Visceral Thromboses in Pancreas Adenocarcinoma: A Systematic Review

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Abstract

Background: Within the spectrum of 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 speculatively improve oncologic outcomes.

Objectives: Perform a systematic review to study occurrences of visceral thromboses (portal, mesenteric and splenic vein thromboses) associated with PDAC and provide a clinical review on this area.

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 after 2007 to 2016.

Results: Eleven articles were 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. PVT was found in 35% (N= 46), SVT in 52% (N= 65). MVT in 13%(N= 15). Mean follow up time was 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, to only rare occurrences with VT received treatment.

Conclusions: Visceral thrombosis in PDAC can be a frequent finding at diagnosis or during disease progression. This literature analysis has shown that VT can be associated with short term survival. Evidence to guide treatment choices are inadequate and current management is based on inferred experience from other non-oncologic populations. Anticoagulation appeared to be a safe modality in visceral thrombosis with most of the large studies recommending a careful assessment for patients with high risk of bleeding.

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.
- 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 has been increasingly encountered in patients with prothrombotic disorders (28%), cirrhosis (13%) and malignancies such as PDAC and hepatocellular carcinoma. (13).
- In one study the prevalence of visceral thrombosis in PDAC was approximately 22.9%(14), and almost all were incidentally discovered on routine surveillance and restaging scans(14).
- Incidental discoveries and lack of therapeutic guidelines for visceral thrombosis management, there are significant uncertainties for physicians and patients with a potential increased risk of complications, reduced survival, and inferior prognosis. (14,15)
- Currently, evidence is scarce on the progression and treatment benefit of therapeutic anticoagulation for visceral thrombosis and survival impact is not known.

Objective

- To identify the most recent available evidence pertaining to diagnosis, treatment and management of visceral thrombosis in pancreatic ductal adenocarcinoma

Rationale

- Our hypothesis being that currently there is limited published data pertaining to this topic and clinical management lacks appropriate recommendations.
- We contemplate that this review will increase clinical awareness of visceral thromboses in PDAC.

Methods: search strategy

- 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.
- The search strategy had two major components that were linked together using the AND operator: (1) pancreatic cancer terms including adenocarcinoma, glandular tumor, pancreatic neuroendocrine tumor, PNET; (2) intra-abdominal thrombosis terms including portal vein thrombosis, venous thromboembolism, VTE, venous thrombosis, thrombotic events, 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*
- Articles related to non-ductal pancreatic adenocarcinoma (e.g. periampullary (N=3), mucinous papillary(N=5), acinar cell(N=4), neuroendocrine(N=3) tumors) hepatocellular carcinoma(N=9) and liver cirrhosis were not included.

Methods: *Inclusion Criteria and Data extraction*

- Table 2, depicts the eligibility inclusion criteria.
- Data extraction was performed by one of the reviewers 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 search flow diagram of the study selection is shown in **Fig. 1.** A total of 10 articles were identified from the electronic search.
- Duplicate articles were removed. After, screening the articles without reporting data about any type of visceral thrombosis (PVT, MVT, SVT) and reference search, 9 articles on visceral thrombosis in PDAC were included and their data was retrieved.
- Two other articles were added after reference search by authors criteria(32,71). Overall these 11 articles included a total of 127 patients with combined thromboses (PVT, SVT, MVT). There were no randomized controlled studies.
- **Table 2** shows the characteristics of the included studies; five studies were case reports, and seven were retrospective studies all articles, were published after 2007 and were published in English language.
- Three patients were from Japan, 1 from Italy, 1 from Mexico, and 20 from Denmark and the remaining were from the United States.
- One patient had a pathologic diagnosis of nonfunctioning endocrine tumor (72). The mean age of patients at diagnosis of all 127 patients was 64.3 years (range: 57-69).
- Only two studies evaluated the role of anticoagulation in visceral thromboses.
- In the study of Menapace et al. (14) almost 40% of patients were treated with anticoagulation, 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).
- Three- month survival after cancer diagnosis was 35% in the group with visceral thrombosis compared to 53% in patients without VT.

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, gonadal vein, renal vein
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	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	cross-sectional study to determine the prevalence of asymptomatic (incidental) venous thromboembolism seen on staging CT scans, in a consecutive series of patients.	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, comparing cancer risk with the general Danish population, in addition to comparing survival among patient with and without SVT	Final conclusion: study found evidence that SVT is a strong marker of occult cancer and a 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.

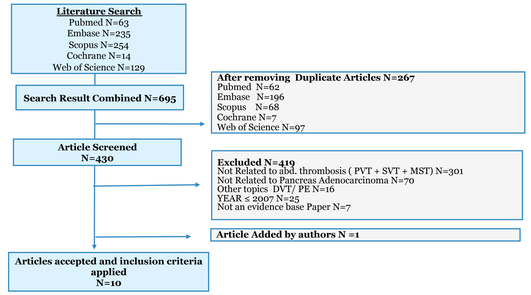

Figure 1. Study Design. N=number of patients

Conclusions

- Visceral thromboses in PDAC represents a commonly occurring thrombotic event secondary to both direct tumor extension and the thrombotic phenomenon associated with this malignancy.
- There is ongoing discussion regarding whether anticoagulation is indicated or not, but extrapolated evidence from patients with no malignancy has not clearly demonstrated yet the favorable impact of low-molecular-weight heparin in patient prognosis.
- However, the 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 indispensable to provide the framework of our understating of the consequence of portal, mesenteric or splenic vein thromboses regarding progression and later complications and treatment.
- This will positively add insight for future clinical trials providing the outline for the development of new therapeutic interventions to determine the risk and benefits of anticoagulation in this subset of patients.
- Expectant evidence from the use of novel oral anticoagulants will provide an additional choice for the clinician and the patient for the treatment and prevention of visceral thrombosis
- Moreover, prospective research studies should describe outcomes of visceral thrombosis based vein location, treatment algorithm and cancer staging.

Future Research

- Pancreas adenocarcinoma is a well-known risk factor for development of visceral thrombosis
- Visceral thrombosis is a poor prognostic indicator for short term survival(14,58).
- 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 remains to be fully defined

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