journal names of the included studies, and extracted the relevant data. The following information was extracted from each article: authors, year of publication, study type, country of origin, mean age, primary working hypothesis and outcomes. These parameters are presented in the following tables: analysis of included studies and included patients (Table 3) and overall treatment and outcomes from studies (Table 3). Disagreements between the two reviewers (AMH, EOR) were resolved by discussion and analysis of the data. This article is reported in accordance with the guidelines set out by the Preferred Reporting Items for Systematic Reviews and Meta analyses (PRISMA).

RESULTS

The flow diagram of the study selection is shown in Fig. 1. A total of 10 articles were identified from the electronic search. After screening the articles, nine articles on VT in PDAC were included and their data was extracted. Two other articles were added after reference search by the authors criteria (68,69). Overall these 11 articles included a total of 127 patients with thromboses (PVT, SVT, MVT). There were no randomized controlled studies. Table 2 shows the characteristics of the included studies; five studies were case reports (70-74), and seven were retrospective studies (14,35,68,69,75-77). All articles, were published after 2007 and were published in the English language. The mean age of patients at diagnosis of all 127 patients was 64.3 years (range: 57-69).

Table 4, denotes some of the studies that assessed treatment and outcomes. Four of the 5 retrospective studies are shown. Median follow up was 26 months. Only two studies evaluated the role of anticoagulation in visceral thromboses. In the study of Menapace et al. (14) 40% of patients were treated with AC, and demonstrated on multivariate analysis that patients with VT had a worsened mortality (HR 2.6, 9% CI 1.6-4.2,p=0.0001), in contrast the use of AC was associated with improved survival (HR 0.30, 95% CI 0.12-74,p=0.009). In another non-randomized study by Søgaard et al.(68) three- month survival after cancer diagnosis was 35% in the group with VT compared to 53% in patients without VT.

Other pertinent large studies related to VT which involved a diverse cohort are displayed in table 4. The largest studies were by Ageno et al(55,79), who performed a prospective cohort study of 604 patients from 2008-2014 with splanchnic vein thrombosis (22.7% of cohort had solid cancer). This study demonstrated firstly that there were no higher rates of hemorrhage between those who received anticoagulants compared to those who did not (77% of the total cohort was treated with AC) and secondly supported the safety and efficacy of AC in most patients with VT. However, the main endpoint of this study was to assess the incidence of bleeding, mortality and thrombotic events and did not evaluate survival in cancer patients.

DISCUSSION

Visceral thrombosis is an emergent topic in the literature (50,55,67,68,77,79-83). Due to the heterogeneity of presentation, thrombosis can be discovered incidentally through the course of the disease, in particular in patients with advanced metastatic disease, or thrombosed may present with symptoms that lead to further abdominal imaging. With this systematic review and literature analysis we confirmed the significant occurrence of VT in PDAC. However, there are no standard therapeutic guidelines. With recently published studies it has been recognized that VT is a prognostic factor for short-term survival (68) and is a marker of occult cancer (77).

In a retrospective study, Menapace at al.(14) identified from a cohort of 135 patients with PDAC, N=31 (22.9%) had visceral thrombosis. This analysis confirmed that in PDAC, the occurrence of VT was significantly associated with worsened survival (HR 2.6, 1.6-4.2 CI, P <.0001). This finding has clinical importance in the context of disease progression. In the same study patients with advanced disease were strongly correlated with a greater proportion of VT. There were only N= 11 patients with localized disease (IB N= 2, IIB N= 4, III N= 5) and VT, in contrast, N= 32 patients had advanced stage (IV). However, N= 4 of the localized stage underwent pancreatic resection with thrombus involvement.

In PDAC, especially of the head of the pancreas, tumor can frequently invade the superior mesenteric vein and portal vein from direct tumor extension. This vascular invasion is an important parameter for determining surgical resectability. Therefore, it is common, when performing initial staging or subsequent imaging studies to discover thrombi with in the visceral vein. These thrombi can be either bland or tumor-related thrombi, which can sometimes be differentiated by on the basis of CT imaging characteristics.(84) A bland thrombus is defined as a benign filling defect that can be idiopathic or reflect an hypercoagulable state, venous stasis or the presence a foreign body.(85). In contrast, a

malignant filling defect or tumor thrombus should be considered when the thrombus itself shows continuity with in the primary mass and enhancement of the filling defect. (85, 86) Additionally, it is important to know that both types of thrombi (bland and tumor) can coexist secondary to the innate hypercoagulable state and from the external compression of a vein (e.g. PV, MV, SV) by the underlying malignancy. (87,88)

Recent research, has explored the significance of incidental visceral thromboses, increasingly discovered during routine CT imaging. (89) Currently, the subcommittee on Hemostasis and Malignancy (90) has recommended use of the term “incidental” and recommended against the use of the term “asymptomatic”. Particularly, because retrospective studies have shown that many of these events are indeed symptomatic, primarily attributed to the malignancy itself.(90)

Evidence supporting therapeutic anticoagulation for incidental VT in cancer patients is not yet clear. In this matter, the ACCP guidelines recommend AC for symptomatic venous thrombosis patients, and no AC for asymptomatic patients with incidentally detected events(49). Conversely, the AASLD, recommends AC in PVT (acute or chronic) and Budd Chiari syndrome. Long-term AC should be reserved for patients with permanent thrombotic risk factors and in the absence of other contraindications(91).

At Memorial Sloan Kettering Cancer Center for patients with an acute visceral thrombosis typically we initiate anticoagulation with a direct oral anticoagulant when the risks are deemed to outweigh the benefits and the patient is otherwise a candidate for active therapy. For patients with chronic thrombosis, the decision to anticoagulate is maded on a case-by-case basis. Of particular significance is the setting of locally advanced/recurrent PDAC where varices may develop related to portal hypertension in the setting of chronic visceral vein thromoboses. These decisions are nuanced and complex and pertain to balancing risks of anticoagulation and bleeding.

Currently, there is no meaningful evidence supporting the use of primary prophylaxis in this setting, however taking into account that most visceral thrombi are diagnosed in advanced stage cancer and there is indirect evidence pointing towards a decrease in survival, anticoagulation should be considered on a case by case basis.

Conclusions

With the aid of increased diagnostic imaging incidental VT is a topical issue in the literature (50,55,67,68,77,79-83). There is ongoing discussion regarding whether AC is indicated or not. Extrapolated evidence from patients with no malignancy has not clearly demonstrated a favorable impact from anticoagulation with low-molecular-weight heparin and improved prognosis. Recommendations are weak as a result of the observational nature of the data, the infrequent finding of visceral thromboses and the limited overall survival in PDAC. Controlled prospective studies are needed to provide the framework of decision making regarding anticoagulation of portal, mesenteric or splenic vein thromboses regarding safety and prevention of longer-term complications. Pending evidence from the use of novel oral anticoagulants will provide an additional choice for management of VT. Moreover,

prospective research studies should describe outcomes and management of visceral thrombosis based on vein location, treatment algorithm and cancer stage.

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Take Home Messages

- Pancreas adenocarcinoma is a well-known risk factor for development of visceral thrombosis.
- Visceral thrombosis is a poor prognostic indicator for short term survival (14,83).
- In order of incidence, portal vein, splenic and mesenteric vein account for most of the visceral thromboses.
- Incidental or non-incidental visceral thromboses should be treated with low-molecular-weight heparin if there are no contraindications (active bleeding, severe thrombocytopenia or end of life care).
- The exact role of anticoagulation in the setting of visceral thromboses with regard to oncologic outcome and prevention of complications remains to be fully defined.

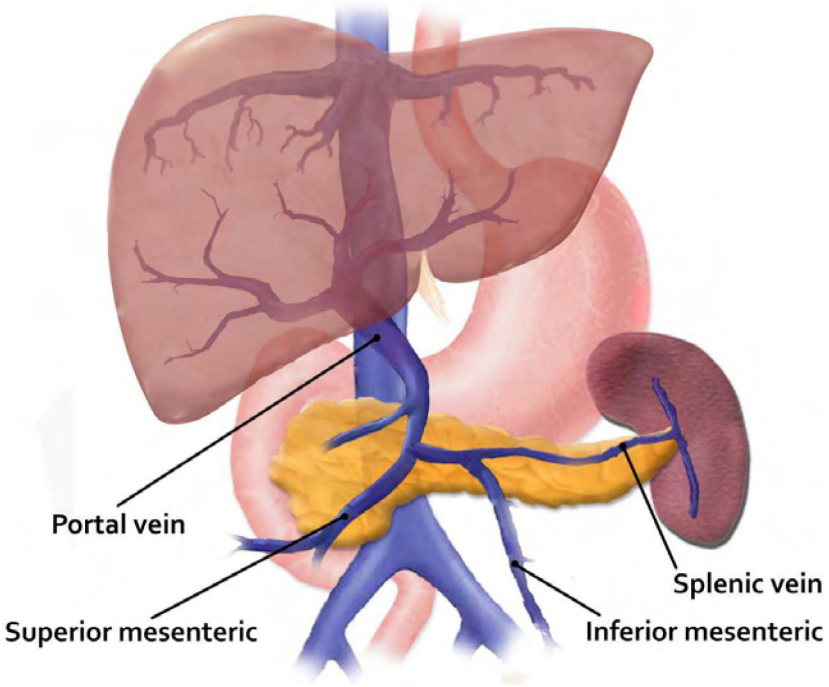

Fig 1.

Anatomic location of the splanchic venous system: Portal Vein, Mesenteric vein(inferior and superior braches) and splenic vein.

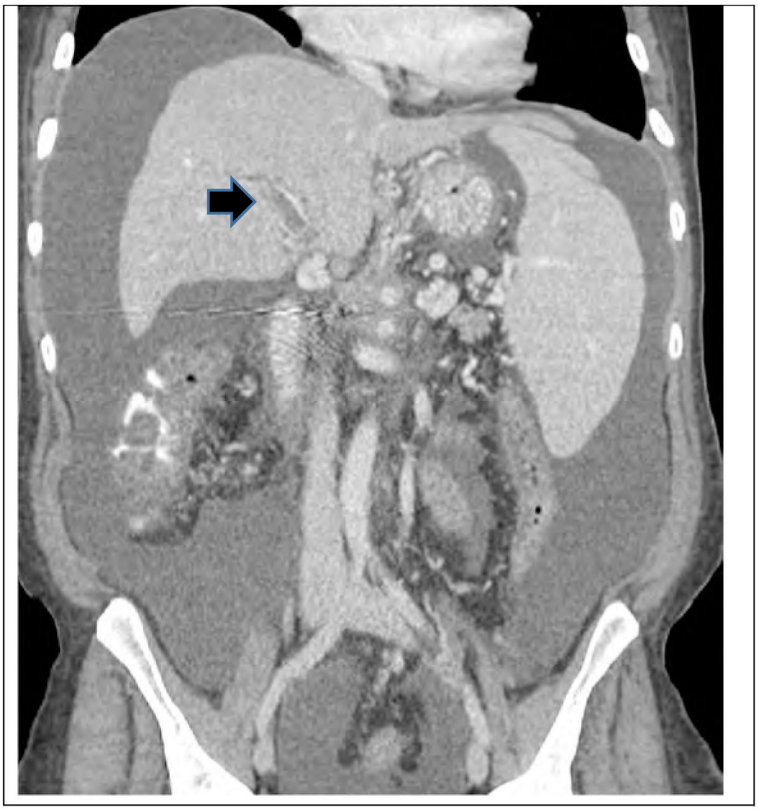

Figure 2.
CT scan with contrast of a 55 year old female patient wtih PDAC who developed portal Vein thrombosis (arrow).

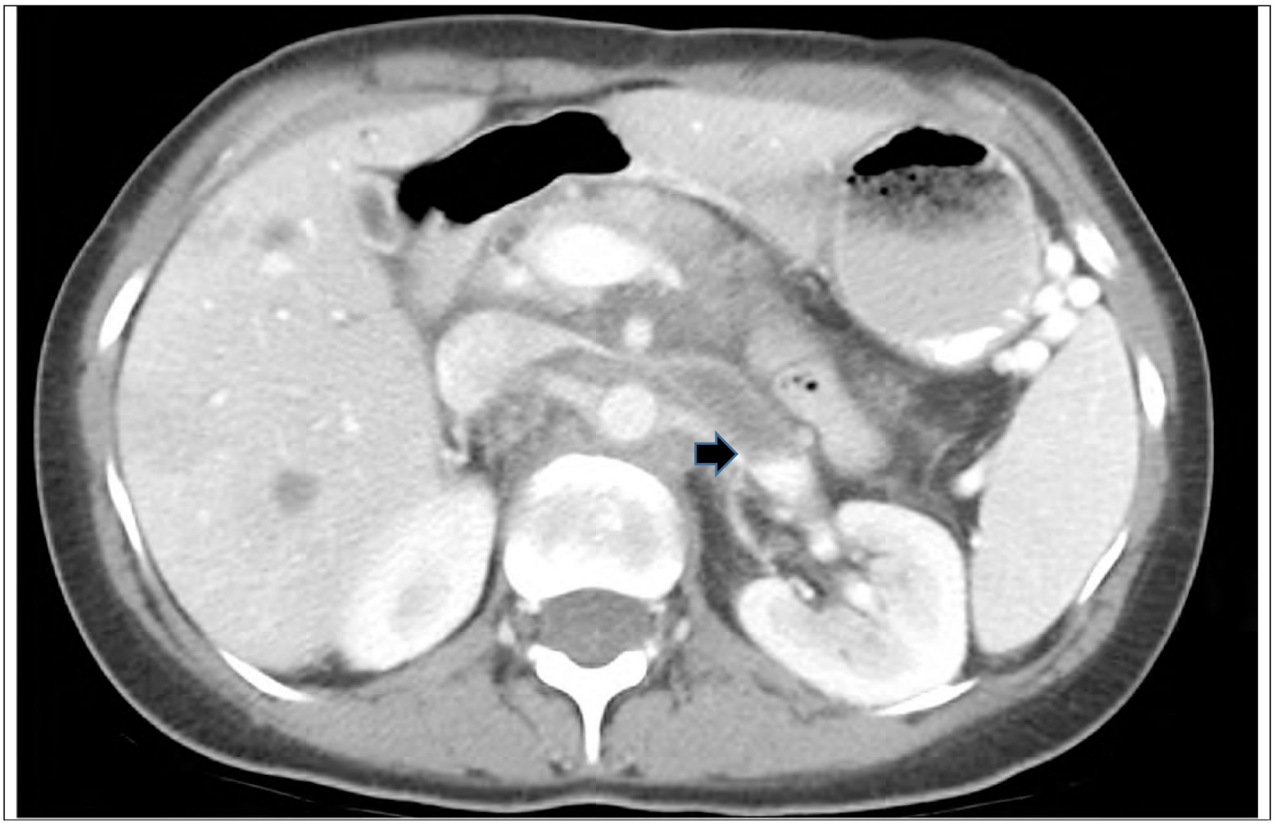

Figure 3.
CT scan with contrast of a 42 year old female with PDAC, diagnosed with renal vein thrombosis (arrow)

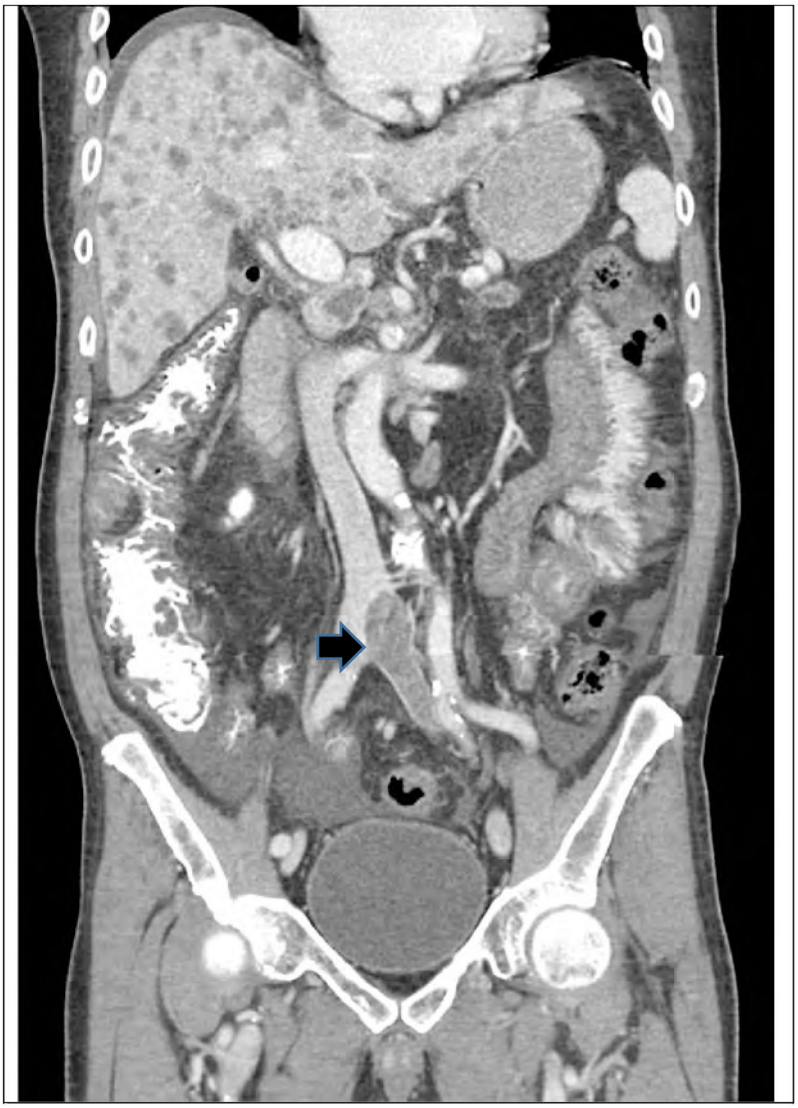

Figure 4.
Ct scan with contrast of a 69 year old male with PDAC, diagnosed with a common iliac vein thrombosis (arrow)

Table 1 –

Description of the PICO strategy used for study design

Population	Patients with Pancreas Adenocarcinoma
Interest	Portal Vein Thrombosis Splenic Vein Thrombosis Mesenteric Vein Thrombosis
Context	Studies published after 2008, that have evaluated patient with visceral thrombosis.
Outcome Measure	Appraise the currently literature in this topic.

Table 2 –

Eligibility Criteria of included studies

Inclusion Criteria **Selected studies were considered eligible if all of the following predefined criteria were met:**
a) Studies related to Portal vein, mesenteric vein and/or splenic vein thrombosis
b) Pathological confirmation of pancreas Adenocarcinoma
c) Year of publication was 2007 or later
d) Studies reported in English language
e) Full text publications

Table 3 –

Selected studies evaluating abdominal thromboses in pancreas ductal adenocarcinoma (N=10)

Author/ Year/ Reference	Study Design	No of Subjects	Country	Vein Location	Age (mean)	Histology	Primary working hypothesis	Observations
Dedania N et al. 2013	Retrospective study	SVT =19	USA	Splenic vein	62.2	Pancreas adeno carcinoma	SVT is associated with increase intraoperative blood loss, pancreas specific complications and reduced long term survival cross-sectional study to determine the prevalence of asymptomatic (incidental) venous thromboembolism seen on staging CT scans, in a consecutive series of patients.	Retrospective study evaluating surgical complications after distal pancreatectomy in PAC
Douma et al. 2015	Retrospective study	T= 9 PVT=5 SVT=3 RVT=1	USA	Portal, Renal and Mesenteric	57	Pancreas adeno carcinoma		A second objective was to assess the subsequent therapeutic implications of these thrombi.
Kawakami H et al. 2007	Case report	1	Japan	Portal Vein	68	Pancreas adeno carcinoma	EUS was helpful to delineate the intraportal growth of the tumor, and ERP to delineate the intraductal growth of the tumor.	tumor with intraductal growth into the main pancreatic duct that presented with tumor thrombus in the portal vein.
Menapace LA et al. 2011	Retrospective study	T= 45 PVT=18 SVT=14 MVT=13	USA	Portal, Splenic and Mesenteric	65.9	Pancreas adeno carcinoma	Determine the prevalence of both symptomatic and incidental VTE in patients with PAC	Large study that assessed for visceral thrombosis on PAC. Incidentally discovered visceral vein thrombi are associated with worsened mortality and clinical consequences who may benefit from therapeutic anticoagulation.
Onesti JK et al. 2013	Retrospective study	SVT=2	USA	Splenic Vein	61	Pancreas adeno carcinoma	Analysis of the pathologic implication of splenectomy in suspected distal pancreatic malignancy.	Only 2 patients were noted to have splenic vein thrombosis.
Roch AM et al. 2015	Retrospective study	26	USA	Splenic Vein	65.4	Pancreas adeno carcinoma	Extended distal pancreatectomy for locally advanced adenocarcinoma is associated with a survival benefit.	Single institution retrospective study, long study period from 1996-2011.
Roldan-Valadez E et al. 2008	Case report	1	Mexico	Portal Vein	68	Pancreas adeno carcinoma	Patient with PAC with clinical findings of portal hypertension who underwent PET/CT with finding of PVT.	PVT did not show enhancement or neovascularity with contrast CT, with the possibility of a bland tumor from altered portal venous hemodynamics.
Søgaard KK et all. 2015	Retrospective study	T= 20 PVT=19 HVT=1	Denmark	PVT, HVT	61	Pancreas adeno carcinoma	Examined cancer risk after a first time SVT diagnosis,	Final conclusion: study found evidence that SVT is a strong marker of occult cancer and a

Author/ Year/ Reference	Study Design	No of Subjects	Country	Vein Location	Age (mean)	Histology	Primary working hypothesis	Observations
							comparing cancer risk with the general Danish population, in addition to comparing survival among patient with and without SVT	predictor of poor prognosis for patients with liver and pancreatic cancer.
Venturi A et al. 2007	Case report	1	Italy	Portal vein	64	Pancreas adeno carcinoma	CEUS is reliable, non-invasive and useful diagnostic technique in the differential diagnosis between benign and malignant PVT outside the setting of chronic liver disease.	This case report evaluated the role of real-time Contrast-enhance ultrasound(CEUS) in the assessment of PVT
Yamato H et al. 2009	Care Reports	2	japan	1.Portal Vein 2.inferior Mesenteric Vein	66	2: Pancreas tubular Adeno carcinoma	Case 1: underwent surgical resection, 14 months after surgery thrombus extended into SMV, patient was alive 19months after surgery. Case 2: surgical exertion performed, tumor recurrence 4 months after, patient died of liver failure.	Description of three case reports of pancreatic carcinoma, one case was omitted due to tumor histology(endocrine carcinoma)
Zyromski NJ et al. 2008	Case report	1	USA	Mesenteric Vein Thrombosis	69	Pancreas adeno carcinoma	patient developed acute MVT-PVT on the first postoperative day, was treated with aggressive anticoagulation and early operative thrombectomy with SMV-PV reconstruction.	Case report to express awareness of early postoperative SMV-PV thrombosis after pancreaticoduodenectomy and its catastrophic complications.

SVT=splenic vein thrombosis(N=62), PVT=portal vein thrombosis(N=41), MVT=mesenteric vein thrombosis(N=15) PAC=pancreas adenocarcinoma, HVT=Hepatic vein thrombosis (N=1) T=total

Table 4 –

Studies that assessed the treatment modalities and outcomes.

Author/ Year/ Reference	Median Follow up	Anticoagulation	Outcomes	Observations
Dedania N et al. 2013	28.4 months	Not evaluated	-SVT had a significantly higher rate of pancreas-specific complications, including pancreatic fistula (33 versus 7%, p<0.01) and delayed gastric emptying (15 versus 0%, p<0.02) -Patients without SVT had a trend toward longer median survival(40 versus 20.8 months, p=0.1)	Group with SVT was younger at 62 years, as compared to 68 years for the non-svt group(p<0.05)
Menapace LA et al. 2011	36 months	39.1% of events were treated with AC	-Visceral vein thrombosis on multivariate analysis was associated with worsened mortality (HR2.6, 9% CI 1.6-4.2,p=0.0001) -Use of Anticoagulation was associated with improved survival(HR0.30, 95% CI 0.12-0.74,p=0.009)	
Roch AM et al. 2015	24 months follow up	Not evaluated	-SVT did not significantly affect morbidity, mortality or survival. -Recurrence was not significantly increased in case of splenic vein thrombosis (30.8% vs 38.8%, P = .63), whether it was local recurrence (11.5% P = .63) or distant metastases (19.2% vs 25.4%, P = .6). -Pathologic invasion of the vein did not impact short- and longterm outcomes.	
Søgaard KK et all. 2015	18 months	Not evaluated	-3 month survival after cancer diagnosis was 35% for patient with SVT and 53% for patients without SVT.	2 patients had localized cancer and 11 had advance disease.
Zyromski NJ et al. 2008	69 yr. (Case report)	Heparin and thrombectomy	-Resolution of acute MVT-PVT postoperative day after pancreaticoduodenectomy	-Patient became oliguric and tachycardic, and not responding to fluid resuscitation which prompted for abdominal sonogram.
Douma et al. 2015	Cross sectional Study	Anticoagulation therapy evaluated	-Authors, observed that patients with DVT and PE were treated with anticoagulants, and none of the patients with VT were treated.	
Other pertinent large studies related to visceral thrombosis in patients with or without malignancies				
Ageno et al. 2015	6 years solid Cancer represented 22.7% of cohort	LMWH=58.6% VKA= 62.4.6%	- Mean duration of AC was 13. 9 months. - The incidence for major bleeding was 3.9 per 100 patient-years (2.6-6.0) and 5.6 per 100 patient-years (3.9-8.0) for thrombotic events. - Did not find higher rates of hemorrhage between those who received anticoagulants compared with those who did not - most patients (77.0%) received some form of anticoagulant treatment - Supports the safety and efficacy of anticoagulant therapy in most patients with SVT	Longest multicentric prospective cohort
Ageno et al. 2014	4 years N=12(with only PAC)	LMWH=58.6% UFH= 4.9% VKA= 31.6%	- One in four patients with SVT did not receive antithrombotic therapy - Patients with solid cancer and gastrointestinal bleeding are more likely to be left untreated	This is a large multi centric prospective cohort study with total of 613 patients.
Derman et al. 2015	2 years	LMWH=20% UFH=12%	-34% of the PVT group received short-term anticoagulation (< 1 month), specifically LMWH (20%), unfractionated heparin (UFH) (12%), fondaparinux (0.4%), and other therapies (1%). -A total of 64% of the PVT + SPVT and 70% of the PVT + MVT groups received short-term anticoagulation. -6% of the PVT group experienced bleeding complications following diagnosis and intervention.	Eight patients had pancreas cancer

SVT=splenic vein thrombosis, PVT=portal vein thrombosis, MVT=mesenteric vein thrombosis PAC=pancreas adenocarcinoma, HVT=Hepatic vein thrombosis