

# Venous Emergencies in Cancer Patients

Endovascular approaches for managing and treating emergent conditions.

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An association between venous thrombosis and malignancy is well established, with the first description of this phenomenon occurring in 1823.<sup>1</sup> Malignancy is associated with a significantly increased risk of venous thrombosis, with relative risk estimates ranging from 4 to 7.<sup>1</sup> In a large study that examined more than 3,000 cancer patients, malignancy was seen to increase the risk of venous thrombosis sevenfold (odds ratio, 6.7).<sup>2</sup> Venous thrombosis risk in this study was particularly high in patients with distant metastasis, factor V Leiden, or prothrombin 20210A mutation, as well as in the first few months after cancer diagnosis. Cancer stage significantly influences the likelihood of thrombosis, with an adjusted relative risk of 2.9 and 17.1 in stage 1 and 4 disease, respectively.<sup>3</sup> The level of risk also relates to malignancy type, with the highest incidence of thrombosis seen in patients with brain, pancreatic, lung, and ovarian cancer.<sup>1</sup>

Venous thrombosis in the setting of malignancy can be associated with a number of emergent medical conditions. These conditions include massive and submassive pulmonary embolism, superior vena cava (SVC) syndrome, phlegmasia cerulea dolens (PCD), and large vessel thrombosis. In this article, we examine the diagnosis and treatment of these emergent conditions, with a focus on the latest options for endovascular intervention.

## PULMONARY EMBOLISM

Pulmonary embolism (PE) is responsible for approximately 300,000 deaths annually, with 20% of these deaths seen in cancer patients, and a greater than threefold increase in cancer mortality when PE develops.<sup>4</sup> Venous thromboembolism is seen most frequently in patients with breast, colon, and lung cancer, although when adjusted for disease prevalence, the highest risk is seen in brain, pancreas, and ovarian cancer.<sup>5</sup> Cancer and chemotherapy both increase the risk of venous

thrombosis, with risk increasing by a factor of 4.1 and 6.5, respectively.<sup>5</sup> Additional risk factors for venous thromboembolism include immobilization, surgery, age, and hereditary thrombophilia—factors that can further compound risk in cancer patients.

Appropriate management of PE is based on careful risk stratification.<sup>6</sup> If a PE patient presents with hemodynamic shock, a high-risk or massive PE is diagnosed (> 15% 30-day mortality risk), and urgent treatment is required. For hemodynamically stable patients, systems such as the Hestia decision rule and Pulmonary Embolism Severity Index (PESI) can be used for further stratification into low-risk (< 1% 30-day mortality risk) and intermediate-risk (3%–15%) groups, which may help to guide management. Additional risk information is provided by laboratory tests (brain natriuretic peptide, N-terminal pro-brain natriuretic peptide) and imaging studies (echocardiography, CT angiography) that can indicate right ventricular strain. Patients with submassive PE, defined as a PE-causing right heart strain without hemodynamic compromise, are also at a higher risk of mortality.

A number of endovascular approaches can be used to treat PE.<sup>7</sup> Patients with massive PE require emergent debulking of obstructive pulmonary arterial thrombus. At this time, we continue to favor the administration of systemic doses of tissue plasminogen activator (tPA) intravenously (50–100 mg), so as to not delay definitive treatment. In patients with a contraindication to systemic doses of thrombolytics, pharmacomechanical thrombolysis and thrombectomy can be utilized with reported clinical success in 86% of cases, and a major complication rate of only 2.4%.<sup>7</sup> These techniques typically involve a combination of local infusion of a low-dose thrombolytic agent and catheter-directed mechanical fragmentation or aspiration. Various thrombectomy devices have also shown potential in treating

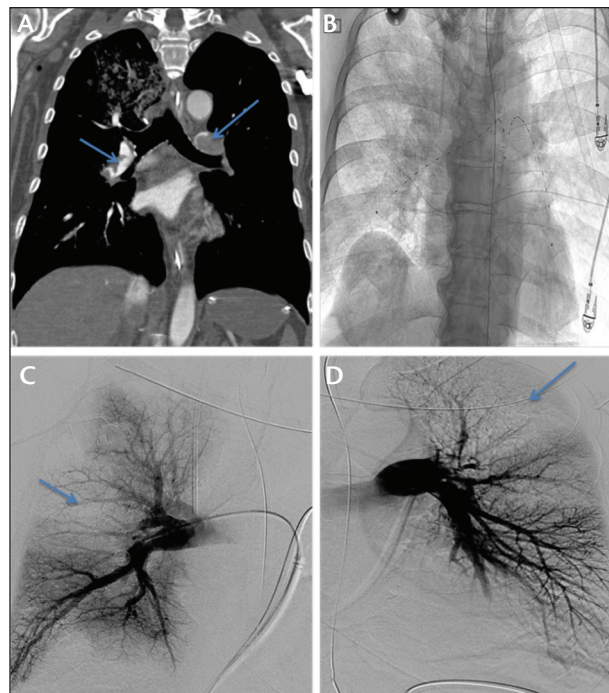
PE, although the available data are limited. Of note, the AngioJet Rheolytic Thrombectomy (ART) system (Boston Scientific Corporation) carries a black box warning for use in the pulmonary arteries. At this time, no particular mechanical device has demonstrated clinical superiority, and there is room in this area for more optimal device development.

There is a growing body of evidence supporting escalated treatment of submassive PE with catheter-directed thrombolysis. Local thrombolysis appears to offer greater benefit when performed intraclot, rather than proximal to the embolus. A technology with promise is ultrasound-assisted, catheter-directed thrombolysis, which uses microsonic energy to increase clot permeability and the availability of binding sites during thrombolytic infusion, potentially reducing thrombolytic dose and infusion time.<sup>8</sup> Low-dose thrombolytic infusion directly into pulmonary artery thrombus using the EkoSonic Endovascular System (Ekos Corporation, a BTG International group company) has demonstrated early decrease in right heart strain, in comparison to anticoagulation alone.<sup>9</sup> This technology is now US Food and Drug Administration approved for the treatment of PE. An example of treatment using the Ekos system is illustrated in Figure 1.

### SUPERIOR VENA CAVA SYNDROME

SVC syndrome is a clinical syndrome developing as a result of obstruction of the SVC or bilateral brachiocephalic veins.<sup>10</sup> Although a large number of cases are due to stenosis resulting from chronic indwelling catheters and pacemaker leads, malignant etiologies are often a factor in acute-onset disease. The highest rates are seen in patients with bronchogenic cancer, Hodgkin lymphoma, and metastatic disease.<sup>10</sup> Malignant etiologies can be due to extrinsic compression of the SVC by surrounding tumor or, less commonly, SVC thrombosis secondary to a hypercoagulable malignant state.

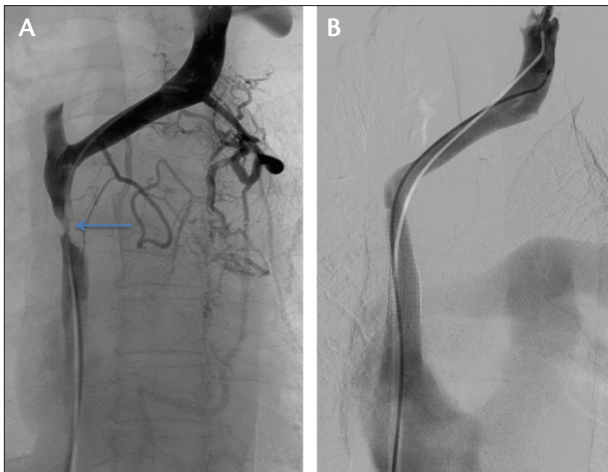
Diagnosis of SVC syndrome is based primarily on history and physical examination, with common clinical findings including facial/neck swelling (82%), distended neck veins (63%), shortness of breath (54%), distended superficial chest veins (53%), and upper extremity swelling (46%).<sup>10</sup> A critical component of SVC syndrome evaluation is determining whether the upper venous pressures are elevated in a life-threatening manner. Emergent manifestations of SVC syndrome include airway compromise secondary to laryngeal/bronchial edema, and coma secondary to cerebral edema.<sup>11</sup> A useful tool in this assessment is the Kishi score, which uses clinical information to create an objective index of SVC syndrome severity.<sup>12</sup> Imaging work-up for SVC



**Figure 1.** A 67-year-old man with a history of melanoma and pancreatic adenocarcinoma presented with hypotension after cardiac arrest. On CT angiography, the patient was found to have a large bilateral PE (arrows, A) with evidence of right heart strain. Systemic dosing of intravenous tPA was contraindicated due to recent gastrointestinal bleeding. Given the patient's hypotension and hemodynamic instability, endovascular therapy was pursued. Right and left Ekos lysis catheters (Ekos Corporation) were placed (B) with local infusion of tPA at 1 mg/h and continued pulmonary artery pressure monitoring. After 2 days of treatment, a lysis check was performed with bilateral pulmonary angiography and suction thrombectomy. On angiography, the patient was found to have a significantly reduced thrombus burden, although small areas of residual thrombus remained (arrows, C, D). In addition, the patient's pulmonary arterial pressure was improved, and hemodynamic stability was established. The Ekos catheters were removed, and the patient was continued on intravenous heparin.

syndrome includes CT or MR angiography to evaluate vascular patency, ultrasound of the neck and arm vasculature to detect thrombus, and in some cases, positron emission tomography/CT to determine if SVC syndrome relates to malignant tumor.<sup>10</sup> Conventional venography remains the gold standard for evaluation of SVC stenosis or occlusion, and it is performed as a prelude to stenting or other interventional therapies.<sup>11</sup>

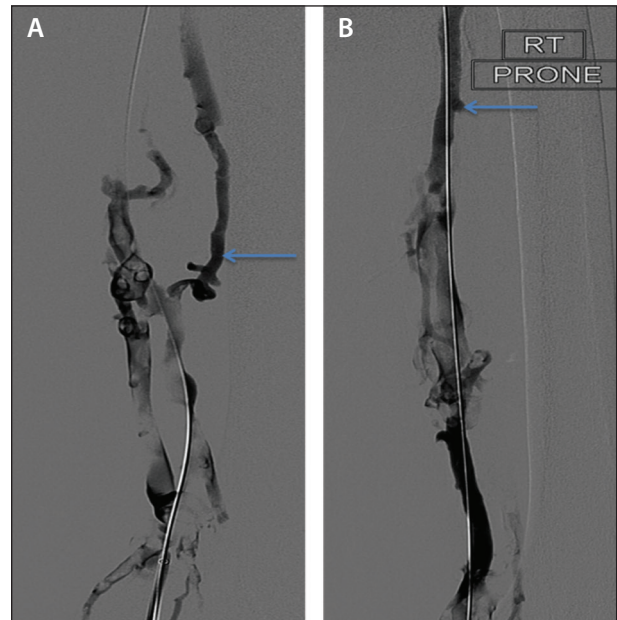
The appropriate management of SVC syndrome relates to the clinical signs and symptoms seen at the



**Figure 2.** A 62-year-old man with a history of metastatic non-small cell lung cancer presented with acute dyspnea and swelling of the face and right upper extremity. On CT imaging (not shown), the patient was seen to have compression of the SVC secondary to mediastinal lymphadenopathy and a large right paratracheal mass. The initial venogram demonstrated high-grade narrowing of the midportion of the SVC (arrow, A) with collateral vessel formation. A 13-mm X 5-cm Gore Viabahn stent (Gore & Associates) was placed across the narrowed midportion of the SVC, resulting in excellent restoration of flow (B). The patient's symptoms improved within hours. He was discharged shortly after the procedure on enoxaparin, with treatment planned for a minimum of 3 months.

time of presentation. If there is evidence of severe or life-threatening disease, emergent endovascular interventional treatment is indicated.<sup>10</sup> In cases of nonemergent malignancy-related SVC syndrome, therapies include treatment of the obstructing tumor with chemotherapy and radiation, systemic steroids to reduce tumor burden and edema, and empiric anticoagulation given the frequency of concomitant thrombosis.<sup>10</sup>

Various endovascular approaches have shown utility in the treatment of SVC syndrome.<sup>10</sup> If venography suggests acute thrombus, benefits have been seen with low-dose thrombolytic infusion over 24 to 48 hours, with favorable outcomes seen for both urokinase and recombinant tPA. Mechanical thrombectomy may also be appropriate in select cases of significant, focal thrombosis. Following these approaches, residual SVC stenosis or occlusion can be treated with angioplasty or stenting, with stenting generally recommended in the setting of malignant venous compression. Complications of stenting include in-stent thrombosis or restenosis and, less commonly, stent migration, embolization, or infection. After successful stent decompression of SVC occlusion, we do not regularly anticoagulate patients unless there

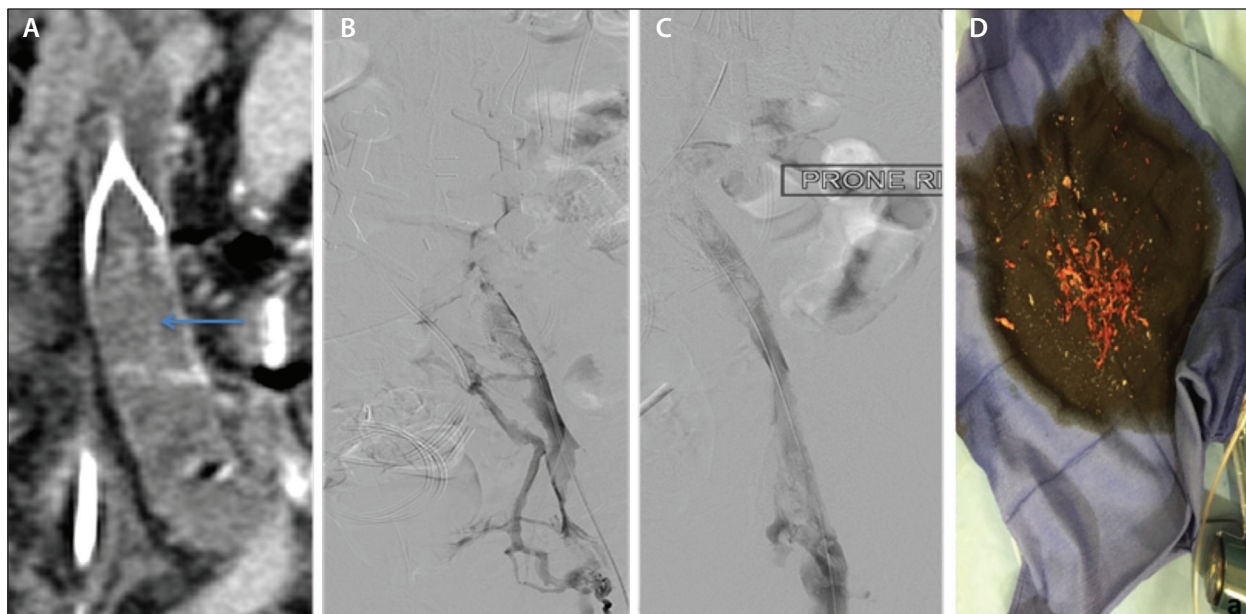


**Figure 3.** A 67-year-old man with a history of metastatic pancreatic adenocarcinoma presented with acute pain, swelling, and discoloration of the right lower extremity. On duplex ultrasonography, the patient was found to have venous thrombus extending from the right common femoral vein to the popliteal vein. The clinical and imaging features were consistent with PCD. On venography, venous collaterals were seen with loss of inline flow (A). Given that he had recent embolization of a splenic artery aneurysm, the patient was deemed unsuitable for thrombolysis. Treatment was performed using angioplasty and AngioJet thrombectomy of the right popliteal, femoral, and common femoral veins. This therapy resulted in decreased thrombus burden and appropriate antegrade flow (arrow, B). After inpatient monitoring, the patient was discharged with clinical improvement on apixaban anticoagulation. He was also given a compression stocking and instructions for mobilization.

is concurrent venous thrombosis. Thanks to advances in endovascular therapy, surgical bypass grafting is rarely utilized in our institution. An example of the endovascular treatment of SVC syndrome is seen in Figure 2.

### PHLEGMASIA CERULEA DOLENS

PCD is a severe venous thrombosis associated with venous gangrene if not urgently treated, with death and amputation rates of 25% to 40% and 20% to 50%, respectively.<sup>13</sup> The clinical triad of PCD includes acute ischemic pain, limb swelling, and blue/purple discoloration. Death can result from large-volume fluid sequestration causing shock, or from gangrene and sepsis. The most common risk factor for PCD is malignancy (which is seen in one-third of PCD patients), followed by



**Figure 4.** A 63-year-old man presented with bilateral lower extremity swelling 2 weeks after a cystoprostatectomy for bladder cancer. On CT venography, the patient was found to have thrombus extending from the suprarenal IVC to the calves (A, displays a portion of the IVC thrombus). The venogram demonstrated venous collaterals with thrombus and loss of inline flow (B). Ekos lysis infusion catheters were placed bilaterally, extending from the superficial femoral vein popliteal junction to the juxtarenal IVC above a previously placed IVC filter. tPA was infused for approximately 24 hours via the Ekos catheters (0.2 mg/h) in conjunction with heparin at 100 units/h. Lytic infusion was terminated due to hematuria during thrombolysis, and the patient was treated with mechanical thrombectomy of the bilateral ilio caval and right femoral thrombus using a Penumbra Indigo CAT 8 aspiration catheter and bilateral iliac angioplasty. On venography after this intervention, the patient was found to have a significant reduction in thrombus burden with reestablishment of antegrade flow through the bilateral legs into the IVC (C). A significant volume of thrombus was extracted (D). The patient improved clinically and was discharged after a heparin bridge to oral anticoagulation.

hypercoagulability, venous stasis, and use of contraceptive agents. Diagnosis is performed using a combination of clinical and imaging data, with duplex ultrasound providing the most rapid and effective noninvasive diagnosis. Supplemental imaging with CT or MR venography can be used to better delineate the extent and potentially the cause of thrombosis.

There are no validated treatment algorithms for the management of PCD, and a variety of approaches are used.<sup>13</sup> Therapy generally consists of anticoagulation with intravenous heparin coupled with surgery, endovascular therapy, or a combined endovascular/surgical approach. Surgical therapy may be necessary for patients with high-grade PCD, which is characterized by venous gangrene or impending venous gangrene. There is some general agreement that the most appropriate initial endovascular therapy for PCD is catheter-directed thrombolysis. Additional useful endovascular approaches include percutaneous mechanical thrombectomy, aspiration, angioplasty, and stenting. Given that these

therapies can result in embolism of macerated or displaced thrombus, some investigators recommend placement of an inferior vena cava (IVC) filter prior to initiating treatment. Further research is needed to clarify the optimal endovascular and surgical management of PCD. An example case of PCD treated using endovascular therapy is seen in Figure 3.

### LARGE VESSEL THROMBOSIS

Another complication of malignancy is obstruction and thrombosis of large vessels, including the portal vein and IVC. Of cancer patients developing deep vein thrombosis (DVT), 43% have involvement of a major central vein.<sup>14</sup> This entity is of particular concern because acute IVC thrombus is associated with increased risk of fatal PE despite anticoagulation, extension of thrombus into the renal veins causing renal failure, and venous gangrene.<sup>15</sup> IVC thrombosis is seen in 2% to 26% of patients with iliofemoral DVT, and most commonly results from extension of pelvic or iliofemoral thrombus. Although extensive ilio-

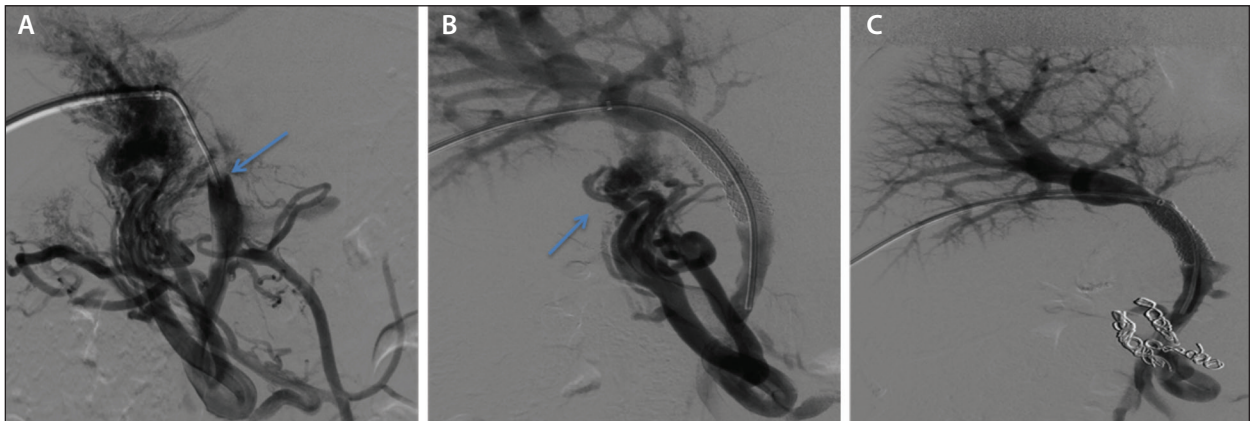
caval thrombosis previously necessitated surgical thrombectomy, a number of endovascular approaches are now possible.<sup>15</sup> Catheter-directed thrombolytic therapy is now generally employed in both acute and chronic caval thrombosis. In our practice, we frequently used EKOS. After thrombolysis of an acute clot, a combination of mechanical techniques (typically involving angioplasty and occasionally stenting) are utilized to disrupt residual chronic thrombus and dilate venous strictures. New-generation mechanical thrombectomy devices with large radial reach (ie, AngioVac [AngioDynamics, Inc.] and Penumbra Indigo CAT 8 [Penumbra, Inc.]) have demonstrated an emerging role in extraction of large volumes of clot, particularly in patients with a contraindication to thrombolysis. Figure 4 illustrates the endovascular treatment of IVC thrombus using a case seen at our institution.

Portal vein obstruction in malignancy can relate to either portal vein compression by extrinsic tumor or portal vein thrombosis. Cancer, commonly liver or pancreatic cancer, is responsible for 21% to 24% of portal vein thrombosis cases.<sup>16</sup> Mechanisms of cancer-related portal vein thrombosis include invasion of the vasculature by surrounding tumor, vessel compression secondary to tumor, or thrombosis secondary to a hypercoagulable

state. Acute portal vein thrombosis can result in a number of emergent complications, including bowel ischemia, rectal bleeding, and intestinal perforation with peritonitis, shock, and death. Diagnosis is made using contrast-enhanced CT or, if CT is unavailable, Doppler sonography. A number of endovascular therapies have shown utility in treating portal vein thrombosis/occlusion, including transjugular or transhepatic catheter-directed thrombolysis, angioplasty, and stenting.<sup>17</sup> In selected cases, transjugular intrahepatic, portosystemic shunts (TIPS) may be used. An example case employing these techniques is seen in Figure 5.

## CONCLUSION

Malignancy is associated with a variety of emergent venous conditions, including PE, SVC syndrome, PCD, and large vessel thrombosis. Endovascular therapies can be both life saving and palliative in these conditions and are well-tolerated by patients with significant medical comorbidities. Additional data are needed to determine the optimal endovascular approach to treating most of these conditions. A number of developing technologies show great potential, including ultrasound-assisted thrombolysis and the recently introduced thrombus aspiration devices. With further



**Figure 5.** A 36-year-old woman with a history of metastatic cholangiocarcinoma undergoing the Whipple procedure and adjuvant chemotherapy/radiation presented with a gastrointestinal bleed. Mesenteric angiography was performed to evaluate the source of the bleeding, and although no arterial bleeding was identified, there was evidence of portal vein obstruction. Given the concern for GI bleed secondary to bowel varices resulting from portal vein obstruction, further evaluation with a transhepatic portal venogram was performed. This examination revealed high-grade stenosis versus occlusion of the portal vein due to extrinsic compression by a porta hepatis tumor (A). In addition, numerous superior mesenteric varices were seen extending along the hepatobiliary limb of the Roux-en-Y and draining into the portal venous system. Treatment was performed with placement of a 7-mm X 38-mm iCAST covered stent (Atrium Medical Corporation) in the main portal vein, with expansion using a 10-mm angioplasty balloon (B). In addition, coil embolization of three large mesenteric varices was performed. After this treatment, there was significant improvement in flow through the portal system and elimination of blood flow through the mesenteric varices (C). The patient was discharged shortly after the procedure, with resolved gastrointestinal bleeding and sustained improvement in anemia and liver function tests.

research and clinical practice, we believe these endovascular techniques will be refined and optimized to offer even more value to the cancer patient. ■

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