Epidemiology, Prevention, Diagnosis, and Management of Venous Thromboembolism in Gastrointestinal Cancers

William J. Chapin, MD[1] Preeti Sudheendra, MD[2] Luis Goity, MD[3] Deepak Sudheendra, MD[3]

[1] Division of Hematology/Oncology, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania
[2] Division of Hematology and Oncology, Cooper University Hospital, Camden, New Jersey
[3] Division of Interventional Radiology, Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

Address for correspondence Deepak Sudheendra, MD, Department of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104 (e-mail: Deepak.Sudheendra@pennmedicine.upenn.edu).

Dig Dis Interv 2020;4:248–259.

Abstract

Venous thromboembolism (VTE) is a leading cause of cardiovascular death and is associated with significant morbidity. Patients with cancer, and gastrointestinal (GI) malignancies in particular, are at increased risk of VTE, increased risk of bleeding with VTE treatment, and increased risk of recurrent VTE compared with the general population. VTE has been shown to be a leading cause of death among patients with cancer. This review will discuss special considerations in the prevention, diagnosis, and management of VTE in patients with GI malignancies. Given the increased risk of VTE observed in ambulatory patients with GI malignancies, multiple trials have examined and demonstrated the efficacy of prophylactic anticoagulation in high-risk patients with cancer undergoing chemotherapy, particularly in patients with gastric and pancreatic cancers. Patients with GI malignancies have also played a central role in discussions of the risks and benefits of the use of direct oral anticoagulants in patients with cancers, with first-line anticoagulation options expanding to include low-molecular-weight heparin, rivaroxaban, edoxaban, and apixaban. However, there continue to be concerns regarding an increased risk of bleeding with edoxaban and rivaroxaban in patients with GI malignancies. In addition to anticoagulation, individualized risk and benefit analysis should be undertaken for interventions including inferior vena cava (IVC) filter placement and catheter-directed thrombolysis in the setting of increased risk of bleeding and recurrent VTE for patients with GI malignancies. Several unique scenarios that may be seen with GI malignancies, including incidental VTE, splanchnic vein thrombosis, IVC thrombosis, and iliac vein compression, require individualized decision making.

Keywords
- venous thromboembolism
- deep vein thrombosis
- pulmonary embolism
- cancer
- anticoagulation

Epidemiology of VTE in GI Cancer

Venous thromboembolism (VTE) is the third leading cause of cardiovascular death.[1] The Centers for Disease Control estimate that nearly 600,000 people each year are affected by VTE, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE). As the leading cause of preventable hospital death, between 10 and 30% of patients diagnosed with VTE will die within 1 month of diagnosis, and an estimated 20 to 25% of initial PE diagnoses present with sudden death.[2]

While there are many risk factors that predispose to VTE, a diagnosis of cancer increases the risk of VTE four to seven

received
April 2, 2020
accepted after revision
July 23, 2020
published online
September 22, 2020

Issue Theme A Multi-disciplinary Approach to Gastrointestinal Malignancies; Guest Editors, Nicholas Fidelman, MD, and R. Peter Lokken, MD

Copyright © 2020 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.
Tel: +1(212) 760-0888.

DOI https://doi.org/10.1055/s-0040-1716738.
ISSN 2472-8721.

times compared with patients without malignancy. Not only are these patients predisposed to VTE but also to VTE recurrence.[3–5] Factors that contribute to these increased risks can be divided into those related to the malignancy itself, cancer-directed treatments and procedures, and patient physiology. The presence of active cancer causes production of procoagulant factors, upregulation of tissue factor, and release of proinflammatory cytokines. Treatment- and procedure-related risk factors include endothelial damage due to chemotherapy, radiation, and surgery, and the presence of indwelling catheters. Patient-specific risk factors include immobility, obesity, and advanced age.[6]

Several studies have shown that, compared with other cancer types, gastrointestinal (GI) malignancies (which include esophageal, gastroesophageal [GE], gastric, hepatobiliary, pancreatic, and colon cancers) are associated with a higher risk of VTE. Multiple studies have attempted to quantify the risk of VTE in this subset of patients. Larsen et al performed a single-center, cross-sectional cohort study examining prevalence of VTE upon initial diagnosis of upper GI malignancies (including esophageal, gastric, extrahepatic cholangiocarcinoma, and pancreatic cancers) by conducting screening and diagnostic lower extremity Doppler ultrasound (US) and computed tomographic pulmonary angiography (CTPA).[7] In this group of symptomatic and asymptomatic patients with no prior VTE diagnosis, the prevalence of DVT and PE was 5.2 and 7.7%, respectively.[7] Population-based cohort studies in Denmark and the United Kingdom have demonstrated incidence rates of 40.9 to 98 per 1,000 person-years in patients with pancreatic cancer, 20.4 to 35 per 1,000 person-years in patients with liver cancer, 37 per 1,000 person-years in patients with GE cancer, and 9.5 per 1,000 person-years in patients with colon cancer.[8,9] All of these incidence rates are significantly higher compared with the overall cancer cohorts in these studies (8–13.9 per 1,000 person-years) and to the patients without cancer (3–4.7 per 1,000 person-years).[8,9] In the Danish study, the absolute incidence of VTE within the first year of diagnosis in patients with pancreatic cancer was 4.4% compared with 1.4% in the overall cancer cohort.[8]

In patients with any cancer type, treatment for VTE is associated with an increased incidence of major bleeding and fatal bleeding compared with a noncancer population.[10–13] When stratified by type of malignancy, a study by Zakai et al demonstrated a rate of major bleeding of 8.6% per patient-year in patients with GI malignancies versus 4.4% per patient-year in all patients with cancer undergoing anticoagulation for VTE.[14] Clinical trials of direct-acting oral anticoagulants (DOACs) have recently raised the question of increased risk of bleeding when patients with GI malignancies and VTE are treated with DOACs.[15–19] In addition to this bleeding risk, patients with cancer and VTE have a higher risk of VTE recurrence compared with patients without cancer with 12-month cumulative incidence up to 20.7%.[10,13,20]

Regarding mortality in patients with cancer-associated VTE, a Dutch study found that among patients diagnosed with cancer at the time of VTE, the rate of 1 year overall survival (OS) was 12% compared with 36% in matched cancer controls resulting in a hazard ratio (HR) of 2.20.[21] Twenty-six percent of patients in this cohort had GI malignancies.[21] In a prospective cohort study of cancer patients undergoing treatment, thrombosis was the second leading cause of death behind progression of underlying cancer.[22] When looking prospectively at cancer patients with PE, Font et al found that the presence of a GI malignancy, in particular, was significantly associated with increased 30-day mortality in multivariate analysis.[23]

Prevention of VTE in Ambulatory Patients with GI Malignancies

Given the increased risk of VTE and death associated with malignancy, there has been much interest in investigating the role of VTE prophylaxis in patients with cancer. Two trials of low-molecular-weight heparin (LMWH) in patients with solid tumors undergoing chemotherapy demonstrated a significant reduction in symptomatic VTE (1.2–2% vs. 3.4–3.9% with placebo) with no increased incidence of major bleeding and no difference in mortality.[24,25] In the subgroup of patients with pancreatic cancer in the SAVE-ONCO trial, the cumulative incidence of VTE was 2.4% of patients in the semuloparin group compared with 10.9% in the placebo group.[25] Several additional trials specifically enrolled patients with advanced pancreatic cancer undergoing chemotherapy and were able to reproduce these results. Maraveyas et al used a therapeutic dose of dalteparin (200 IU/kg subcutaneously daily for 1 month followed by 150 IU/kg daily for 2 months) and found the 100-day VTE incidence was 3.4% in the LMWH group and 23% in the control group.[26] The 100-day incidence of fatal VTE was 8.3% in the control arm and 0% in the LMWH group.[26] Pelzer et al compared prophylactic doses of enoxaparin (1 mg/kg subcutaneously daily) versus placebo and found incidence rates of symptomatic VTE of 9.8% in the control group and 1.3% in the LMWH group with no increased risk of major bleeding.[27]

Despite significant VTE risk reduction in cancer patients undergoing chemotherapy, the absolute risk reduction was small, which prompted attempts to better identify the highest risk populations.[28] Khorana et al utilized a prospective cohort design to derive and validate a scoring system identifying outpatients with malignancy starting a new chemotherapy regimen (►**Table 1**).[28] Based on prior large epidemiologic studies, the presence of gastric or pancreatic malignancy was the strongest predictor of VTE risk incorporated into the model.[8,9,28] When combined with one or more additional risk factors to total a Khorana score of $\geq$3, the observed VTE incidence was 7.1 and 6.7% in the derivation and validation cohorts, respectively, over a median follow-up of 2.5 months on the study. A separate study validated this model in a cohort of patients with cancer undergoing chemotherapy and demonstrated a 6-month cumulative incidence of VTE of 9.6% in those with a Khorana score of 2 and 17.7% in those who had a score of $\geq$3.[29]

The advent of the Khorana score has allowed investigators to examine the role of VTE prophylaxis in the highest risk patients. Both the AVERT and CASSINI trials studied prophylactic DOAC administration in ambulatory cancer patients who were initiating chemotherapy and had a Khorana score of $\geq$2. The AVERT trial examined apixaban 2.5 mg twice daily for 3 months versus

Table 1 Khorana score for VTE risk in outpatients with cancer

Factor	Risk score
Primary tumor site	
Very high risk: stomach, pancreas	2
High risk: lung, lymphoma, gynecologic, bladder, testicular	1
All other sites	0
Prechemotherapy platelet count $\geq 350 \times 10^9$/L	1
Prechemotherapy WBC $> 11.0 \times 10^9$/L	1
Hemoglobin < 10 g/dL or use of red cell growth factors	1
Body mass index ≥ 35 kg/m^2	1
Risk of symptomatic VTE	Total score
Low (0.3–0.8% rate of VTE at 2.5 months)	0
Intermediate (1.8–2.0% rate of VTE at 2.5 months)	1–2
High (6.7–7.1% rate of VTE at 2.5 months)	≥ 3

Abbreviations: VTE, venous thromboembolism; WBC, white blood cell.

placebo in the above population. The 6-month incidence of VTE was 4.2% in the apixaban group compared with 10.2% in the placebo group. There was an increased risk of major bleeding of 3.5% in the apixaban group compared with 1.8% in the placebo group and no difference in OS between the groups.[30] The CASSINI trial was conducted on a similar cohort of patients, including 32.6% with pancreatic cancer and 20.9% with gastric or GE junction cancers.[31] Unlike the AVERT trial, patients underwent baseline screening with Doppler US and 4.5% of patients were found to have DVT and were excluded from participation in the trial. The treatment arm received rivaroxaban 10 mg daily for 180 days and the control arm received a placebo. Rivaroxaban did not significantly reduce the primary endpoint of VTE during the 6-month follow-up period (6% in rivaroxaban group vs. 8.8% in placebo). The risk of VTE was reduced approximately 4% (2.6% in the rivaroxaban group vs. 6.4% in the placebo group) during the mean intervention period of 4.3 months. Approximately 40% of patients in the rivaroxaban group prematurely discontinued the treatment medication. There was an increased risk of major bleeding (2 vs. 1%) in the treatment arm that was not statistically significant.[31] There was no difference in OS between the groups. While both of these trials used the Khorana score as part of their eligibility criteria, any patient with gastric or pancreatic cancer undergoing a new course of chemotherapy met VTE risk inclusion criteria for these trials. The American Society of Clinical Oncology (ASCO) guidelines now recommend that high-risk outpatients with cancer (Khorana score of 2 or higher prior to starting a new systemic chemotherapy regimen) may be offered thromboprophylaxis with apixaban, rivaroxaban, or LMWH after considering bleeding risks and drug interactions.[32] Prophylactic anticoagulation is also recommended for hospitalized patients with cancer and patients with cancer undergoing major surgical intervention with data supporting these recommendations.[32,33]

Table 2 Signs and symptoms in patients with DVT

Signs and symptoms of DVT
Leg pain
Leg swelling
Redness
Bluish or whitish skin discoloration
Calf cramps/Charley horses
Positive Homan's sign (calf pain with dorsiflexion)

Clinical Presentation and Diagnosis of VTE in Patients with GI Malignancies

The clinical signs and symptoms of DVT are familiar to most clinicians (►**Table 2**) and apply to patients with and without cancer. In patients with inferior vena cava (IVC) thrombosis secondary to complications from an IVC filter (IVCF), mechanical compression, or invasion of the IVC from tumor, lower back and abdominal pain may precede typical symptoms of DVT, in up to 48% of patients in one series.[34] Patients with GI malignancies are also at risk of splanchnic vein thromboses (SVTs), which include portal vein, mesenteric vein, and splenic vein thromboses. Clinical presentation of acute SVT may include abdominal pain, ascites, hepatomegaly, nausea, vomiting, anorexia, or diarrhea. Fever and peritoneal signs on exam may also be present for patients who develop intestinal infarction.[35] Chronic SVT may be asymptomatic due to the formation of collateral veins, though patients can present with abdominal pain, nausea, vomiting, anorexia, edema, or splenomegaly.[35] Additionally, up to 50% of VTE in patients with cancer is discovered incidentally on imaging performed for another reason, with one retrospective single center review in unselected patients with GI malignancies noting a 7.3% rate of unsuspected or incidental DVT and 2.7% rate of unsuspected or incidental PE.[36,37]

Notably, patients with cancer are more likely to present with bilateral DVT (8.5 vs. 4.6%), iliocaval DVT (22.6 vs. 14%), and upper limb DVT (9.9 vs. 4.8%) than patients without cancer.[38]

The approach to diagnosis of VTE in patients with and without cancer involves evaluation of the clinical likelihood of VTE followed by confirmatory testing for patients with sufficiently high pretest probability and no further testing for those with sufficiently low pretest probability.[39] The revised Wells criteria for DVT and PE (►**Table 3**) and modified Geneva score for PE (►**Table 4**) are the most common objective criteria used to risk stratify patients suspected of VTE, and studies have validated that they can be safely used for cancer patients, which both scoring systems take into account.[40–42] In addition to clinical decision rules, D-dimer is commonly utilized to risk stratify patients and to help guide further testing for VTE. Several analyses examining patients with active malignancy, including a meta-analysis in which 11% of patients had GI malignancies, demonstrated the safety

Table 3 Modified Wells criteria for predicting pulmonary embolism

Clinical characteristic	Score
Clinical signs of DVT	3
PE is #1 diagnosis or equally likely	3
Heart rate > 100	1.5
Immobilization for at least 3 days OR surgery in the last 4 weeks	1.5
Previous PE or DVT	1.5
Hemoptysis	1
Active malignancy within the past 6 months	1
Clinical Pretest probability of pulmonary embolism	
Low	0–1
Intermediate	2–6
High	≥7

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

Table 4 Modified Geneva Score for Predicting Pulmonary Embolism

Risk factors	Score
Previous DVT/PE	3
Surgery or fracture within 1 month	2
Active malignancy	2
Age > 65	1
Symptoms	
Unilateral leg pain	3
Hemoptysis	2
Clinical signs	
Heart rate ≥ 95 bpm	5
Unilateral leg edema	4
Heart rate 75–94 bpm	3
Clinical probability	
Low	0–3 total
Intermediate	4–10 total
High	≥11 total

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

of employing a clinical decision rule and negative age-adjusted D-dimer to rule out PE without further imaging.[42,43] Using this approach, PE could be ruled out in 12.6% of patients with cancer compared with 38% of patients without cancer.[43]

For patients in whom VTE cannot be ruled out with clinical decision rules demonstrating low probability and negative D-dimer, confirmatory testing is required. For the diagnosis of DVT, a negative whole-leg compression US exam from the iliac veins down to the deep calf veins is sufficient to rule out DVT.[44] A recent meta-analysis noted a pooled sensitivity and specificity of whole-leg compression US of 94 and 97.3%, respectively.[45] The limitation of US includes being unable to adequately visualize the common and external iliac veins, especially in patients with large body habitus. Given the increased presentation of iliocaval DVT in patients with cancer,[38] additional imaging with CT or magnetic resonance (MR) venography should be considered if there is a high clinical suspicion for proximal DVT. For the diagnosis of PE, CTPA has demonstrated a sensitivity of 86% and a specificity of 94% compared with a sensitivity of 39% and a specificity of 97% with ventilation/perfusion (VQ) scanning.[46] While sensitive, a patient-level meta-analysis determined that in patients with likely probability of PE based on the modified Wells criteria and negative CTPA, the 3-month incidence of PE was as high as 2% and as high as 6% in patients with Wells criteria >6 points, respectively.[47] In the setting of a high pretest probability of PE with normal CTPA findings, additional diagnostic imaging, such as a VQ scan, may be considered.

Management of VTE in Patients with GI Malignancies

The mainstay of treatment for VTE is anticoagulation. In patients in whom anticoagulation is contraindicated, an IVCF may be appropriate.[32] Additionally, catheter-directed thrombolysis (CDT) or pharmacomechanical CDT (PCDT) in select patients may be viable options to reduce symptoms, minimize long-term complications, and improve quality of life (QOL).[48]

Anticoagulation

In patients with or without malignancy, systemic anticoagulation is the standard of care for the treatment of VTE.[49] In patients presenting with proximal DVT (defined as involving the IVC, iliac veins, femoral veins, or above-knee popliteal vein), 50% will progress to develop a PE if not anticoagulated.[50] While anticoagulation reduces the risk of VTE recurrence, treatment must be balanced with the risk of bleeding from anticoagulation. Patients with GI cancers have a significantly higher risk of major bleeding with anticoagulation with rates ranging from 6.5 to 21%.[10,11,18]

Regarding choice of anticoagulation, LMWH is considered a first-line therapy for acute VTE in cancer patients, including patients with GI malignancies. In several meta-analyses, LMWH reduced rates of recurrent VTE compared with vitamin K antagonists with the relative risk (RR) ranging from 0.58 to 0.6 with no increased risk of major bleeding (RR: 1.07–1.09).[51,52]

Recent trials have examined the efficacy and safety of DOACs compared with LMWH in patients with cancer, with GI malignancies playing a central role in the discussion. The Hokusai VTE cancer trial randomized 1,050 patients with active cancer and acute VTE to LMWH for 5 days followed by edoxaban (60 mg by mouth daily for 6–12 months) or dalteparin (200 IU/kg subcutaneously daily for 1 month followed by 150 IU/kg subcutaneously daily to complete 6–12 months) and examined the combined primary outcomes of recurrent VTE or major bleeding within 12 months.[15] Recurrent VTE occurred in 7.9% in the edoxaban arm and 11.3% in the dalteparin arm (HR: 0.71, 95% confidence interval [CI]:

0.48–1.06), and major bleeding occurred in 6.9% in the edoxaban arm and 4% in the dalteparin arm (HR: 1.77; 95% CI: 1.03–3.04). In the subgroup analysis of GI cancers, major bleeding occurred in 13.2% in the edoxaban group and 2.4% in the LMWH group ($p = 0.017$).[15] While edoxaban was noninferior in the combined primary endpoint of VTE recurrence or major bleeding, it was associated with increased major bleeding overall and there was a strong signal for increased major bleeding with edoxaban in the subgroup of patients with GI malignancies. The SELECT-D trial employed a similar design and randomized 406 cancer patients with acute VTE to dalteparin at standard dosing or rivaroxaban 15 mg by mouth twice daily for 3 weeks followed by 20 mg by mouth daily to complete 6 months.[16] The primary outcome of the rate of VTE recurrence in the 6-month study period was observed in 4% of the rivaroxaban group and in 11% in the dalteparin group (HR: 0.43; 95% CI: 0.19–0.99). Major bleeding in the 6-month study period occurred in 6% in rivaroxaban group versus 4% in dalteparin group (HR: 1.83; 95% CI: 0.68–4.96) and clinically relevant nonmajor bleeding occurred in 13% of the rivaroxaban group versus 4% in the dalteparin group (HR: 3.76; 95% CI: 1.63–8.69).[16] During an interim safety analysis, a nonsignificant increase in major bleeding with rivaroxaban was observed in patients with esophageal or GE junction cancers, and patients with these cancers were excluded from further enrollment. At final analysis for these patients, a higher rate of major bleeds was observed in the rivaroxaban group compared with dalteparin (36 vs. 11%; no statistical testing performed).[16]

Based on the concern for the potentially increased risk of major bleeding with DOACs for patients with GI malignancies, multiple retrospective studies have compared rates of major bleeding in patients with GI malignancy treated with DOACs versus LMWH. Lee et al examined a retrospective cohort of patients with gastric or pancreatic cancer, and acute VTE treated with rivaroxaban or LMWH. There was no difference in the rate of major bleeding (5.1% with rivaroxaban vs. 8.9% with LMWH) or rate of VTE recurrence. Kim et al and Recio-Boiles et al compared rates of bleeding between all GI cancer patients with acute VTE who were treated with rivaroxaban or LMWH. This study demonstrated a trend toward increased major bleeding and a significant increased risk of any bleeding event with rivaroxaban (17.4 vs. 7.6%, $p = 0.072$ for major bleeding; 40.6 vs. 19%, $p = 0.01$ for total bleeding). Recio-Boiles et al demonstrated increased major bleeding with rivaroxaban compared with LMWH (21.5 vs. 5%, $p = 0.04$).[18,19] These results were consistent with the increased risk of bleeding in the small subgroup of patients with esophageal or GE junction cancers in the SELECT-D trial.[16]

Most recently, the Caravaggio trial randomized 1,155 patients with cancer and acute DVT to dalteparin at standard dosing or apixaban 10 mg by mouth twice daily for 7 days followed by 5 mg by mouth twice daily, both to complete 6 months of treatment. Recurrent VTE in the 6-month treatment period occurred in 5.6% of patients in the apixaban arm compared with 7.9% in the dalteparin arm (HR: 0.36; 95% CI: 0.37–1.07). Major bleeding occurred during the 6-month treatment period occurred in 3.8% in the apixaban arm compared with 4% with dalteparin (HR: 0.82; 95% CI: 0.4–1.69), and clinically relevant nonmajor bleeding occurred in 12.2% in the apixaban group and 9.7% in the dalteparin group (HR: 1.16; 95% CI: 0.77–1.75).[53] One-third of patients on the trial had GI cancers, including 4.7% of patients with upper GI cancers. While results were not stratified by cancer type, there was no difference in major GI bleeding between the apixaban and dalteparin groups.[53] Overall, this demonstrated noninferiority of apixaban to dalteparin without a propensity for increased major bleeding or major GI bleeding in a study that included 32.5% patients with GI malignancies. A retrospective analysis of patients with GI cancers and VTE corroborates this result with apixaban, demonstrating a similar risk of recurrent VTE compared with LMWH with no increased risk of major bleeding.[18] Updated National Comprehensive Cancer Network (NCCN) guidelines for cancer-associated VTE recommend DOACs, with apixaban and edoxaban listed as category 1 recommendations, as the preferred agents for patients without gastric or GE tumors, but LMWH remains the preferred option for patients with gastric or GE tumors due to the increased risk of bleeding with DOACs in these patients.[54]

Incidental VTE represents up 50% of VTE in patients with malignancy.[36] Several retrospective cohort studies in patients with cancer, including one examining patients with pancreatic cancer, have noted no difference in OS between patients with suspected and incidentally discovered VTE[55,56] and ASCO guidelines recommend treating incidental VTE in the same manner as symptomatic VTE given similar clinical outcomes.[57]

Inferior Vena Cava Filters

There are few randomized trials examining the benefit of IVCF placement in patients with VTE, and none specifically in patients with GI cancers. The PREPIC trial randomized 400 patients to permanent IVC filter plus anticoagulation versus anticoagulation alone and included patients with cancer (16% in the IVCF plus anticoagulation arm and 12% in the anticoagulation alone arm).[58] The IVCF plus anticoagulation arm had a reduced rate of PE at 12 days (1.1 vs. 4.8%, odds ratio [OR]: 0.22; 95% CI: 0.05–0.90), but had an increased rate of recurrent DVT at 2 years (20.8 vs. 11.6%; OR: 1.87: 95% CI: 1.10–3.20) with no difference in OS.[58]

Additional large retrospective studies have attempted to evaluate IVCF for patients with DVT or PE in whom anticoagulation is contraindicated, as no randomized trials have been performed in this clinical setting. A cohort study evaluated 371 patients with DVT who underwent IVC filter placement due to known significant bleeding risk and compared outcomes with 344 propensity-score-matched patients who did not undergo IVCF placement. This study found no difference in all-cause death, a lower risk-adjusted PE mortality rate with IVCF (1.7 vs. 4.9%, $p = 0.03$), and an increased risk-adjusted rate of recurrent VTE with filter insertion (6.1 vs. 0.6%, $p < 0.001$).[59] Notably, 39.5% of patients in the IVCF group had active cancer compared with 21% in the nonfilter group.[59] Among 2,747 cancer patients with IVCF placed and propensity-score-matched controls, IVCF use was associated with no difference in 30-day mortality (HR: 1.12; 95% CI: 0.99–1.26,

Table 5 Indications for inferior vena cava filter insertion

Indications	• Contraindication to anticoagulation
	• Failure of therapeutic anticoagulation
	• Complication of anticoagulation

$p = 0.08$) or risk of PE at 180 days (HR: 0.81; 0.52–1.27; $p = 0.36$), but was associated with an increased adjusted risk of recurrent DVT (HR: 2.10; 1.53–2.89; $p < 0.0001$).[60] Unfortunately, data on how many patients in the IVCF group received anticoagulation were not available and the percentage of patients with GI malignancies was not reported.[60] Based on these limited data, ASCO guidelines note that IVCF may be offered to patients with absolute contraindication to anticoagulant therapy in the setting of acute VTE (within the past 4 weeks) if the thrombus burden is life-threatening.[32] While patients with GI malignancies were not specifically addressed in these studies, high rates of VTE compared with patients with other cancers and high risk of bleeding with anticoagulation compared with patients with other cancers suggest that the decision regarding placement of an IVCF for acute VTE would occur more commonly in this subgroup of patients.[8,9,14]

In patients with an absolute contraindication to anticoagulation, a retrievable IVCF rather than a permanent filter should be considered. This is due to the potential long-term complications from IVCF that may occur, including recurrent DVT (30–40%), IVC thrombosis (3–30%), and filter fracture (1–2%).[61,62] Once the risk of VTE has resolved and/or the patient can receive anticoagulation, the IVCF should be removed (►**Table 5**).[63]

Catheter-Directed Thrombolysis

In any patient with a proximal DVT, the risk of post-thrombotic syndrome (PTS) is as high as 50% with symptoms including leg pain, swelling, heaviness, and leg ulcers.[64] PTS has a significant negative impact on health-related QOL.[64] In addition to anticoagulation, strategies for the treatment of acute DVT such as systemic thrombolysis, CDT, and PCDT aim to improve short-term pain and swelling and reduce the long-term development of PTS. The ATTRACT trial enrolled 692 patients (excluding patients with active cancer) and randomized to PCDT plus anticoagulation or to anticoagulation alone. The primary outcome measures was incidence of PTS between 6 and 24 months of follow-up.[65] There was no difference in the incidence of PTS between the groups (47 vs. 48%, $p = 0.56$) and PCDT increased major bleeding events within 10 days (1.7 vs. 0.3%, $p = 0.049$) but significantly reduced the incidence of moderate-to-severe PTS (18 vs. 24%, $p = 0.04$).[65] Subsequent analyses demonstrated that within the group with iliofemoral DVT, PCDT improved disease-specific QOL at all time points up to 24 months,[66] improved PTS severity at all time points up to 24 months, and led to a greater reduction in leg pain and swelling at 10 and 30 days.[67]

Unfortunately, most trials of CDT or PCDT have excluded patients with cancer or have not stratified patients by type of cancer, and no prospective or retrospective studies have focused on CDT or PCDT in patients with GI cancers, specifically. In a small, single-center retrospective review of patients undergoing PCDT for iliofemoral DVT, no episodes of recurrent DVT, major bleeding, or PTS were observed in six patients with cancer and 12 patients without cancer with 3.42 month and 4.5 month mean follow-up, respectively.[68] It was noted that stenting was employed more frequently in cancer patients compared with noncancer patients in this study.[68] A larger retrospective propensity-score-matched cohort study evaluated safety of CDT plus anticoagulation versus anticoagulation alone in patients with cancer.[69] No difference was noted in in-hospital mortality (2.6% in CDT vs. 1.9% in anticoagulation alone, $p = 0.23$), but CDT was associated with increased rates of intracranial hemorrhage (1.3 vs. 0.4%, $p = 0.017$) and increased blood transfusion rates (18.6 vs. 13.1%, $p < 0.001$).[69] This observed rate of intracranial hemorrhage compared unfavorably to a rate of 0.9% in a similar retrospective study of CDT in patients without cancer.[70] Kim et al employed a distinct study design which retrospectively compared outcomes of patients treated with CDT between patients with and without cancer and found no difference in rates of complete clot lysis (66.7 vs. 64.6%, $p = 0.76$) or major bleeding (4.9 vs. 3.4%, $p = 0.69$).[71]

Based on the existing data, the Society of Interventional Radiology guidelines note that patients most likely to benefit from CDT include those with iliofemoral DVT, symptoms present for less than 14 days, good functional status, and life expectancy over 1 year with low risk of bleeding with the goals of treatment being early symptomatic benefit and reduction in the severity of PTS symptoms in the long term.[48] In patients with cancer, it is also recommended that patients undergo evaluation for brain metastases prior to CDT if there is a propensity for their cancer to spread to the central nervous system. However, the incidence of brain metastases in GI malignancies is low, ranging from 0.33% with pancreatic cancer to 4% in colorectal cancer and imaging for brain metastases is primarily guided by clinical suspicion and symptoms.[72–74]

Although there is a lack of prospective or retrospective data evaluating CDT and PCDT specifically in GI malignancies, several factors are important to consider when evaluating a patient for CDT or PCDT. Patients with GI malignancies are at higher risk of bleeding with anticoagulation,[14] thus, careful consideration and patient selection is warranted to prevent significant bleeding complications that can occur with overnight infusion of thrombolytics. Fortunately with newer advanced thrombectomy devices, it may be unnecessary to perform overnight thrombolysis and acute DVT can be treated with single-session thrombectomy, sometimes even without the use of thrombolytics (►**Fig. 1**).[75] Additionally, patients with cancer are more likely to present with iliofemoral DVT than patients without cancer,[38] which places them among a group that is more likely to benefit from CDT or PCDT.[65] These competing factors highlight the importance of an individualized approach to risk and benefit analysis for CDT and PCDT in patients with GI malignancies.

Compression Stockings

Elastic compression stockings (ECSs) have been examined as an adjunctive treatment to reduce PTS. The SOX trial was a

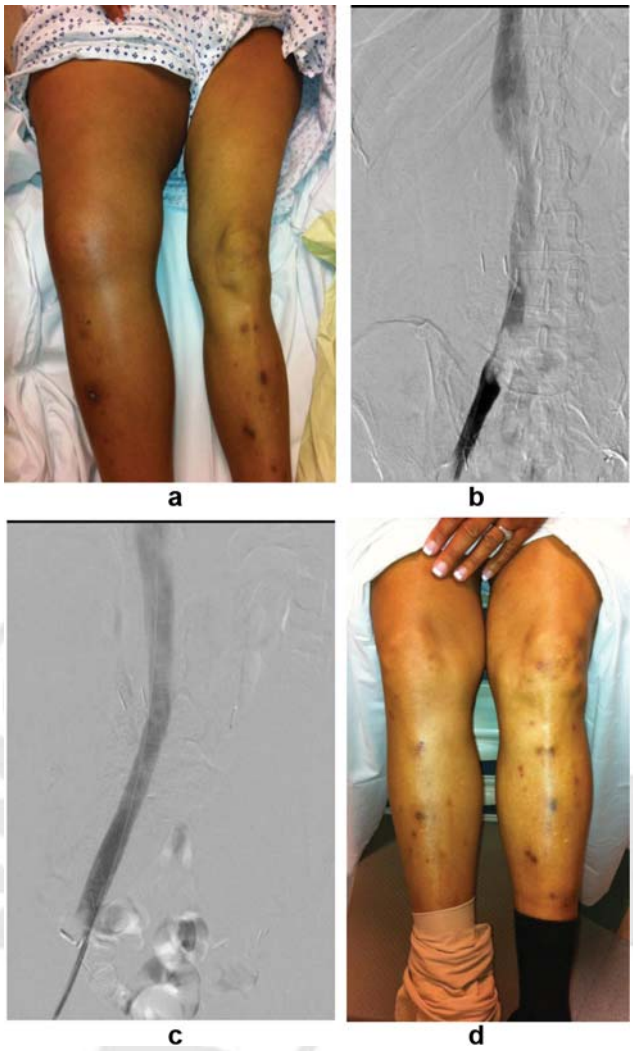


Fig. 1 Sixty-two year-old woman with metastatic colon cancer presents with acute DVT of the right common iliac vein and distal IVC. (**a**) Photograph of the right leg at presentation shows significant swelling. (**b**) Initial venogram shows occlusive thrombus in the right common iliac vein extending into the distal IVC. (**c**) CDT with mechanical thrombectomy is performed along with stent placement in the right common iliac vein. (**d**) 48 hours after the procedure, pain and swelling have nearly resolved. CDT, catheter-directed thrombolysis; DVT, deep vein thrombosis; IVC, inferior vena cava.

multicenter randomized placebo-controlled trial of 410 patients assigned to use active ECS or placebo ECS for 2 years to prevent DVT after a first proximal DVT. Although the study showed that there was no benefit of ECS in preventing PTS, several meta-analyses have suggested a reduction in the risk of PTS with the application of ECS compared with sham stockings or no stockings.[76–78] Based on these data, the American College of Chest Physicians guidelines recommend against routine use of ECS for the prevention of PTS, but note that a trial of ECS for acute or chronic symptoms associated with DVT is often justified and may provide symptomatic relief to patients.[49] Patients with GI malignancies who may have additional factors contributing to lower extremity edema including hypoalbuminemia, ascites, and venous compression by tumor may especially benefit from stockings.

Special Considerations

There are some unique and challenging VTE presentations that require distinct management. These include May–Thurner syndrome (MTS) and extrinsic iliac vein compression, IVC thrombosis, and SVT.

May–Thurner Syndrome and Extrinsic Iliac Vein Compression

MTS, often referred to as iliac vein compression syndrome, is an anatomic condition affecting over 20% of the population. In this syndrome, the left common iliac vein is compressed by the overlying right common iliac artery and predisposes to the formation of venous thrombosis. Of all lower extremity DVT cases, approximately 2 to 3% are attributable to MTS. This low occurrence rate likely reflects that only a portion of patients with the anatomic MTS develop a DVT as well as the underdiagnosis of MTS.[79] Individuals that present with left lower extremity iliofemoral DVT should be considered for evaluation of MTS as treatment involves stent placement in the left common iliac vein rather than monotherapy with anticoagulation.[79] Due to anatomic compression of the iliac vein occurring in the pelvis, US may not reliably visualize MTS and catheter venography or CT/MR venography is recommended based on clinical suspicion.[79]

In addition to the possibility of classic MTS, patients with GI malignancies, and other cancers with intra-abdominal presentations, are at risk for an analogous situation: mechanical compression of the iliac vein by extrinsic compression or invasion by tumor. In a case series of patients with iliac vein obstruction (including nine patients with extrinsic compression of the iliac vein by tumor and five patients with MTS), iliac vein stenting led to clinical patency and reduced swelling in 85% of patients at follow-up.[80] In a separate case series including 36 patients with 42% having MTS and 20% having extrinsic compression related to malignancy, patients with extrinsic compression were more likely to experience in-stent thrombosis or rethrombosis than patients with MTS in multivariate analysis.[81] A third case series corroborates this risk for stent failure. Nineteen patients with cancer and iliocaval obstructive disease with painful swelling in the lower extremities underwent iliac vein (84%) or IVC (16%) stenting with immediate technical success in 100% and immediate clinical success in 94.7%.[82] During follow-up, however, 36.8% of patients presented with recurrent limb swelling.[82] As data are derived primarily from clinical experience and case series, expert consultation should be sought when extrinsic compression of the iliac vein is identified.

Thrombosis of the Inferior Vena Cava

Acute thrombosis of the IVC occurs in 1.5% of patients hospitalized for VTE, with 37.5% of those patients having a malignancy.[83] IVC thrombosis can be secondary to congenital anomalies of the IVC, coagulopathy, pregnancy, radiation fibrosis, and malignancy.[84] In addition, patients with IVC filters are particularly prone to IVC thrombosis with a reported incidence of 2 to 30%.[61] Hepatocellular carcinoma (HCC), in particular, is among the most common malignant

causes of IVC thrombosis with one single-center series noting the presence of IVC invasion in 4% of patients with HCC undergoing chemoembolization.[85,86] In the acute setting, patients with IVC thrombosis can present with severe back pain, shortness of breath, severe bilateral leg swelling, abdominal distention, and dilation of superficial abdominal vessels.[84,87] Imaging evaluation commonly includes duplex US with confirmation by CT or MR venography.[84,87]

Management is guided by case reports and case series, but endovascular approaches with IVC stenting have been used in malignant and nonmalignant IVC thromboses with immediate symptomatic improvement in up to 93% of patients in one series of patients.[87–89] For IVC thrombosis secondary to IVC invasion by HCC in particular, local therapeutic options include surgical resection, transcatheter arterial chemoembolization, and external beam radiation therapy. These decisions are guided primarily by individual clinical scenarios, including cancer stage and multidisciplinary discussion given the paucity of comparative studies to guide management.[90,91]

Splanchnic Vein Thrombosis

SVT is defined as thrombosis of mesenteric, portal, and/or splenic veins.[92] SVT comprises up to 49.4% of VTE in patients with pancreatic cancer.[55] In addition, portal vein thrombosis occurs in up to 31% of patients with HCC.[93] In several retrospective cohort studies in patients with pancreatic cancer, SVT was discovered incidentally on abdominal imaging in 96 to 100% of cases.[55,94] Furthermore, multiple retrospective studies have established that the presence of SVT in patients with pancreatic and HCC is associated with worse OS in multivariate analysis.[55,92,93,95,96]

Decisions regarding management of SVT in patients with GI malignancy are based on the acuity of SVT.[54] Factors suggesting acute thrombosis include symptoms less than 8 weeks, lack of cavernous transformation of the portal vein, lack of collateral vein development, and lack of evidence of portal hypertension.[54] The management of acute SVT in patients with GI malignancies is based on limited retrospective analyses. One analysis based on a registry of 604 consecutive patients with SVT (22.7% with solid malignancy) found rates of major bleeding of 3.9 per 100 patient-years and rates of thrombosis of 5.6 per 100 patient-years for those on anticoagulant therapy. This is in comparison to rates of major bleeding of 1 per 100 patient-years and rates of thrombosis of 10.5 per 100 patient-years after treatment discontinuation with the highest rates of bleeding and thrombotic events occurring in patients with cirrhosis.[97] There was no difference in thrombotic outcomes in this study between patients with symptomatic SVT and incidentally discovered SVT.[97]

Additional studies have focused specifically on patients with incidentally discovered SVT. One recent retrospective cohort study identified 122 patients with pancreatic cancer and SVT and found that anticoagulant therapy did not affect mortality, but increased the risk of hemorrhage (HR: 2.7; 95% CI: 1.02–7.07). In this series, 19% of patients receiving anticoagulation experienced a major bleed compared with 8% of patients who did not receive anticoagulation.[95] The ability to fully assess the risk versus benefit ratio of anticoagulation for SVT in this cohort was difficult as recurrent thrombosis was not one of the measured outcomes.[95] In contrast, a prospective multicenter cohort study that enrolled patients (35% with malignancies) with incidentally discovered SVT found that anticoagulant treatment reduced the incidence of thrombotic events (HR: 0.85; 95% CI: 0.76–0.96) without increasing the risk of major bleeding.[98] Given the paucity of data regarding the benefit of anticoagulation in SVT, ASCO and NCCN guidelines currently recommend offering anticoagulation on a case-by-case basis after carefully considering the risks and benefits for acute SVT with the goals of preventing the development and sequelae of portal hypertension and reducing the risk of recurrent VTE.[32,54] In addition to anticoagulation, thrombectomy and/or thrombolysis is considered a rescue measure in patients who, despite anticoagulation, develop worsening abdominal pain and extension of SVT or impending/ongoing intestinal necrosis.[99]

Chronic SVT is suggested by the symptoms or presence on imaging for >8 weeks of venous collaterals and cavernous transformation of the portal vein and signs of portal hypertension.[54] Several retrospective studies have found that the presence of esophageal varices, in patients with or without cirrhosis, is independently associated with bleeding events in patients with SVT.[100,101] Based upon the increased risk of bleeding in patients with chronic SVT and portal hypertension, the NCCN guidelines recommend measures to reduce risk of esophageal variceal bleeding including prescribing a β blocker and considering esophageal variceal banding or sclerosis.[54] Anticoagulation should be considered after individualized risk and benefit assessment, understanding the increased risk of bleeding in this population.[54]

In addition to the acuity of SVT in patients with GI malignancy, attempts are also made to distinguish between bland thrombus and tumor thrombus, which represents direct extension of tumor into splanchnic veins and may or may not be accompanied by thrombosis. Recently a set of criteria including four factors assessable from MR imaging or contrast-enhanced CT and alpha-fetoprotein level were validated and demonstrated sensitivity of 100% with 94% specificity for tumor thrombus in a large retrospective cohort of patients with HCC who underwent liver transplant.[102] Presence of tumor thrombus has implications for risk and benefit assessment of anticoagulation, as lack of bland thrombus might reduce the potential benefits of anticoagulation. Presence of tumor thrombus also impacts liver transplant candidacy in patients with HCC, as macroscopic tumor invasion into the portal vein is an absolute contraindication to liver transplant due to high rates of recurrence posttransplant.[102]

Reflecting the lack of randomized data, there is significant variation in clinical practice over time and between centers regarding anticoagulation in SVT in patients with GI malignancies. One single-center retrospective study of patients with pancreatic cancer reported 10.6% of SVT events were treated with anticoagulation, while another noted 47% of events were treated with anticoagulation.[55,103]

Key Learning Points

- In comparison to noncancer patients, VTE prevalence, recurrence, and mortality rates are higher in cancer patients, and specifically, in patients with GI malignancies.[8–10,13,20,21,23]
- Ambulatory cancer patients undergoing chemotherapy who are at high risk of VTE, including patients with pancreatic and gastric cancer, can be offered prophylaxis with LMWH, rivaroxaban, or apixaban after discussing the risks and benefits.[32]
- For cancer-associated DVT, recommended anticoagulants include LMWH, rivaroxaban, edoxaban, and apixaban, though there is an increased risk of bleeding with rivaroxaban and edoxaban in patients with GI malignancies. Apixaban recently demonstrated noninferiority for recurrent VTE and major bleeding in a trial in which one-third of the patients had GI malignancies.[15,16,53,54]
- Catheter-directed thrombolysis (CDT) or pharmacomechanical CDT (PCDT) should be considered for cancer patients in which DVT is demonstrating a significant negative impact on quality of life given the observed short-term symptomatic improvement in clinical trials. The best candidates for CDT or PCDT include those with iliofemoral DVT, good performance status, presence of symptoms for less than 14 days, life expectancy greater than 1 year, and low bleeding risk.[48]
- IVC filters should not be inserted prophylactically for cancer patients unless there is a clear contraindication to systemic anticoagulation. If bleeding risk changes and patients are able to be anticoagulated, the IVC filter should be removed to avoid future complications including recurrent DVT, IVC thrombosis, and filter fracture or migration.[32,63]
- While compression stockings have not prevented postthrombotic syndrome in patients with DVT, a trial of compression stockings should be considered to improve pain and swelling. Factors associated with GI malignancies that contribute to pain and swelling can include hypoalbuminemia, ascites, iliofemoral compression, and IVC thrombosis.[49]
- Hepatocellular carcinoma is a risk factor for IVC thrombosis. Management with endovascular approaches and stenting can provide symptomatic benefit, though data are limited.[85–89]
- Up to 50% of VTE in pancreatic cancer involves the splanchnic veins and is incidental. Due to lack of clear data, anticoagulation should be offered on a case-by-case basis.[32,54,55]

Conflicts of Interest

Dr. Chapin reports no conflict of interest; Dr. P. Sudheendra reports no conflict of interest; Dr. Goity reports no conflict of interest; Dr. D. Sudheendra is a consultant for Boston Scientific, Sirtex, and Vesper Medical. Dr. D. Sudheendra reports personal fees from Boston Scientific, personal fees from Vesper Medical, personal fees from Sirtex, outside the submitted work.

References

1 Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. Lancet 2012;379(9828):1835–1846
2 Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. Am J Prev Med 2010;38 (4, Suppl):S495–S501
3 Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. Blood 2013;122(10): 1712–1723
4 Cohen AT, Katholing A, Rietbrock S, Bamber L, Martinez C. Epidemiology of first and recurrent venous thromboembolism in patients with active cancer. A population-based cohort study. Thromb Haemost 2017;117(01):57–65
5 Khalil J, Bensaid B, Elkacemi H, et al. Venous thromboembolism in cancer patients: an underestimated major health problem. World J Surg Oncol 2015;13:204
6 Ay C, Pabinger I, Cohen AT. Cancer-associated venous thromboembolism: burden, mechanisms, and management. Thromb Haemost 2017;117(02):219–230
7 Larsen AC, Dabrowski T, Frøkjær JB, et al. Prevalence of venous thromboembolism at diagnosis of upper gastrointestinal cancer. Br J Surg 2014;101(03):246–253
8 Cronin-Fenton DP, Søndergaard F, Pedersen LA, et al. Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997-2006. Br J Cancer 2010;103(07):947–953
9 Walker AJ, Card TR, West J, Crooks C, Grainge MJ. Incidence of venous thromboembolism in patients with cancer - a cohort study using linked United Kingdom databases. Eur J Cancer 2013; 49(06):1404–1413
10 Prandoni P, Lensing AWA, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002;100(10):3484–3488
11 Farge D, Trujillo-Santos J, Debourdeau P, et al; RIETE Investigators. Fatal events in cancer patients receiving anticoagulant therapy for venous thromboembolism. Medicine (Baltimore) 2015;94(32):e1235
12 Monreal M, Falgá C, Valdés M, et al; Riete Investigators. Fatal pulmonary embolism and fatal bleeding in cancer patients with venous thromboembolism: findings from the RIETE registry. J Thromb Haemost 2006;4(09):1950–1956
13 Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG, Büller HR. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. J Clin Oncol 2000;18(17):3078–3083
14 Zakai NA, Walker RF, MacLehose RF, Adam TJ, Alonso A, Lutsey PL. Impact of anticoagulant choice on hospitalized bleeding risk when treating cancer-associated venous thromboembolism. J Thromb Haemost 2018;16(12):2403–2412
15 Raskob GE, van Es N, Verhamme P, et al; Hokusai VTE Cancer Investigators. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018;378(07):615–624
16 Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clin Oncol 2018;36(20): 2017–2023
17 Lee JH, Oh YM, Lee SD, Lee JS. Rivaroxaban versus low-molecular-weight heparin for venous thromboembolism in gastrointestinal and pancreatobiliary cancer. J Korean Med Sci 2019;34 (21):e160
18 Recio-Boiles A, Veeravelli S, Vondrak J, et al. Evaluation of the safety and effectiveness of direct oral anticoagulants and low molecular weight heparin in gastrointestinal cancer-associated venous thromboembolism. World J Gastrointest Oncol 2019;11 (10):866–876

19 Kim JH, Seo S, Kim K-P, et al. Rivaroxaban *versus* low-molecular-weight heparin for venous thromboembolism in advanced upper gastrointestinal tract and hepatopancreatobiliary cancer. In Vivo 2020;34(02):829–837
20 Douketis JD, Crowther MA, Foster GA, Ginsberg JS. Does the location of thrombosis determine the risk of disease recurrence in patients with proximal deep vein thrombosis? Am J Med 2001; 110(07):515–519
21 Sørensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. N Engl J Med 2000;343(25):1846–1850
22 Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 2007;5 (03):632–634
23 Font C, Carmona-Bayonas A, Beato C, et al; Asociación para la Investigación de la Enfermedad Tromboembólica de la región de Murcia. Clinical features and short-term outcomes of cancer patients with suspected and unsuspected pulmonary embolism: the EPIPHANY study. Eur Respir J 2017;49(01):1600282
24 Agnelli G, Gussoni G, Bianchini C, et al; PROTECHT Investigators. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. Lancet Oncol 2009;10(10):943–949
25 Agnelli G, George DJ, Kakkar AK, et al; SAVE-ONCO Investigators. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. N Engl J Med 2012;366(07):601–609
26 Maraveyas A, Waters J, Roy R, et al. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. Eur J Cancer 2012;48(09):1283–1292
27 Pelzer U, Opitz B, Deutschinoff G, et al. Efficacy of prophylactic low-molecular weight heparin for ambulatory patients with advanced pancreatic cancer: outcomes from the CONKO-004 trial. J Clin Oncol 2015;33(18):2028–2034
28 Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008;111(10):4902–4907
29 Ay C, Dunkler D, Marosi C, et al. Prediction of venous thromboembolism in cancer patients. Blood 2010;116(24):5377–5382
30 Carrier M, Abou-Nassar K, Mallick R, et al; AVERT Investigators. Apixaban to prevent venous thromboembolism in patients with cancer. N Engl J Med 2019;380(08):711–719
31 Khorana AA, Soff GA, Kakkar AK, et al; CASSINI Investigators. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. N Engl J Med 2019;380(08):720–728
32 Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol 2020;38(05):496–520
33 Park DY, Khorana AA. Risks and benefits of anticoagulation in cancer and noncancer patients. Semin Thromb Hemost 2019;45 (06):629–637
34 Kraft C, Hecking C, Schwonberg J, Schindewolf M, Lindhoff-Last E, Linnemann B. Patients with inferior vena cava thrombosis frequently present with lower back pain and bilateral lower-extremity deep vein thrombosis. Vasa 2013;42(04):275–283
35 Kumar S, Sarr MG, Kamath PS. Mesenteric venous thrombosis. N Engl J Med 2001;345(23):1683–1688
36 Moore RA, Adel N, Riedel E, et al. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. J Clin Oncol 2011;29(25): 3466–3473
37 Singh R, Sousou T, Mohile S, Khorana AA. High rates of symptomatic and incidental thromboembolic events in gastrointestinal cancer patients. J Thromb Haemost 2010;8(08):1879–1881
38 Imberti D, Agnelli G, Ageno W, et al; MASTER Investigators. Clinical characteristics and management of cancer-associated acute venous thromboembolism: findings from the MASTER Registry. Haematologica 2008;93(02):273–278
39 Wells PS, Ihaddadene R, Reilly A, Forgie MA. Diagnosis of venous thromboembolism: 20 years of progress. Ann Intern Med 2018; 168(02):131–140
40 Le Gal G, Righini M, Roy P-M, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med 2006;144(03):165–171
41 Wells PS, Hirsh J, Anderson DR, et al. Accuracy of clinical assessment of deep-vein thrombosis. Lancet 1995;345(8961):1326–1330
42 van Es N, van der Hulle T, van Es J, et al. PO-07 - Excluding pulmonary embolism in cancer patients using the Wells rule and age-adjusted D-dimer testing: an individual patient data meta-analysis. Thromb Res 2016;140(Suppl 1):S179
43 Wilts IT, Le Gal G, Den Exter PL, et al. Performance of the age-adjusted cut-off for D-dimer in patients with cancer and suspected pulmonary embolism. Thromb Res 2017;152:49–51
44 Johnson SA, Stevens SM, Woller SC, et al. Risk of deep vein thrombosis following a single negative whole-leg compression ultrasound: a systematic review and meta-analysis. JAMA 2010; 303(05):438–445
45 Bhatt M, Braun C, Patel P, et al. Diagnosis of deep vein thrombosis of the lower extremity: a systematic review and meta-analysis of test accuracy. Blood Adv 2020;4(07):1250–1264
46 Hayashino Y, Goto M, Noguchi Y, Fukui T. Ventilation-perfusion scanning and helical CT in suspected pulmonary embolism: meta-analysis of diagnostic performance. Radiology 2005;234 (03):740–748
47 van der Hulle T, van Es N, den Exter PL, et al. Is a normal computed tomography pulmonary angiography safe to rule out acute pulmonary embolism in patients with a likely clinical probability? A patient-level meta-analysis. Thromb Haemost 2017;117(08):1622–1629
48 Vedantham S, Sista AK, Klein SJ, et al; Society of Interventional Radiology and Cardiovascular and Interventional Radiological Society of Europe Standards of Practice Committees. Quality improvement guidelines for the treatment of lower-extremity deep vein thrombosis with use of endovascular thrombus removal. J Vasc Interv Radiol 2014;25(09):1317–1325
49 Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016; 149(02):315–352
50 Kearon C. Natural history of venous thromboembolism. Circulation 2003;107(23, Suppl 1):I22–I30
51 Kahale LA, Hakoum MB, Tsolakian IG, et al. Anticoagulation for the long-term treatment of venous thromboembolism in people with cancer. Cochrane Database Syst Rev 2018;6:CD006650
52 Posch F, Königsbrügge O, Zielinski C, Pabinger I, Ay C. Treatment of venous thromboembolism in patients with cancer: a network meta-analysis comparing efficacy and safety of anticoagulants. Thromb Res 2015;136(03):582–589
53 Agnelli G, Becattini C, Meyer G, et al; Caravaggio Investigators. Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med 2020;382(17):1599–1607
54 National Comprehensive Cancer Network. Cancer-associated venous thromboembolic disease (Version 1.2020). Available at: https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf. Accessed May 10, 2020
55 Menapace LA, Peterson DR, Berry A, Sousou T, Khorana AA. Symptomatic and incidental thromboembolism are both associated with mortality in pancreatic cancer. Thromb Haemost 2011; 106(02):371–378
56 den Exter PL, Hooijer J, Dekkers OM, Huisman MV. Risk of recurrent venous thromboembolism and mortality in patients with cancer incidentally diagnosed with pulmonary embolism: a comparison with symptomatic patients. J Clin Oncol 2011;29 (17):2405–2409

57 Lyman GH, Khorana AA, Kuderer NM, et al; American Society of Clinical Oncology Clinical Practice. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2013;31(17):2189–2204

58 Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prévention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. N Engl J Med 1998;338(07):409–415

59 Muriel A, Jiménez D, Aujesky D, et al; RIETE Investigators. Survival effects of inferior vena cava filter in patients with acute symptomatic venous thromboembolism and a significant bleeding risk. J Am Coll Cardiol 2014;63(16): 1675–1683

60 Brunson A, Ho G, White R, Wun T. Inferior vena cava filters in patients with cancer and venous thromboembolism (VTE) does not improve clinical outcomes: a population-based study. Thromb Res 2017;153:57–64

61 Grewal S, Chamarthy MR, Kalva SP. Complications of inferior vena cava filters. Cardiovasc Diagn Ther 2016;6(06):632–641

62 Martin MJ, Blair KS, Curry TK, Singh N. Vena cava filters: current concepts and controversies for the surgeon. Curr Probl Surg 2010;47(07):524–618

63 Health C for D and R. Safety Communications - Removing Retrievable Inferior Vena Cava Filters. FDA safety communication. Available at: https://wayback.archive-it.org/7993/20170111070016/http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm396377.htm. Accessed April 30, 2020

64 Kahn SR, Shbaklo H, Lamping DL, et al. Determinants of health-related quality of life during the 2 years following deep vein thrombosis. J Thromb Haemost 2008;6(07):1105–1112

65 Vedantham S, Goldhaber SZ, Julian JA, et al; ATTRACT Trial Investigators. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. N Engl J Med 2017;377(23): 2240–2252

66 Kahn SR, Julian JA, Kearon C, et al; ATTRACT Trial Investigators. Quality of life after pharmacomechanical catheter-directed thrombolysis for proximal deep venous thrombosis. J Vasc Surg Venous Lymphat Disord 2020;8(01):8.e18–23.e18

67 Comerota AJ, Kearon C, Gu C-S, et al; ATTRACT Trial Investigators. Endovascular thrombus removal for acute iliofemoral deep vein thrombosis. Circulation 2019;139(09):1162–1173

68 Yoon WJ, Halandras P, Aulivola B, Crisostomo P. Malignancy does not affect outcomes of pharmacomechanical thrombolysis in acute symptomatic iliofemoral deep vein thrombosis. Ann Vasc Surg 2018;51:234–238

69 Brailovsky Y, Yeung H-M, Lakhter V, Zack CJ, Zhao H, Bashir R. In-hospital outcomes of catheter-directed thrombolysis versus anticoagulation in cancer patients with proximal deep venous thrombosis. J Vasc Surg Venous Lymphat Disord 2020;8(04):538.e3–544.e3

70 Bashir R, Zack CJ, Zhao H, Comerota AJ, Bove AA. Comparative outcomes of catheter-directed thrombolysis plus anticoagulation vs anticoagulation alone to treat lower-extremity proximal deep vein thrombosis. JAMA Intern Med 2014;174(09): 1494–1501

71 Kim HS, Preece SR, Black JH, Pham LD, Streiff MB. Safety of catheter-directed thrombolysis for deep venous thrombosis in cancer patients. J Vasc Surg 2008;47(02):388–394

72 Park K-S, Kim M, Park S-H, Lee K-W. Nervous system involvement by pancreatic cancer. J Neurooncol 2003;63(03):313–316

73 Cascino TL, Leavengood JM, Kemeny N, Posner JB. Brain metastases from colon cancer. J Neurooncol 1983;1(03):203–209

74 Lin L, Zhao C-H, Ge F-J, et al. Patients with brain metastases derived from gastrointestinal cancer: clinical characteristics and prognostic factors. Clin Transl Oncol 2016;18(01):93–98

75 Crowner JR, Marston W. Percutaneous thrombectomy using a novel single-session device for acute ilio-caval deep vein thrombosis. J Vasc Surg Cases Innov Tech 2019;5(03):302–304

76 Kahn SR, Shapiro S, Wells PS, et al; SOX trial investigators. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. Lancet 2014;383(9920):880–888

77 Appelen D, van Loo E, Prins MH, Neumann MH, Kolbach DN. Compression therapy for prevention of post-thrombotic syndrome. Cochrane Database Syst Rev 2017;9:CD004174

78 Avila ML, Montoya M, Lumia C, Marson A, Brandão LR, Tomlinson G. Compression stockings to prevent post-thrombotic syndrome in adults, a Bayesian meta-analysis. Thromb Res 2019;182:20–26

79 Peters M, Syed RK, Katz M, et al. May-Thurner syndrome: a not so uncommon cause of a common condition. Proc Bayl Univ Med Cent 2012;25(03):231–233

80 O'Sullivan GJ, Sheehan J, Lohan D, McCann-Brown JA. Iliofemoral venous stenting extending into the femoral region: initial clinical experience with the purpose-designed Zilver Vena stent. J Cardiovasc Surg (Torino) 2013;54(02):255–261

81 Titus JM, Moise MA, Bena J, Lyden SP, Clair DG. Iliofemoral stenting for venous occlusive disease. J Vasc Surg 2011;53(03): 706–712

82 Maleux G, Vertenten B, Laenen A, et al. Palliative endovascular treatment of cancer-related iliocaval obstructive disease: technical and clinical outcomes. Acta Radiol 2016;57(04):451–456

83 Stein PD, Matta F, Yaekoub AY. Incidence of vena cava thrombosis in the United States. Am J Cardiol 2008;102(07):927–929

84 Linnemann B, Schmidt H, Schindewolf M, et al. Etiology and VTE risk factor distribution in patients with inferior vena cava thrombosis. Thromb Res 2008;123(01):72–78

85 Lee IJ, Chung JW, Kim H-C, et al. Extrahepatic collateral artery supply to the tumor thrombi of hepatocellular carcinoma invading inferior vena cava: the prevalence and determinant factors. J Vasc Interv Radiol 2009;20(01):22–29

86 Shapero KS, Jelani Q-U-A, Mena C. Endovascular treatment of inferior vena cava thrombosis in metastatic malignancy: a case report and review of literature. Vasc Endovascular Surg 2019;53 (06):507–511

87 McAree BJ, O'Donnell ME, Fitzmaurice GJ, Reid JA, Spence RA, Lee B. Inferior vena cava thrombosis: a review of current practice. Vasc Med 2013;18(01):32–43

88 Wallace MJ. Transatrial stent placement for treatment of inferior vena cava obstruction secondary to extension of intracardiac tumor thrombus from hepatocellular carcinoma. J Vasc Interv Radiol 2003;14(10):1339–1343

89 Razavi MK, Hansch EC, Kee ST, Sze DY, Semba CP, Dake MD. Chronically occluded inferior venae cavae: endovascular treatment. Radiology 2000;214(01):133–138

90 Chen Z-H, Zhang X-P, Wang K, et al. Liver resection versus transcatheter arterial chemoembolization for the treatment of patients with hepatocellular carcinoma and hepatic vein or inferior vena cava tumor thrombus: a propensity score matching analysis. Hepatol Res 2019;49(04):441–452

91 Rim CH, Kim CY, Yang DS, Yoon WS. External beam radiation therapy to hepatocellular carcinoma involving inferior vena cava and/or right atrium: a meta-analysis and systemic review. Radiother Oncol 2018;129(01):123–129

92 Søgaard KK, Darvalics B, Horváth-Puhó E, Sørensen HT. Survival after splanchnic vein thrombosis: a 20-year nationwide cohort study. Thromb Res 2016;141:1–7

93 Connolly GC, Chen R, Hyrien O, et al. Incidence, risk factors and consequences of portal vein and systemic thromboses in hepatocellular carcinoma. Thromb Res 2008;122(03):299–306

94 Pachón Olmos V, Garcia Adrian S, Cavanagh Podesta M, et al. Splanchnic vein thrombosis in ambulatory pancreatic cancer patients receiving chemotherapy. J Clin Oncol 2015;33 (15_suppl):e20658

95 Afzal A, Suhong L, Gage BF, et al. Splanchnic vein thrombosis predicts worse survival in patients with advanced pancreatic cancer. Thromb Res 2020;185:125–131
96 Cabibbo G, Enea M, Attanasio M, Bruix J, Craxì A, Cammà C. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. Hepatology 2010;51(04):1274–1283
97 Ageno W, Riva N, Schulman S, et al. Long-term clinical outcomes of splanchnic vein thrombosis: results of an international registry. JAMA Intern Med 2015;175(09):1474–1480
98 Riva N, Ageno W, Schulman S, et al; International Registry on Splanchnic Vein Thrombosis (IRSVT) study group. Clinical history and antithrombotic treatment of incidentally detected splanchnic vein thrombosis: a multicentre, international prospective registry. Lancet Haematol 2016;3(06):e267–e275
99 Sharma AM, Zhu D, Henry Z. Portal vein thrombosis: When to treat and how? Vasc Med 2016;21(01):61–69
100 Condat B, Pessione F, Hillaire S, et al. Current outcome of portal vein thrombosis in adults: risk and benefit of anticoagulant therapy. Gastroenterology 2001;120(02):490–497
101 Thatipelli MR, McBane RD, Hodge DO, Wysokinski WE. Survival and recurrence in patients with splanchnic vein thromboses. Clin Gastroenterol Hepatol 2010;8(02):200–205
102 Sherman CB, Behr S, Dodge JL, Roberts JP, Yao FY, Mehta N. Distinguishing tumor from bland portal vein thrombus in liver transplant candidates with hepatocellular carcinoma: the A-VENA criteria. Liver Transpl 2019;25(02):207–216
103 Mier-Hicks A, Raj M, Do RK, et al. Incidence, management, and implications of visceral thrombosis in pancreatic ductal adenocarcinoma. Clin Colorectal Cancer 2018;17(02):121–128

THIEME