Venous Diseases in Malignancy

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Abstract

Malignancy is known to induce a hypercoagulable state and literature evidence has long supported that a significant proportion of morbidity and mortality in patients with a known malignancy is attributable to thromboembolic events. A high incidence of venous and, to a lesser extent, arterial thrombosis is observed and in several instances a thromboembolic event such as deep venous thrombosis or pulmonary embolism may be the presenting event that leads to unmasking an underlying malignancy. This dates back to Trousseau's astute description in 1860s of migratory thrombophlebitis harboring an occult malignancy [1].

Keywords

Venous disease • Malignancy

Malignancy is known to induce a hypercoagulable state and literature evidence has long supported that a significant proportion of morbidity and mortality in patients with a known malignancy is attributable to thromboembolic events. A high incidence of venous and, to a lesser extent, arterial thrombosis is observed and in several instances a thromboembolic event such as deep venous thrombosis or pulmonary embolism may be the presenting event that leads to unmasking an underlying malignancy. This dates back to Trousseau's astute description in 1860s of migratory thrombophlebitis harboring an occult malignancy [1].

The primary mechanism by which a prothrombotic state is induced is complex, and fundamentally involves increase in expression of hemostatic proteins (tumor factor), inflammatory cytokines (tumor necrosis factor-alpha, interleukin-1), angiogenic factors (vascular endothelial growth factor) and adhesion molecules [2]. Recent evidence demonstrates that alteration in host response and hemostatic mechanisms also promotes tumor progression, and certain types of malignancies specifically activate clotting and upregulate procoagulant molecules as part of the neoplastic transformation [2]. Independent host risk factors associated with increased thrombosis such as advanced age, sex, obesity, immobilization and treatment related risk factors of hypercoagulability, both surgical and medical, add to the increased incidence of thromboembolic events in patients with a malignancy. The clinical presentation of a patient in a procoagulant state is not always predictable and the spectrum ranges from subclinical thrombophilia sometimes evidenced only by laboratory abnormalities in coagulation studies, or present with fatal pulmonary embolism or stroke. Clinicians have advocated the use of risk assessment models to stratify patients for better screening and prompt institution of treatment. In this chapter, we present a variety of primary venous thromboembolic (VTE) manifestations of malignancy, the diagnosis and management of complications related to such events.

Deep Venous Thrombosis

Venous thromboembolic disease can be broadly categorized into deep venous thrombosis (DVT) and pulmonary embolism (PE) and is thought to represent 1% of hospital admissions in the US. In the general public, there are approximately 900,000 cases of VTE per year resulting in up to 300,000 deaths [3], and is now the third most common cause of life-threatening cardiovascular disease in the United States. Although DVT and PE are categorized separately, the underlying pathophysiology is identical and represents two entities in the spectrum of VTE.

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Over the years, there has been an increase in overall reports of VTE in cancer patients and can be attributed to an increased awareness of risk and more patients undergoing cancer treatments [4]. Population based studies have assessed risk factors for development of DVT and demonstrated malignancy as an independent risk factor in 18–34% of cases [3, 5]. In fact, depending on the type of malignancy and presence of metastases, the risk of acquiring a first time venous thrombosis rises up to seven fold (odds ratio 6.7; 95% confidence interval, 5.2–8.6) [6]. When combined with additional risk factors such as surgery, hospitalization, immobility, and chemotherapy, the risk of DVT rises substantially. This has been validated both in the US and Europe. A cohort study from the UK estimated that incidence of venous thrombosis for all types of cancer was 13.9 per 1000 person-years (95% CI: 13.4–14.4) and up to 68 per 1000 person-years (95% CI: 48–96) among cancer patients with high-grade or metastatic disease or those treated with therapeutic strategies that increased thromboembolic risk [4, 7]. In another study by Blom et al., patients with metastatic disease were 20 times more likely to have a VTE than those with local disease, and 50 times more likely to have an event than controls without cancer [6, 8].

Primary factors that contribute to development of thrombosis can be attributed to Virchow's triad of hypercoagulability, stasis and endothelial injury. In a healthy adult, small thrombi form in the deep veins, however, an intact thrombolytic system is able to prevent progression to a larger thrombus. When the thrombolytic system is overwhelmed or impaired, this dynamic process is interrupted and leads to larger thrombus formation that eventually may lead to clinical symptoms.

Classification

Diagnosis of DVT is most commonly confirmed by ultrasound examination of the extremities, which demonstrates echogenic intraluminal thrombus, which may be non-compressible or partially compressible, with or without blood flow (Fig. 11.1). Findings vary depending on the severity and duration of occlusion. In the lower extremity, DVT can be further subcategorized based on location—proximal DVT such as those affecting the iliofemoral and popliteal veins (*see Iliofemoral*) and distal DVT that are primarily below the popliteal trifurcation affecting the calf and distal veins. In the past, distal (below the knee) DVTs were thought to be clinically insignificant and were not screened for in an asymptomatic patient. However, the rate of proximal extension of distal DVTs has been debated, and there is evidence from smaller studies to suggest that, in the short term, patients harboring a malignancy with distal DVTs are still at high risk for PE and recurrent VTE [9–12].

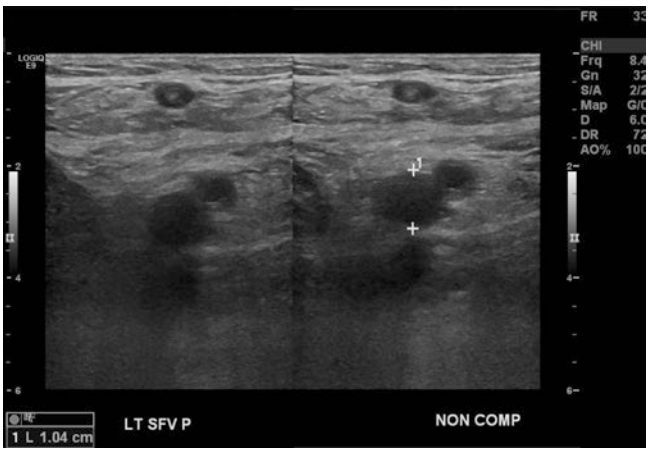

Fig. 11.1 Grayscale images demonstrating echogenic, non-compressible clot within the left femoral vein and peroneal veins

Iliofemoral

Acute iliofemoral DVT is defined as complete or partial occlusion of the iliac vein and/or the common femoral vein that has been present for less than 14 days [13]. The commonly described scenario involves compression of the left iliac vein between the right iliac artery and a lumbar vertebral body (May Thurner Syndrome, Fig. 11.2). The distinction between iliofemoral and a more distal DVT (e.g. infrapopliteal) is important, as the latter group is more amenable to endogenous recanalization and development of collateral circulation. An occluded iliac or proximal femoral vein rarely recanalizes and leads to chronic venous outflow obstruction [14]. Increased incidences of post-thrombotic syndrome (discussed below), valve incompetency leading to venous reflux and claudication, poor physical functioning and worsening quality of life have all been reported [15]. Due to serious long-term complications, identification of this particular entity is important as management varies from a popliteal DVT (discussed under treatment).

Complications

Although pulmonary embolism is the most feared complication of DVT, long-term complications such as post-thrombotic syndrome (PTS) and to a lesser extent chronic pulmonary hypertension are also debilitating. PTS is reported in 20–50% of patients even with appropriate treatment [16, 17] and is a constellation of findings wherein patients present with chronic limb pain, swelling, cramping, heaviness, edema and in extreme cases, venous ulcers. Recurrent DVT is an additional complication of VTE with an approximately 30% 10 year recurrence rate, with the highest recurrence occurring within the first 6 months [18]. A population cohort study of residents in Olmsted County, MN by Heit et al. evaluated effectiveness of anticoagulation and reported that active cancer was the

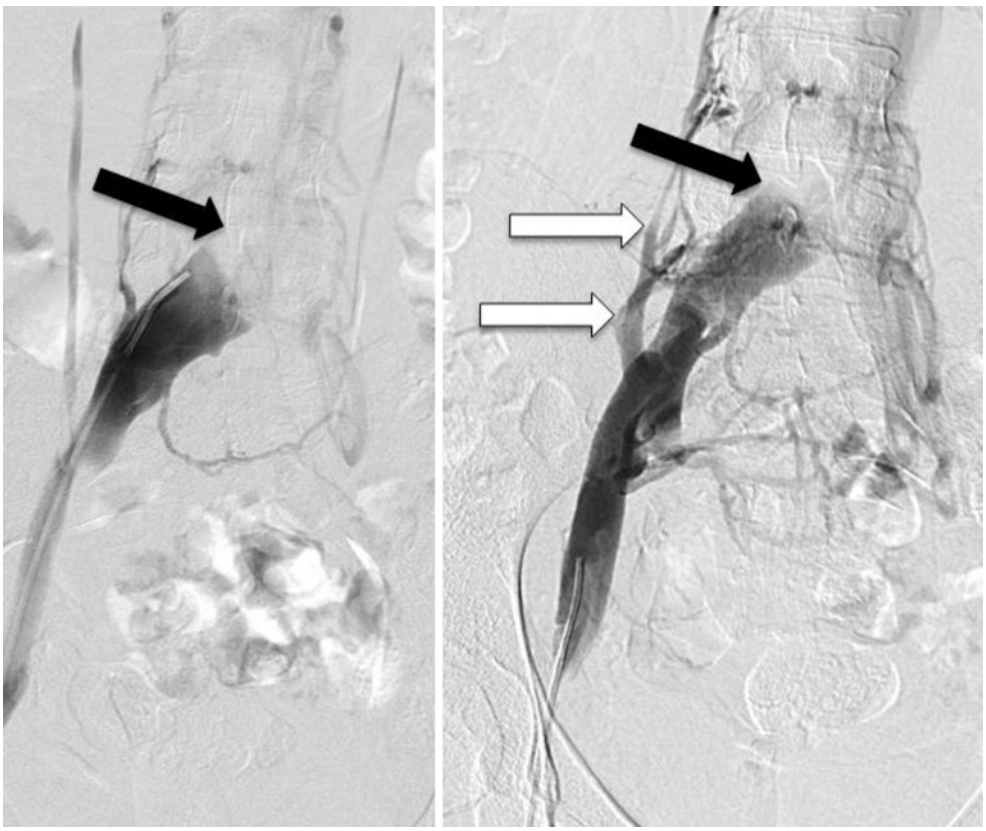

Fig. 11.2 Eighteen year old female who originally presented with left lower extremity swelling and suspicion for May Thurner syndrome presents again with worsening swelling. Digital subtraction angiography images of the left common iliac vein (LCIV) demonstrate complete occlusion of the LCIV at the confluence (*black arrow*) and no flow of contrast in the inferior vena cava. There are multiple lumbar collaterals (*white arrows*) that drain centrally

only independent predictor of early VTE recurrence, with about a three-fold increased hazard rate [19]. Another study, utilizing the same cohort of patients, showed that malignant neoplasms accounts for almost one fifth of all cases of VTE in the community [20]. About 16% of active cancer patients develop recurrence within 6 months compared to 4% of patients with idiopathic VTE [18].

Presentation

The clinical presentation of DVT varies depending on the site of thrombosis but classically, patients present with swelling, pain and erythema of the involved extremity (Fig. 11.3). There is significant overlap in presentation with other conditions and differential considerations include cellulitis, musculoskeletal strain or injury, superficial thrombophlebitis, lymphatic obstruction and chronic venous insufficiency [21]. While patients with cancer are at highest risk for developing DVTs, finding a DVT in an otherwise "normal" patient should not lead to a malignancy workup [22]. In the setting of malignancy, however, patients are at highest risk for developing DVTs within the first few months of diagnosis [6].

For patients with large iliofemoral clot burden, acute phlegmasia may be a rare but potentially fatal presentation with evidence of arterial insufficiency due to severe venous outflow obstruction. There is evidence of marked swelling

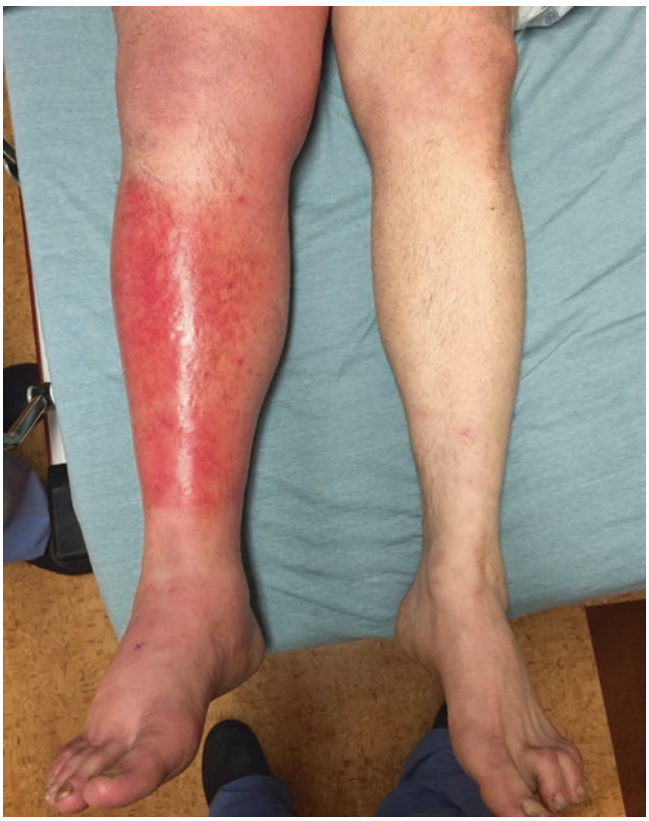

Fig. 11.3 Right lower extremity acute DVT. Note swelling, erythema and skin changes

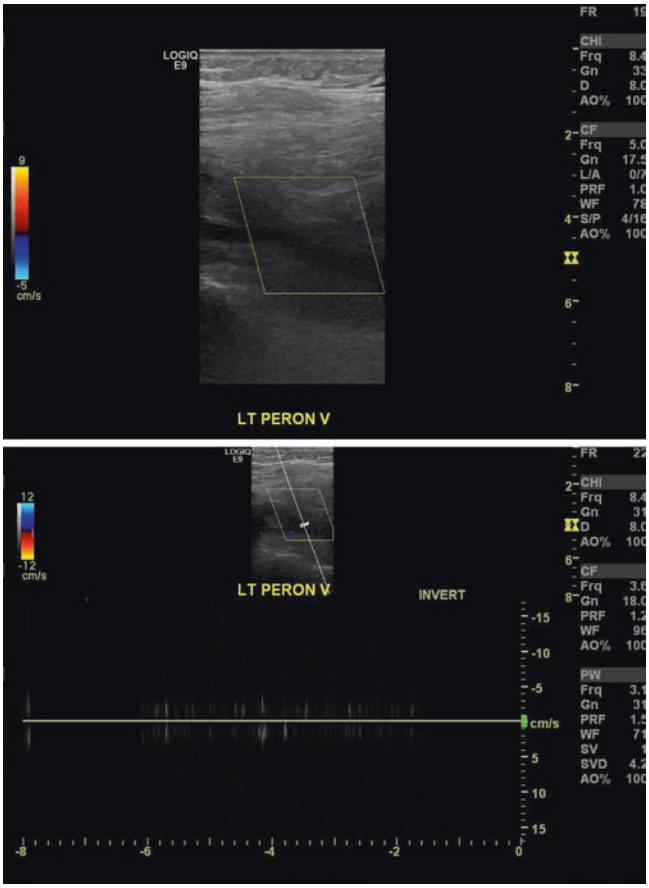

Fig. 11.4 Color Doppler images of the peroneal vein ("distal DVT") demonstrating no color flow (*top image*). Spectral Doppler tracing reveals no waveforms compatible with occlusive thrombus

and discoloration, which eventually leads to compartment syndrome, arterial compromise and venous gangrene. Malignancy is the most common risk factor in patients presenting with phlegmasia cerulea dolens [23].

Diagnosis

Diagnosis of DVT should initially start with a clinical probability assessment such as the Wells score [24] or the Geneva score [25]. D-dimer is a degradation product of a cross-linked fibrin clot frequently used an adjunct laboratory marker and in combination with a low pre-test probability, has a high negative predictive value for isolated DVT [11]. For peripheral extremity DVT, venous ultrasound with compression has remained the mainstay of noninvasive imaging and has largely replaced venography (Figs. 11.4, 11.5, and 11.6). For the deep pelvic veins, however, ultrasound is limited by poor acoustic windows and in these scenarios CT, or less commonly MR venography offers a more sensitive evaluation (Fig. 11.7). Catheter-based diagnostic venography is rarely used, though this technique was the historical gold standard for diagnosis (Fig. 11.8). Catheter venography is still used in preparation for catheter based intervention.

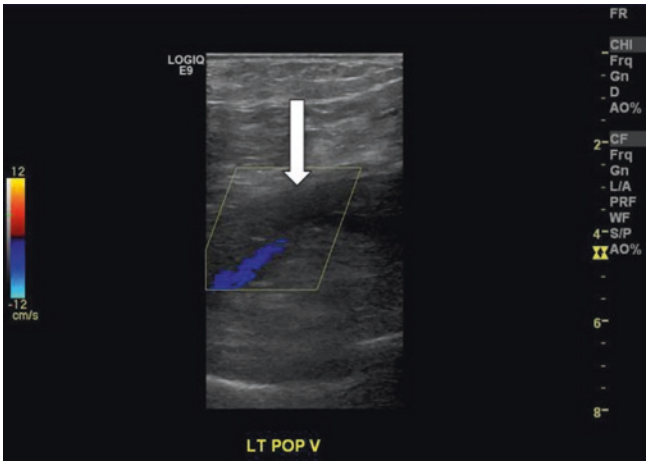

Fig. 11.5 Color Doppler image of the popliteal vein demonstrates echogenic thrombus within the vein (*arrow*). Color flow is demonstrated in the adjacent popliteal artery

Treatment

The treatment algorithm of venous thromboembolic disease is aimed at preventing pulmonary embolism, to decrease the risk of clot propagation, DVT recurrence and post-thrombotic syndrome. Treatment can be broadly categorized as medical, surgical or catheter directed. Surgical thrombectomy is reserved for very few scenarios (see iliofemoral).

Medical

Pharmacologic approach classically has involved initiation of IV heparin such as unfractionated heparin (UFH), a mixture of sulphated glucosaminoglycans that binds to antithrombin (AT), and inactivates several clotting factors (Xa, IXa, XIa, XIIa) including thrombin (factor IIa). In the unfractionated form, UFH contains polymers of several lengths and weights that are not fractioned with nonspecific binding affinities to endothelial cells and platelets. This contributes to its unpredictable pharmacokinetics and increased incidence of side effects. Low molecular weight heparin (LMWH) on the other hand is the fractionated form that is derived from UFH by depolymerization, with a more predictable dose-response and fewer side effects. Although UFH had been used for several decades, the improved and desired safety profile and equal effectiveness of LMWH has mostly replaced UFH. Vitamin K antagonist (VKA), mainly warfarin, is the most common anticoagulant used for prevention and long-term treatment of VTE. The main disadvantages include slow onset of action, various interactions with food and other drugs, narrow therapeutic window and need for close monitoring. Patients can easily under treat or over treat and adverse effects can be fatal if compliance is not strict, both by providers and patients.

Newer generation of anticoagulants have been developed to increase the safety and efficacy of systemic therapy, and target specific factors in the coagulation cascade. Fondaparinux

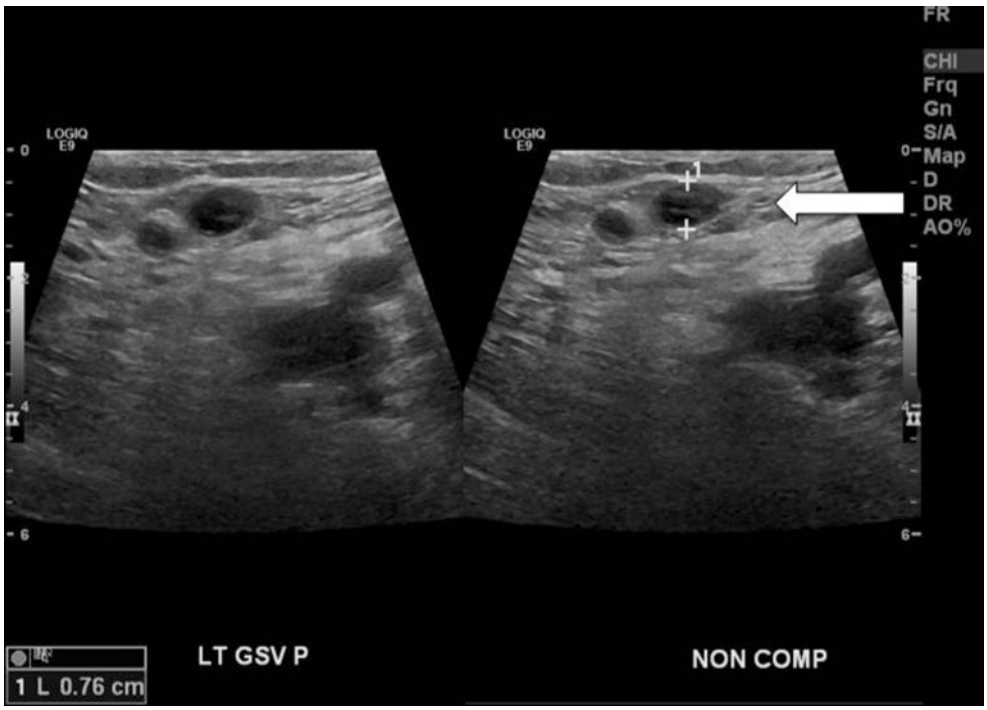

Fig. 11.6 Non-compressible and echogenic intraluminal thrombus in the left greater saphenous vein (GSV). Although the GSV is considered a superficial vein, there should be a thorough investigation as there is a high incidence of concomitant DVT, especially in those patients harboring a malignancy

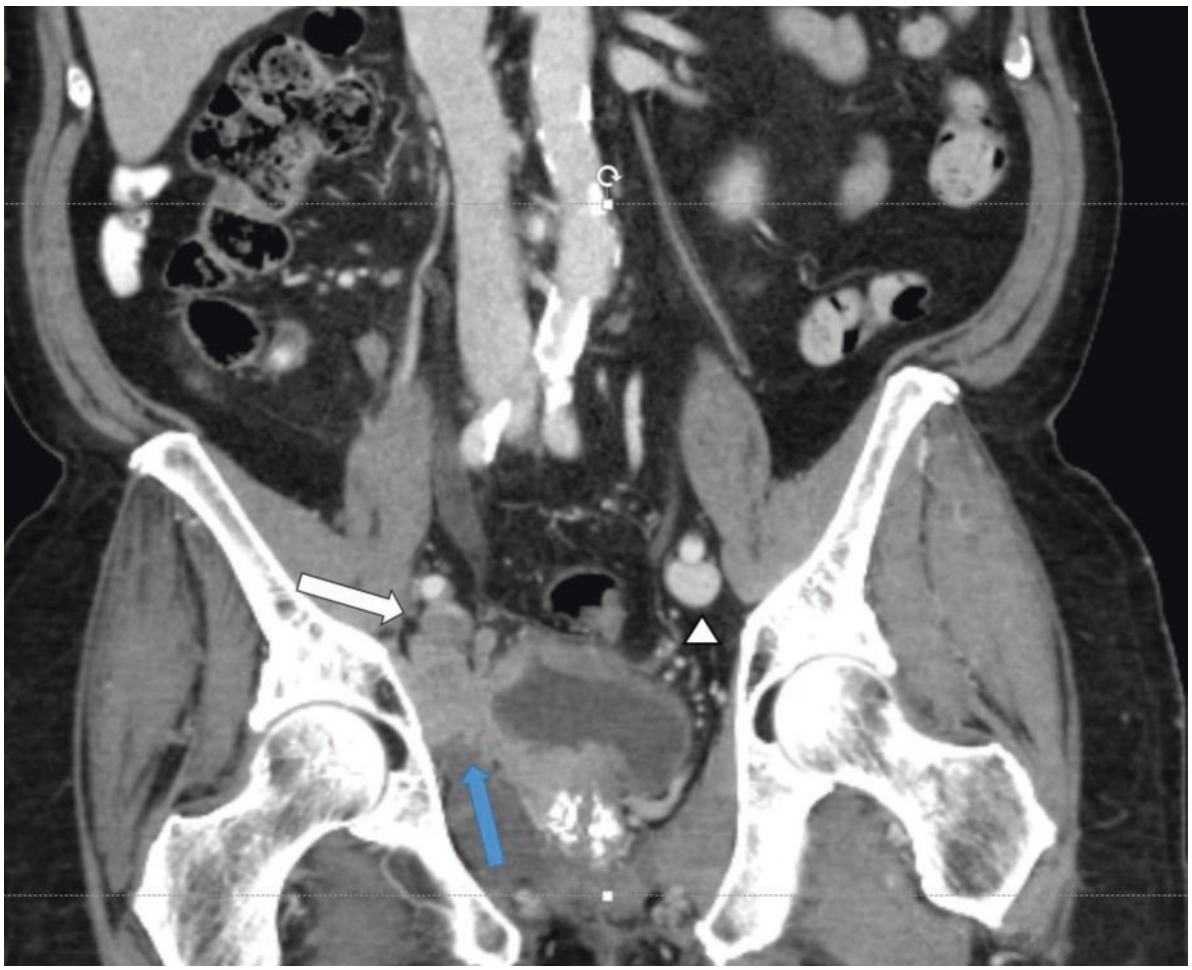

Fig. 11.7 Acute right iliac deep venous thrombosis on CT venogram. Intraluminal filling defect in the right iliac vein (*white arrow*) compared with appearance of normal iliac vein appearance on the left side (*arrowhead*). More distally, the right external ilia vein was compressed by exophytic bladder mass (*blue arrow*)

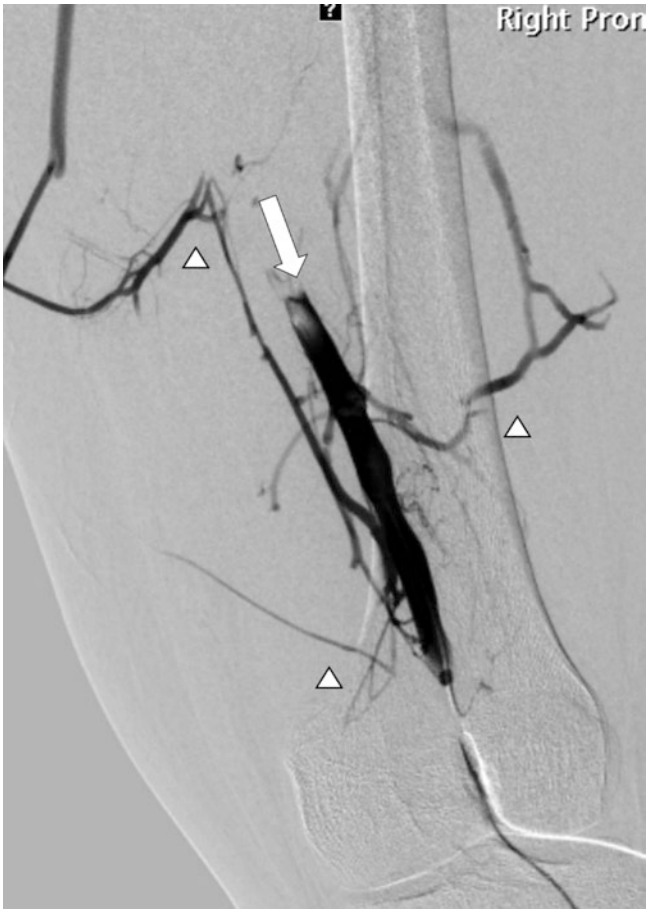

Fig. 11.8 Digital subtraction venogram from catheter in the right popliteal vein shows abrupt filling defect in the femoral vein (*arrow*). Small caliber, "immature" collaterals (*arrowheads*) suggest relative acuity of the obstruction

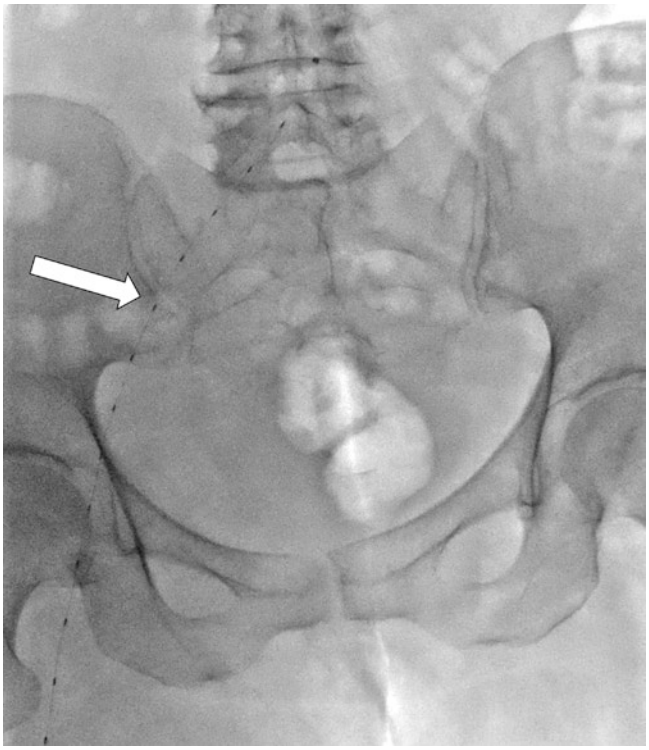

Fig. 11.9 Fluoroscopic spot image of the pelvis demonstrates an EKOS infusion catheter placed in the left femoral, external and common iliac veins for catheter directed thrombolysis

inhibits factor Xa by binding to AT and is administered subcutaneously as an alternative to LMWH. Rivaroxaban, edoxoban and apixaban also inhibit factor Xa and dabigatran inhibits thrombin and are all administered orally and referred to as non-vitamin K oral anticoagulants (NOACs). There is now enough evidence (RE-COVER, RE-COVER II, EINSTEIN DVT, EINSTEIN PE, AMPLIFY, Holusai-VTE trials) [26–31] that the newer oral anticoagulants are safer and equally effective, that in the most recent AT10 guidelines, ACCP now recommends NOACs over VKA therapy for patients with DVT of the leg or PE and without cancer [32]. For patients with cancer, LMWH is still preferred over VKA and the NOACs [32].

Acute therapy should be aimed at prevention extension of thrombus or PE, and should continue for a transient period until the thrombus has recanalized or organized, or the "activated" inflammatory state has resolved [18]. ACCP has specific recommendations for various clinical scenarios, but generally, medical therapy is continued for 3 months for patients without cancer. In patients with DVT or PE and active cancer (cancer-associated thrombosis), who do not have high bleeding risk the recommendation is for extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 1B) [32]. For cancer associated thrombosis, LMWH is preferred over oral anticoagulants [32]. In the setting of cancer-associated thrombosis, treatment for longer than 3 months is recommended even for those patients with high bleeding risk (Grade 2B), however, with periodic reassessment [32, 33]. For extended therapy, there should generally be no need to change the choice of anticoagulant after the first 3 months unless patient's circumstances change [32, 33].

Catheter Directed Therapy

Catheter directed therapy can be divided into pharmacological, mechanical and pharmacomechanical techniques. Pharmacologic catheter directed therapy involves gaining catheter access to the thrombosed vessel and administering thrombolytic medications directly into the clot, usually alteplase (tPA). The advantage of local delivery is the ability to achieve high concentrations of tPA within the clot without high systemic concentrations, thereby minimizing the risk of systemic bleeding complications. Catheter directed thrombolysis (CDT) is usually administered via a multiside hole infusion catheter (Fig. 11.9).

Mechanical catheter techniques include clot disruption, rheolytic aspiration, suction thrombectomy and stent-assisted thrombectomy. Pharmacomechanical thrombolysis refers to a combination of catheter directed thrombolysis in

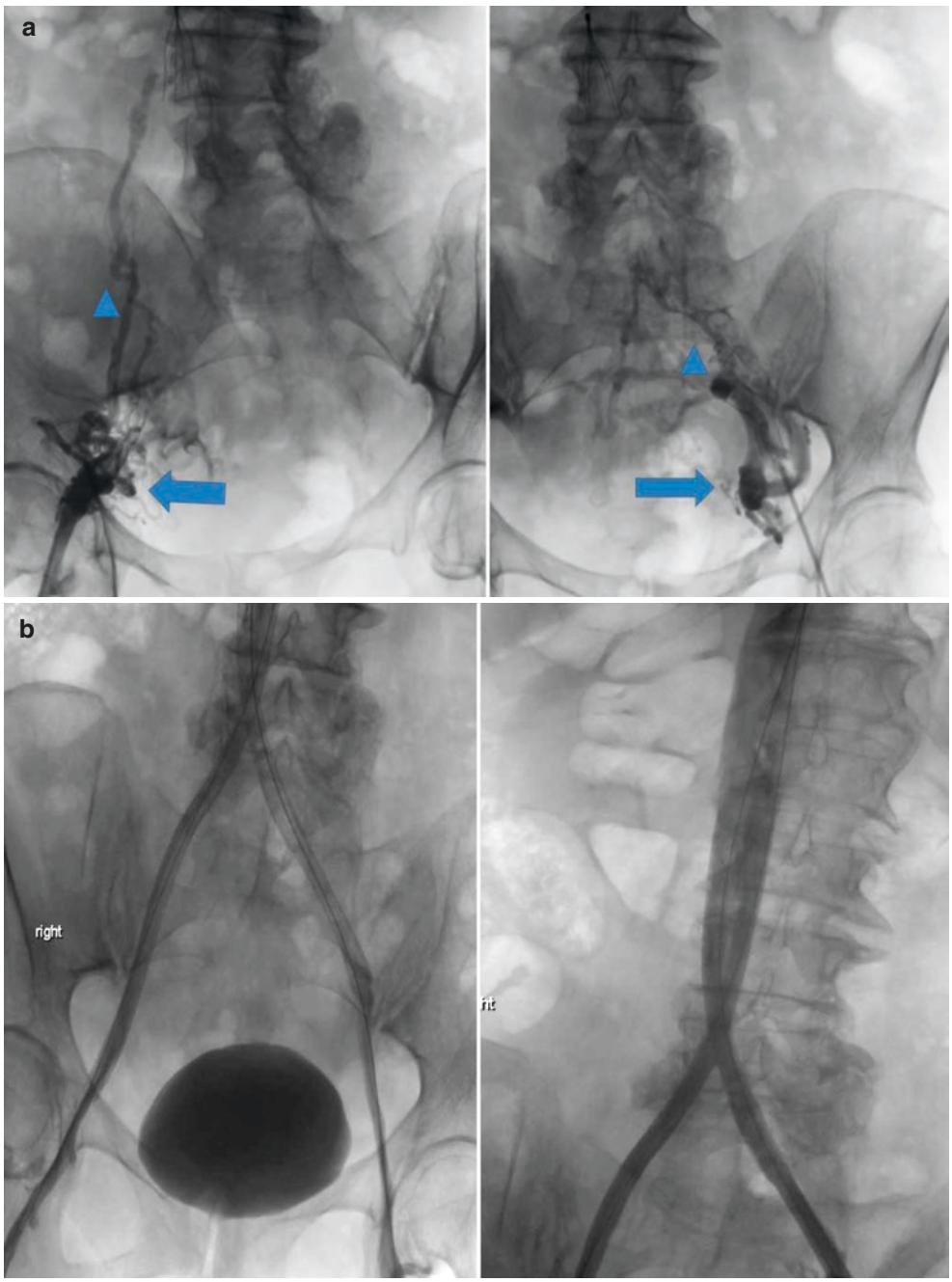

Fig. 11.10 (**a**) 71F with bilateral leg swelling and pain. Bilateral iliac venograms from catheters in the common femoral veins show chronic total occlusion of both external iliac veins (*arrows*). Collateral veins (*arrowheads*) have formed in an attempt to circumvent the occlusions. (**b**) Bilateral venograms after bilateral iliac stent placement and angioplasty show restored venous flow without filling of collaterals. Note the IVC filter has been removed

conjunction with mechanical disruption or thrombectomy. Result in experimental model indicates that ultrasound exposure causes reversible disaggregation of the uncrossed linked fibers into smaller fibers, which may alter flow resistance and improve fibrinolytic therapy [34]. A subtype of pharmacomechanical thrombolysis is ultrasound-assisted thrombolysis (UAST). In this technique, a catheter (Ekos catheter, Ekos, Bothell, WA) is placed across the thrombosed vessel that both infuses thrombolytic medications and delivers high frequency, low power sound waves to loosen clot and expose plasminogen receptor sites [35]. Once the acute thrombus is removed, any underlying cause of obstruction can be treated with angioplasty or stent placement (Fig. 11.10).

The main complications of CDT are related to major bleeding risks such as intracranial hemorrhage and those extra-cranial bleeds that are significant to require transfusions, cessation of therapy, or cause death. In a pooled analysis the cumulative major bleeding rate for CDT was reported to be 8% [35–37]. However, with lower doses of tPA gaining favor, rates of major bleeding complications have been decreasing.

For patients with acute iliofemoral or proximal DVT, ACCP recommends systemic anticoagulation as first line therapy [32, 33]. However, due to long-term morbidity associated with PTS, catheter directed thrombolysis techniques are supported by the Society of Interventional Radiology (SIR) for those patients who have acute iliofemoral DVT for

<14 days, good functional status, and low risk of bleeding, and in rare cases limb threatening venous compromise [32, 33, 37]. Both the SIR and AACP recognize the limitations of published studies and available evidence. Therefore, an individualized approach to stratify patients that may benefit from CDT is recommended until further evidence is established [32, 33, 37].

Pulmonary Embolism

Acute pulmonary embolism (PE) is the most feared complication of deep venous thrombosis. As mentioned earlier (see DVT), most thrombi form in the deep veins of the calf, and propagate proximally. PE is thought to be the sequela of treated or untreated thrombi commonly in the proximal lower extremity veins. Once thrombus is in the popliteal or femoral veins, approximately 50% patients are at risk for acute symptomatic pulmonary embolism [38]. A systemic review demonstrated that up to 95% of PE are caused by thrombus in the deep veins of the lower limbs [39]. Diagnosis of PE is most commonly done with CT angiography of the pulmonary artery (CTPA) (Fig. 11.11). In patients unable to have a CT scan, a nuclear medicine ventilation/perfusion scan (VQ) is most commonly used (Fig. 11.12). Catheter-based pulmonary arteriography is no longer used as a diagnostic modality but is performed as part of any catheter based intervention (see treatment below).

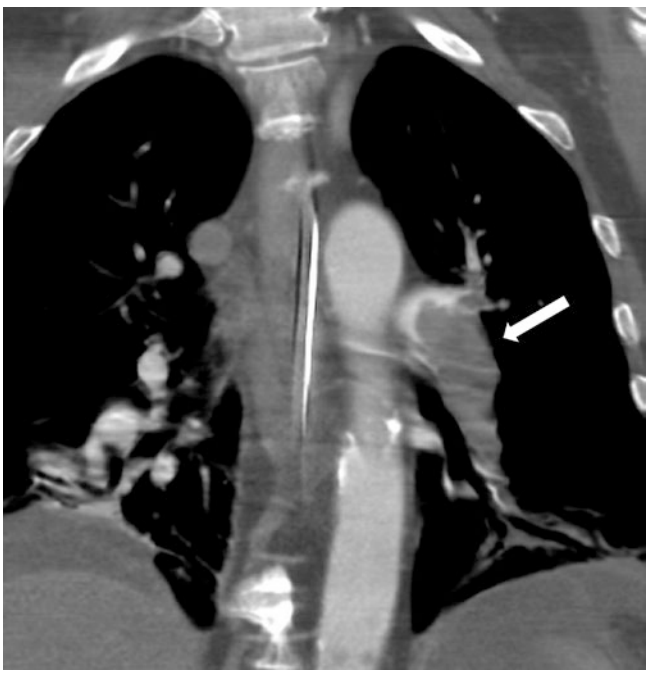

Fig. 11.11 Coronal projection from CT angiogram of the pulmonary artery shows large filing defect (*arrow*) in the left main and lower lobe pulmonary arteries

A risk-based classification taking into account patient presentation and morbidity stratifies PE as non-massive or low-risk, submassive and massive.

Massive or high risk PE is defined as acute PE with sustained hypotension (systolic blood pressure <90 mmHg for at least 15 min or requiring inotropic support), not due to a cause other than PE (i.e. arrhythmia, hypovolemia, sepsis, or left ventricular dysfunction), pulselessness, or persistent profound bradycardia (heart rate < 40 bpm with signs or symptoms of shock) [40]. Submassive PE is defined as acute PE without systemic hypotension (systolic blood pressure ≥ 90 mmHg) but with either right ventricular (RV) dysfunction (RV dilation, brain natriuretic peptide elevation, echocardiographic changes) or myocardial necrosis (elevated troponin I or troponin T) [40]. The ratio of diameters of the right ventricle to the left ventricle (RV:LV ratio) on CT is the most commonly used metric for imaging evidence of right heart dysfunction owing to its availability (Fig. 11.13). An RV:LV ratio greater than 1 is a significant predictor of persistent pulmonary symptoms and mortality at 3 months post PE. Echocardiography can be used to further investigate right heart function. Low-risk PE is defined as acute PE and the absence of the clinical markers of adverse prognosis that define massive or submassive PE [40]. The distinction is important not only for risk stratification and morbidity but also for management as discussed below.

Treatment

Systemic pharmacologic treatment for acute PE is dictated by classification. Patients with low-risk acute PE are treated with systemic anticoagulation alone. There is no role for systemic lytic treatment in this group.

For patients in the massive or high risk PE group, prompt aggressive therapy is warranted given an estimated 30% mortality for patients with acute PE and hypotension [41]. All patients in this group should be started on weight based heparin infusion with bolus dose, except where absolutely contraindicated. Current ACCP guidelines recommend administration of systemic thrombolytic therapy if no contraindication exists [32, 33]. Current guidelines are based on multiple randomized trials [42, 43], as well as analysis showing thrombolysis improves pulmonary arterial pressures, oxygenation, and pulmonary perfusion [44].

A meta-analysis by Wan et al. analyzed 11 randomized trials comparing heparin alone to heparin and systemic

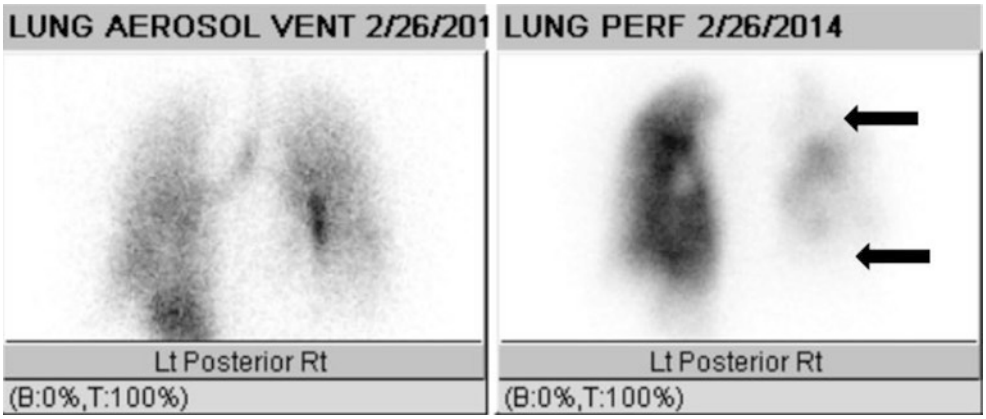

Fig. 11.12 Posterior projections of a high risk ventilation perfusion scan. The *right* images shows physiologic disruption of ventilator tracer. Image on the *left* shows multiple peripheral areas of decreased lung perfusion (*arrows*) indicating pulmonary embolism

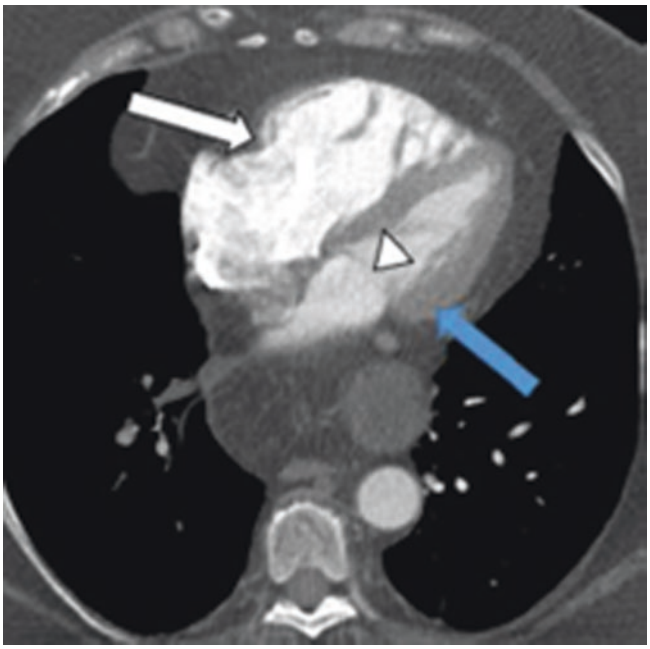

Fig. 11.13 Axial image from CT of the chest and abdomen in a patient with acute pulmonary embolism. The right ventricle (*white arrow*) is dilated and is larger in diameter than the left ventricle (*blue arrow*). The RV:LV ratio is 2.1, indicating severe right heart strain. The normally convex intraventricular septum (with respect to the ventricle) is flattened and slightly bowed toward the left ventricle (*arrowhead*)

thrombolysis, involving 748 patients with acute PE [45]. There were no significant differences in recurrent PE/death or major bleeding complications in an unselected population. However, in trials that enrolled patients with high-risk PE, patients treated with systemic thrombolysis and heparin had a significantly less recurrent PE or death compared to patients treated with heparin alone (9.4% vs. 19%, OR 0.45 95% CI 0.22–0.92). In most centers, administration of systemic thrombolytic therapy for acute high-risk PE is standard of care, except where contraindicated. Contraindications to systemic thrombolysis are the same as those encountered for acute ischemic stroke and ST segment elevation MI. Of particular note is that cancer itself does not present a contraindication to systemic thrombolysis.

For patients in the sub-massive or intermediate-risk group, current ACCP guidelines (2016) do not recommend treatment with systemic thrombolysis for most patients with intermediate-risk PE [33]. However, more recent trials addressing this issue have been completed and are worth consideration. The PEITHO trial, conducted by Meyer et al., was a randomized double-blind trial comparing treatment with heparin alone vs. heparin plus systemic thrombolysis for 1006 patients with intermediate-risk PE, specifically defined in this trial as RV dysfunction on imaging AND evidence of myonecrosis via a positive troponin test [46]. Patients treated with systemic thrombolysis had a significantly decreased incidence of the composite endpoint death/hemodynamic collapse compared with heparin alone (2.6% vs. 5.6%, p = 0.015). It is worth

noting that there was no significant difference in mortality alone. Patients treated with systemic thrombolysis did have increased incidence of major bleeding compared with the patients treated with heparin alone (11.5% vs. 2.4%, $p < 0.0001$), including a 2.0% rate of hemorrhagic stroke in the thrombolysis group. A recent meta-analysis by Goa et al. analyzed prospective randomized controlled trials of patients with intermediate-risk PE treated with systemic thrombolysis, including PEITHO and seven additional trials encompassing 1755 patients [47]. Patients treated with systemic thrombolysis and heparin had significantly lower mortality than patients treated with heparin alone (1.39% vs. 2.92%, RR 0.52; 95% CI 0.28–0.97). However, as shown in the PEITHO trial, this decrease in mortality was at the expense of increased major bleeding events in the group treated with systemic thrombolysis (7.8% vs. 2.28% RR 3.35; 95% CI 2.03–5.54). It is worth noting that one of the randomized trials included in the study (MOPETT trial, Sharifi et al.), showed that compared with heparin alone, patients treated with low-dose systemic tPA (50 mg rather than 100 mg) and heparin had decreased incidence of recurrent PE, pulmonary hypertension, and length of hospital stay without a significant increase in major bleeding complications [48].

Further studies are needed to evaluate the impact on mortality of low dose systemic tPA as well as to identify predictive factors for subgroups of patients with submassive PE who will benefit most from systemic thrombolysis.

Catheter Directed Therapy

Catheter directed therapy (CDT) includes catheter based thrombolysis, pharmacomechanical thrombectomy and mechanical thrombectomy (Fig. 11.14). CDT has proven to be useful in patients with acute PE and systemic hypotension (massive or high-risk PE), particularly when there is a relative or absolute contraindication to systemic thrombolysis. In a systematic review by Kuo et al., six prospective and 29 retrospective uncontrolled studies were identified in which catheter directed therapy was used to treat 594 patients with acute high-risk PE [49]. Clinical success, defined as stabilization of hemodynamics, resolution of hypoxia and survival from massive PE, was achieved in 86.5% of patients, with 2.4% of patients experiencing major complications. It is worth noting that 96% of patients in this analysis did not receive systemic thrombolysis, while 66% of patients received thrombolytic during catheter directed therapy, presumably at a low dose. Although uncontrolled, the results of this analysis are favorable when compared with historical rates of survival (77%) and major hemorrhage (22%) following systemic thrombolysis and to overall mortality from acute high risk PE (30%) [41]. Therefore, catheter directed therapy for acute high-risk PE should be considered in cases where there is a relative or absolute contraindication to systemic thrombolysis or in the case of ineffective systemic thrombolysis.

Multiple recent prospective, randomized clinical trials have shown that treatment of patients with intermediate-risk (submassive) PE with systemic thrombolysis and heparin significantly improves patient mortality, RV function, risk of recurrent PE and hemodynamic collapse compared with patients treated with heparin alone [46–48]. However, this benefit comes at the expense of a significant increase in major bleeding complications, including >2% risk of hemorrhagic stroke. It has been postulated that catheter directed therapy, specifically catheter directed ultrasound assisted thrombolysis (USAT), can achieve the same benefit

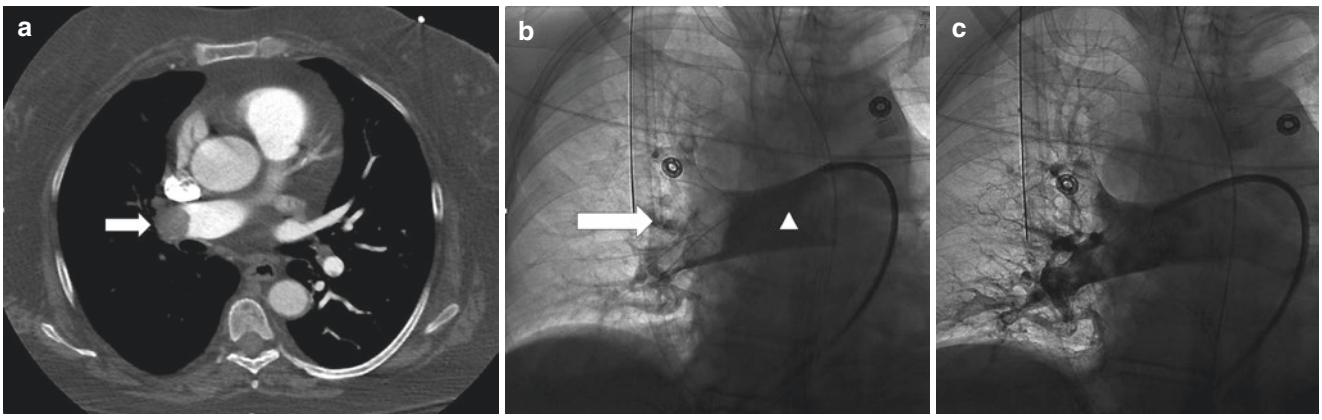

Fig. 11.14 (**a**) 53F with history of colon cancer presents with hypoxia and hypotension. Axial CT angiogram of the pulmonary artery shows thombus in the right main pulmonary artery (*arrow*). (**b**) Pulmonary angiogram showing corresponding filling defect in the right pulmonary artery (*arrow*) causing total absence of flow to the right lung and increased right ventricular afterload. Note the enlargement of the contrast-opacified main pulmonary artery (*arrowhead*). (**c**) After mechanical clot disruption, there is restored flow to the right lung. This caused an immediate reduction in pulmonary resistance and prevented acute right heart failure. Multiple filling defects remain, particularly in the right upper lobe. These were further treated with catheter directed thrombolysis

in these patients with lower systemic doses and bleeding complications. The SEATTLE II trial by Piazza et al. was a prospective non-controlled study of UAST in patients with high-risk and intermediate-risk PE [50] where a total of 24 mg of tPA was administered via the Ekos catheter in 150 patients. This study found significant decreases in RV strain, pulmonary pressure and pulmonary artery obstruction compared with baseline. Importantly, there were no intracranial hemorrhages and a 10% rate of major hemorrhage. Multiple additional non-controlled studies have found efficacy of catheter directed therapy for intermediate-risk PE with low rates of bleeding [51–53]. In the only prospective controlled randomized trial (Ultima trial), Kucher et al. randomized 59 patients with intermediate-risk PE to heparin alone vs. heparin with USAT (10–20 mg tPA). Significant improvements in right heart strain, as measured by RV/LV ratio, were seen in the USAT group compared with heparin alone (1.28–0.99 vs. 1.20–1.17, $p < 0.001$). Significantly, there were no major bleeding events or deaths in the USAT group [54]. Although not currently recommended for most patients with submassive or intermediate risk PE [32], these more recent studies support the claim that catheter directed therapy can deliver similar cardiovascular benefit as systemic thrombolysis with significantly fewer bleeding complications. As such, catheter directed therapy should be considered in the treatment algorithm for patients with intermediate risk PE.

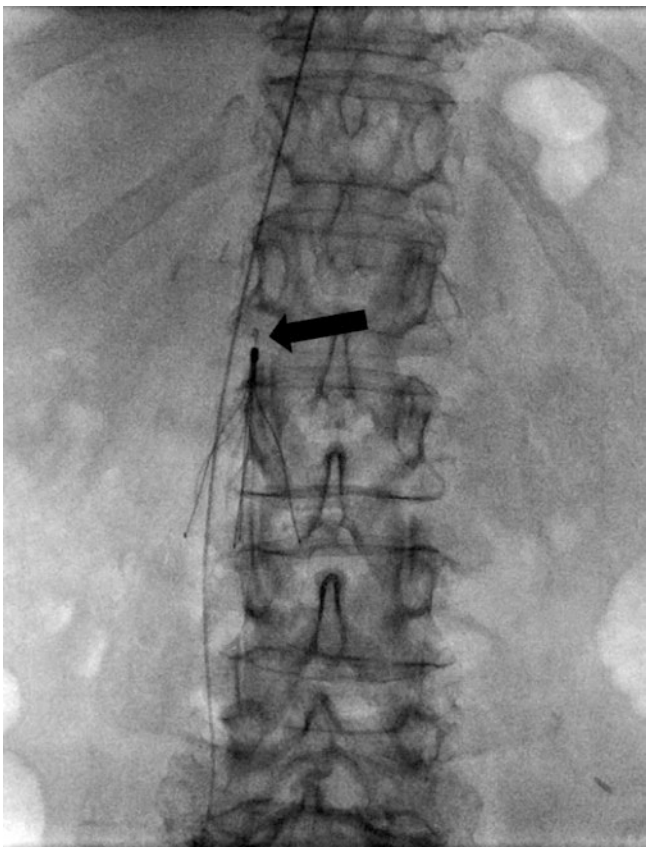

Fig. 11.15 Retreivable infrarenal IVC filter. Note the hook on the superior tip of the filter (*arrow*) to facilitate endovascular retreival

IVC Filter

IVC filters have been placed for over 40 years since the Greenfield filter was first introduced in 1973. The original filter was conical in shape, which helped trap clot within its central seams while still providing enough caval blood flow [55, 56]. There have been several filters that have adopted a similar design and several others that are entirely different in shape (Figs. 11.15 and 11.16). However, all filters are designed to primarily prevent significant PE by trapping venous emboli originating from the deep veins of the lower extremity.

The PREPIC trial was the first randomized control trial to evaluate the effectiveness of IVC filters [55, 57], which demonstrated a statistically significant 78% reduction in the risk of an acute pulmonary embolic event [57]. A follow up study 8 years after filter placement revealed a statistically significant 6.2% reduction in symptomatic PEs, however, with a 35% increased risk of symptomatic DVT in the filter group [57]. More recently, PREPIC 2 randomized trial found that even in high risk patients who are anti-coagulated systemically, placement of an IVC filter for 3 months actually did not reduce recurrent PE, including fatal PE [32, 58]. In the Olmsted cohort study, IVC filter placement increased the risk of VTE recurrence by almost 50%, and one third of early recurrences were related to PE [19]. In light of DVT complications, placement of IVC filters has been controversial and highly debated topic.

There have been no randomized controlled trials that have demonstrated superiority of a particular filter. However, modern filters have evolved to be less thrombogenic, less prone to breakage, and are MRI compatible [56]. There are two broad groups of IVC filters: retrievable and permanent. Permanent filters have been available for several years and are placed in patients who have lifelong risk of PE [55, 56]. Complications related to long-term filters and need for short-term prophylaxis, has resulted in a rise in placement of retrievable filters [55]. Subgroup of retrievable filters includes temporary filters (*must* be retrieved) that are tethered to the skin by a wire/catheter, and optionally retrievable filters that can be left in situ as a permanent device [55]. More recently, there has been a dramatic shift towards placement of retrievable/optional filters as they offer flexibility of retrieval if clinically indicated [59]. The ideal time frame for filter retrieval is within the first 3 months. However, it is possible to remove filters that have been in for much longer time periods, in some cases up to 10 years. Chronic indwelling filters, or filters with significant tilting of the tip, usually require retrieval with endovascular forceps (Fig. 11.17) or laser assisted.

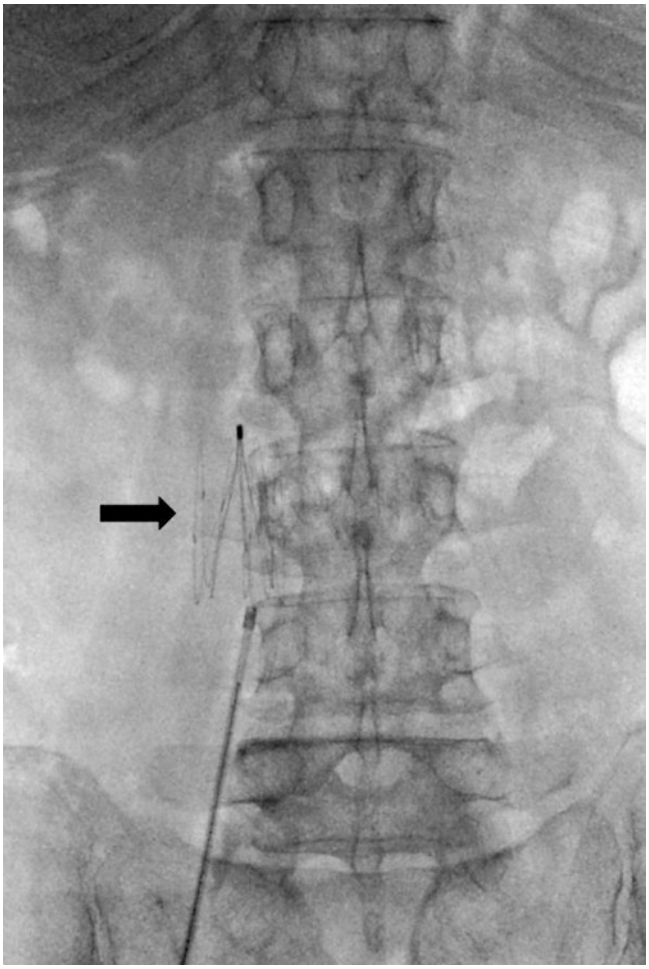

Fig. 11.16 Permanent infrarenal IVC filter. In addition to conical shape, permanat filters do not have a retreiveal hook and have more contact with the caval wall

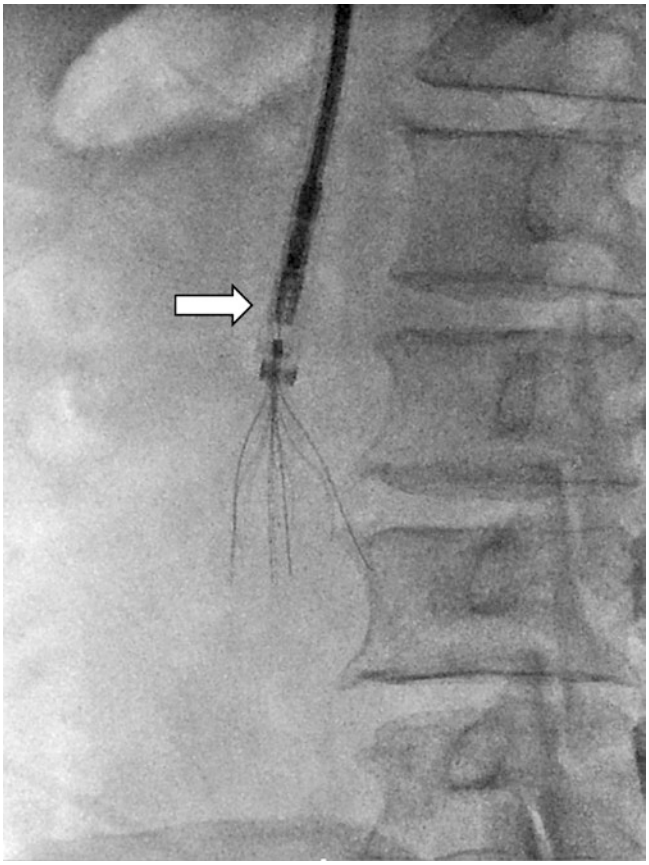

Fig. 11.17 Endobronchial forceps (*white arrow*) used to grasp a retrievable filter that had been indwelling for 3 years. The forceps are used to stabilize the filter as vascular sheath is advanced over the forceps and filter to collapse the filter legs and ultimately free the filter from the caval wall. Note this is an off-label use of endobronchial forceps

Majority of IVC filters for lower extremity DVTs are placed in an infra renal location. Suprarenal IVC filters are also placed, however, should be performed judiciously in select patients with specific indications due to a shorter length of the suprarenal IVC, and theoretical risk of filter induced renal vein thrombosis and subsequent renal failure. Recent retrospective evidence however, supports the original finding from Greenfield that suprarenal filters are equally effective in preventing PE without added risk of complications compared to infra-renal filters [60, 61]. Filters have also been placed for upper extremity DVTs that occur in the axillary, subclavian, brachiocephalic veins or SVC (Fig. 11.18). Although upper extremity DVTs are rare and are less likely to result in PE, if indicated, filters can be placed in the SVC just distal to the confluence of brachiocephalic veins, albeit with a slightly higher rate of complications such as caval perforation (4% in the SVC compared to 0.5% in the IVC) [62].

Indications for placement of both therapeutic and prophylactic IVC filters have been formulated by the American College of Radiology ACR/Society of Interventional Radiology (SIR) and are similar to those recommended by the American College of Chest Physicians (ACCP). The 10th edition of Antithrombotic guidelines (AT 10) from the ACCP however, recommended against placement of an IVC filter as primary prophylaxis for any patient or for VTE treated with anticoagulants [33]. Although filters have been around for several years, lack of significant level I evidence for IVC filter placement and research questions remain to be addressed. Nevertheless, there are several circumstances such as pregnancy, and trauma where a filter has shown significant benefit. In the setting of malignancy, however, the evidence is mixed. Filters still offer protection for PE related mortality, however, the stage of disease and type of cancer also questions the validity of placement in patients with advanced disease who succumb to the cancer earlier [63]. In one study that included 116 patients with malignancy, 46% of patients with stage IV disease who had a filter placed died of cancer within 6 weeks, and only 14% of patients were still alive after 1 year [64]. However, another study at a major cancer center examined 308 patients

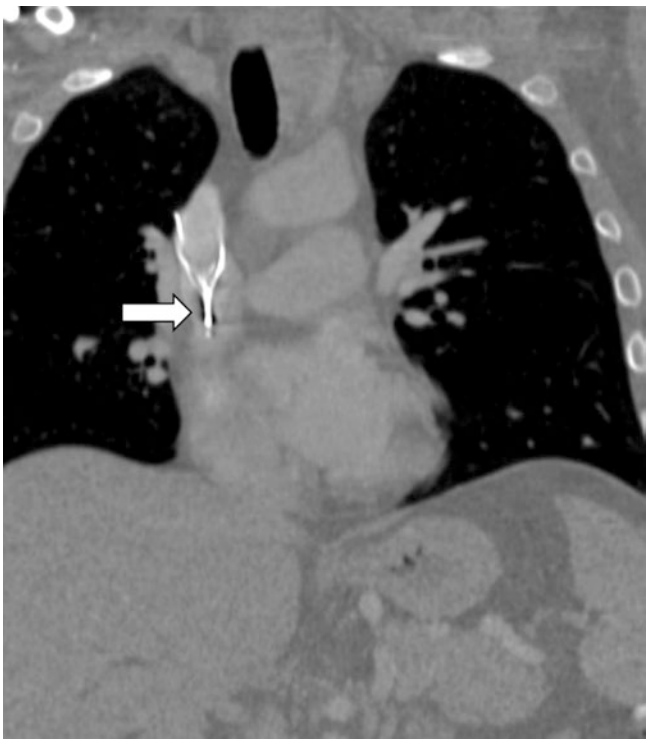

Fig. 11.18 Superior vena cava filter

with cancer and VTE, and found substantial mortality benefit for those patients with IVC filters in preventing PE-related deaths [65]. Given the controversy and lack of significant level 1 evidence, an individualized approach taking into account the stage and prognosis will likely offer the most benefit.

Additional filter complications include filter tilt, fracture, migration, embolization, caval wall perforation, IVC stenosis/occlusion and in some cases PTS (Figs. 11.19, 11.20, and 11.21). In response to growing complications, in 2010 the FDA issued a medical device Alert and Notice titled "Removing Retrievable Inferior Vena Cava Filters: Initial Communication," in which it cited concerns that retrievable filters are not retrieved after the patients' risk profile for PE has diminished, resulting in increased complications. The FDA recommended all physicians carefully evaluate patients for filter retrieval at regular intervals and prudent decision-making is imperative for any patient who receives a filter.

Superior Vena Cava Syndrome

Superior vena cava (SVC) syndrome was first described by William Hunter in 1757 and is a clinical manifestation of compression of the SVC, originally described in a patient with a syphilitic aortic aneurysm [66]. Compression may be extrinsic of the SVC itself, or of the greater veins emptying into the SVC. Although infectious causes accounted for a majority of the cases when originally described, over the last

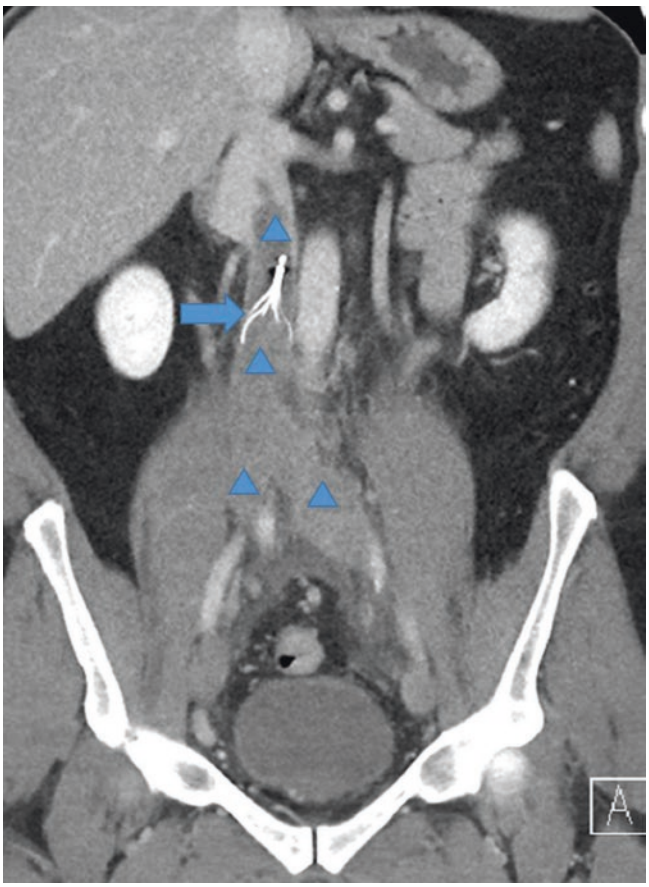

Fig. 11.19 Coronal CECT showing indwelling IVC filter (*arrow*) with filter associated IVC and iliac thrombosis (*arrowheads*)

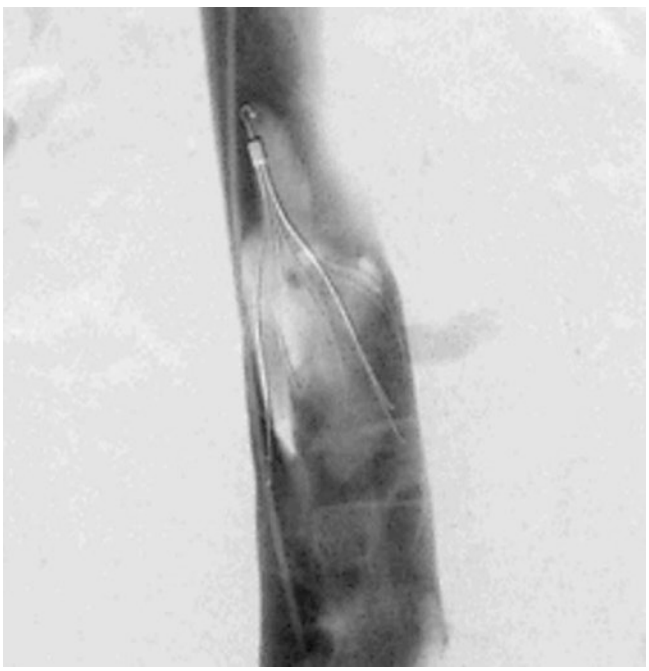

Fig. 11.20 Digital subtraction cavogram demonstrating intraluminal thrombus in and around the IVC filter

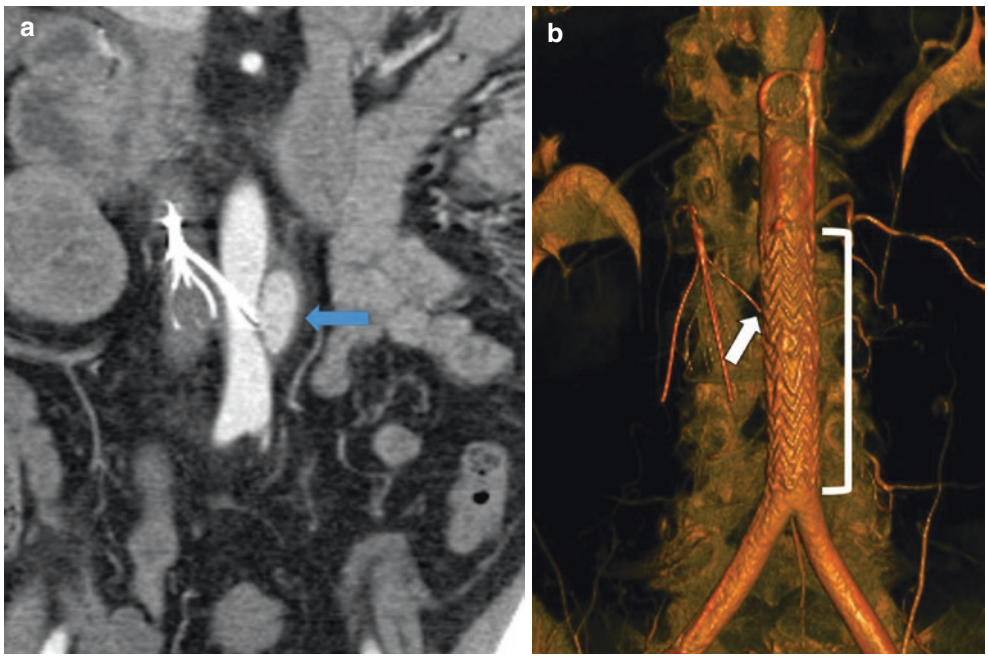

Fig. 11.21 (**a**) Coronal CECT showing perforation of the IVC by filter strut. The strut extends into the aorta and results in aortic pseudoaneurysm (*arrow*). (**b**): 3D reconstruction of aortogram after placement of aortic stent graft (*bracket*) with successful exclusion of the pseudoaneurysm. Filter, with perforated strut (*arrow*) was then successful removed

few decades SVC syndrome is most often a result of a malignant process in the thorax, most commonly lung cancer [67] and up to 35% of cases are due to non-malignant causes mostly secondary to use of intravascular devices resulting in thrombotic occlusion [68]. Once the SVC is occluded, venous return is impaired and alternate pathways mainly the azygous venous system, internal mammary/epigastric system, and superficial subcutaneous venous system act as collateral pathways (Fig. 11.22).

Early recognition of presentation of SVC syndrome is crucial since cerebral edema can be fatal if not treated promptly. Diagnosis is most often apparent by clinical assessment; however, CT of the chest with contrast offers a more sensitive evaluation of the etiology and in some cases MRI may be used if contrast medium is not tolerated. The constellation of signs and symptoms include edema of the head, neck and upper extremities, distention of subcutaneous vessels in the upper thorax, head and neck, laryngeal and nasal edema, and rarely cerebral edema [67]. Unless absolutely emergent, diagnosis of the underlying cause should be first established with tissue sampling or cytological analysis. Prognosis and survival in these patients are primarily related to the underlying cause of obstruction.

Management of SVC syndrome depends on the underlying cause of obstruction and acuity of presentation. A scoring system has been developed in order to stratify patients based on symptom severity and help guide management [69, 70] (Table 11.1).

Radiation therapy has been used since the 1970s used for emergent, palliative or definitive therapy. Emergency radiotherapy is started without histologic diagnosis when patients present acutely with severe symptoms [71]. In some cases of malignant obstruction from lymphoma or lung cancer, fractionated radiotherapy has shown to improve clinical symptoms with relief noted as early as 3–4 days in some patients [72]. In other cases, chemotherapy may be preferable if there is prior histologic diagnosis and the tumor is chemosensitive (e.g. small cell lung cancer, non-Hodgkin's lymphoma, germ cell tumors). However, more recently percutaneous stent placement, if feasible, has become the first line of treatment especially for those patients with malignant obstruction and results in immediate symptomatic relief when compared to emergent radiation. Radiation therapy and/or chemotherapy generally follows stent placement in the emergent setting, however, in the non-emergent setting may precede stent placement. Stent placement was introduced in the 1980s and has been refined over the years to reduce complications related to stent migration [73]. A prospective study by Gwon et al. reported a 94% patency rate for covered stents vs. 48% patency for non-covered stents over a 12-month period [74]. Despite this, non-covered stents are most often used owing to anatomic considerations when covered stents may cover collateral pathways or contralateral venous drainage. Although no randomized control trials exist to prove superiority of stenting compared to alternative therapies, there are several smaller case reports and studies that have established long

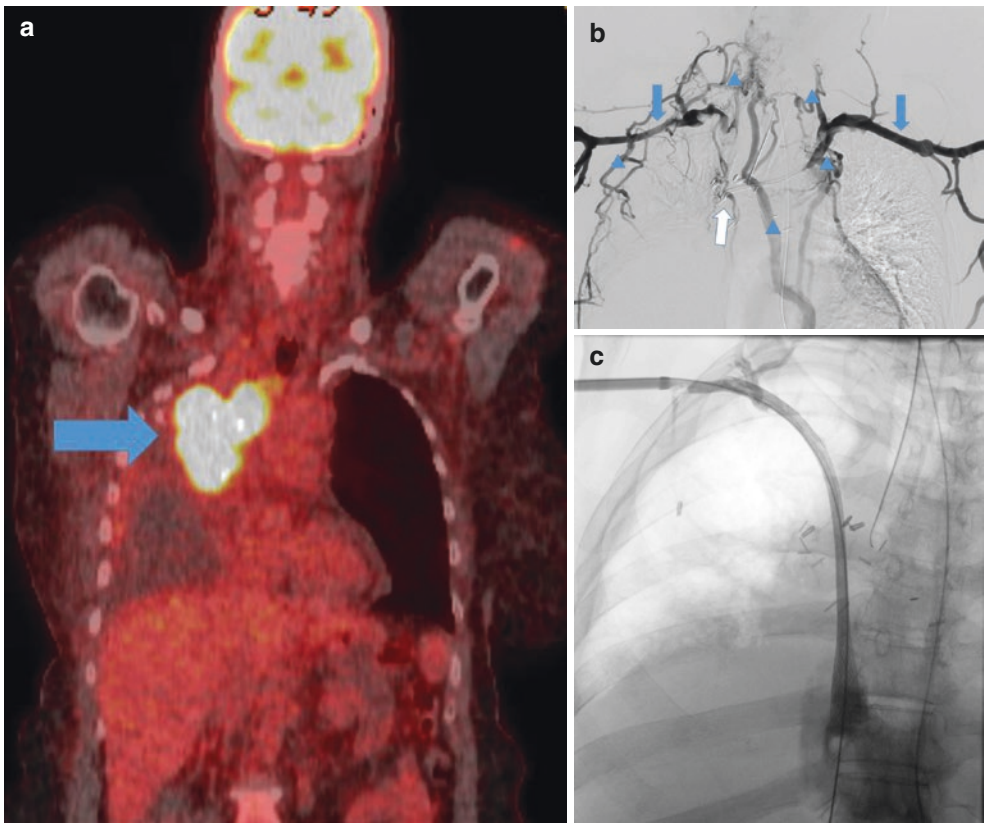

Fig. 11.22 (**a**) 61F with PET avid non-small cell lung carcinoma in the right upper lobe. (**b**) Patient developed face/arm swelling and shortness of breath while laying down 6 months after right upper and middle lobectomy. She was found to have mediastinal recurrence. Digital subtraction angiogram from both arms show patent subclavian veins (*blue arrows*). There is no flow into the superior vena (*white arrow*). There is filling of multiple collateral venous pathways (*blue arrowheads*). (**c**) Restoration of antegrade flow from the right subclavian vein to the heart after placement of 22 mm wallstent. Patient's symptoms resolved

Table 11.1 Superior vena cava (SVC) syndrome

Grade	Category	Estimated incidence (%)	Definition[a]
0	Asymptomatic	10	Radiographic superior vena cava obstruction in the absence of symptoms
1	Mild	25	Edema in head or neck (vascular distention), cyanosis, plethora
2	Moderate	50	Edema in head or neck with functional impairment (mild dysphagia, cough, mild or moderate impairment of head, jaw or eyelid movements, visual disturbances caused by ocular edema)
3	Severe	10	Mild or moderate cerebral edema (headache, dizziness) or mild/moderate laryngeal edema or diminished cardiac reserve (syncope after bending)
4	Life-threatening	5	Significant cerebral edema (confusion, obtundation) or significant laryngeal edema (stridor) or significant hemodynamic compromise (syncope without precipitating factor, hypotension, renal insufficiency)
5	Fatal	<1	Death

[a]Adopted from Yu et al. [70]

term success with minimal complication rate. Major complications include stent migration, bleeding, pericardial tamponade, pulmonary edema and pulmonary embolism [75].

Although stenting has changed management over the last few decades, not every patient is a candidate. Until further evidence is established, stent placement should be reserved for patients who have significant, life style altering symptoms that are either too great to wait for chemotherapy or radiation or who do not respond to these modalities. In general stenting should be avoided or used as a last resort in patients with a good chance of recovery and longer life expectancy, to prevent long-term complications such as stent occlusion [75]. In these patients, primary angioplasty with local catheter directed thrombolytic therapy and early institution of systemic anticoagulation is generally preferred [75]. Adjunct therapies to alleviate symptoms include head elevation, supplemental oxygen, diuretics and corticosteroids to decrease laryngeal and cerebral edema [73]. As with most interventions, approach to patient selection for the appropriate mode of therapy is vital in improving overall outcomes.

Splanchnic Vein Thrombosis and Stenosis

Splanchnic venous thrombosis (SVT) is an uncommon yet potentially fatal manifestation of VTE. The splanchnic system encompasses the hepatic veins, and the portal circulation. Primary presentations of SVT are Budd-Chiari syndrome, portal vein thrombosis (PVT) and mesenteric vein thrombosis (MVT) with the PVT and MVT constituting the majority of cases.

Risk factors of SVT include cirrhosis, and abdominal malignancies (mainly gastrointestinal, pancreatic or hepatobiliary system) present in 34% and 31% of PVT patients, respectively [76, 77]. In the last few decades, myeloproliferative neoplasm has accounted for a majority of SVT cases [76]. A gain-of-function mutation of the tyrosin-kinase JAK2 (JAK2V617F), has also been strongly associated with development of both myeloproliferative neoplasm and SVT [76, 78–80]. A recent meta-analysis found a prevalence of JAK2 mutation of 32.7% (95% CI, 25.5–35.9%) in patients with known SVT, and also reported a strong association between JAK2 mutation and the development of SVT (OR 54; 95% CI, 13–222) [76, 80]. Given the strong association, peripheral blood screening for JAK2 mutation is recommended in patients with idiopathic SVT [81].

Clinical presentation of SVT patients varies depending on the size and extent of thrombosis, vessels involved, chronicity of thrombosis and presence of bowel wall ischemia. Acute SVT presents with nausea, vomiting, diarrhea and sudden onset, colicky, mid-abdominal pain sometimes with signs of bowel infarction and peritonitis in up to two thirds of patients [82, 83]. In the subacute form, abdominal pain continues for days to weeks, however, without significant risk of bowel infarction. In the chronic setting of slow and progressive portal vein stenosis, most commonly from pancreatic cancer, patients do not complain of pain and present with nonspecific symptom of several months duration, and is sometimes even diagnosed incidentally. When the portal or splenic vein is severely stenosed or thrombosed, patients may have signs of portal hypertension including splenomegaly, ascites, hypersplenism and upper or lower GI bleeding from esophageal and mesenteric variceal hemorrhage, respectively [82]. Elevated mesenteric venous pressures can also cause bowel wall edema, which can result in malabsorption, weight loss and diarrhea. Distinguishing venous hypertensive bowel dysfunction and chronic mesenteric arterial ischemia is key in patients where tumors may be compressing both the SMA and the SMV.

Diagnosis of SVT is challenging since the clinical presentation overlaps with several other abdominal conditions; however, given a high mortality rate, a high degree of suspicion in patients with abdominal malignancy remains crucial to avoid delays in diagnosis. Doppler ultrasonography is excellent at depicting thrombus in the proximal portal, hepatic and mesenteric veins, however, it is highly operator dependent and may be obscured by shadowing artifacts from bowel gas. CT has been a widely established technique excellent at defining extent of bowel involvement, depicting bowel wall thickening, abnormal wall enhancement, filling defects in the vasculature and collateral circulation [84]. Late findings of pneumatosis and portal venous gas are sometimes seen radiographically, however, CT is excellent at ruling out other conditions that can cause abdominal symptoms (Fig. 11.23). CT can have false negatives if the thrombus is in a smaller, distal branch or related to suboptimal contrast timing opacifying the venous circulation. Mesenteric angiography is rarely performed as a diagnostic procedure and is reserved for those patients with a high suspicion of venous thrombosis with an intention to treat.

Treatment of SVT is not straightforward due to the challenging and complicated nature of affected patients and low level of evidence and lack of controlled trials. Several patients have underlying cirrhosis and the chronic form of SVT present with variceal bleeding, anticoagulation is not always indicated. However, if there are no major contraindications, anticoagulant therapy with LMWH or UFH along with Vitamin K antagonists is recommended for those presenting with acute symptomatic thrombosis [32, 76, 85]. More recently, direct thrombin inhibitors such as rivaroxaban has also been a cost effective alternative therapeutic option for those patients with preserved renal function. In general, treatment is recommended for at least 3 months, but in cases of un-resolving SVT for those patients in a persistent procoagulant state, the treatment is continued indefinitely. Acute SVT with evidence of ischemic bowel warrants immediate surgical management.

Given the risks associated with systemic thrombolysis, endovascular techniques for local thrombolysis is preferred for selective patients. Catheter directed thrombolysis, aspiration thrombectomy and stent placements have been described in several small case series' [86–94] for portal venous and mesenteric venous thrombosis (Fig. 11.24) with good long-term clinical success rates [95]. Pharmacological thrombolysis is performed with both urokinase and r-tPA with feared complications such as vessel perforation, worsening bowel ischemia, and gastrointestinal bleeding vary significantly, however, meticulous approach and technical improvements over the years have minimized major complications. Indirect methods such as intra-arterial infusion via the superior mesenteric artery (SMA) have also been performed, however, only in select patients with small venous thrombus burden, with longer infusion times and a larger dose of local thrombolytic [96, 97]. In patients with symptomatic portal vein stenosis, most commonly from tumor compression or after transplant, portal vein stenting is effective at reducing symptoms, thought have moderately high rates of stent thrombosis (43% at 16 months) [98].

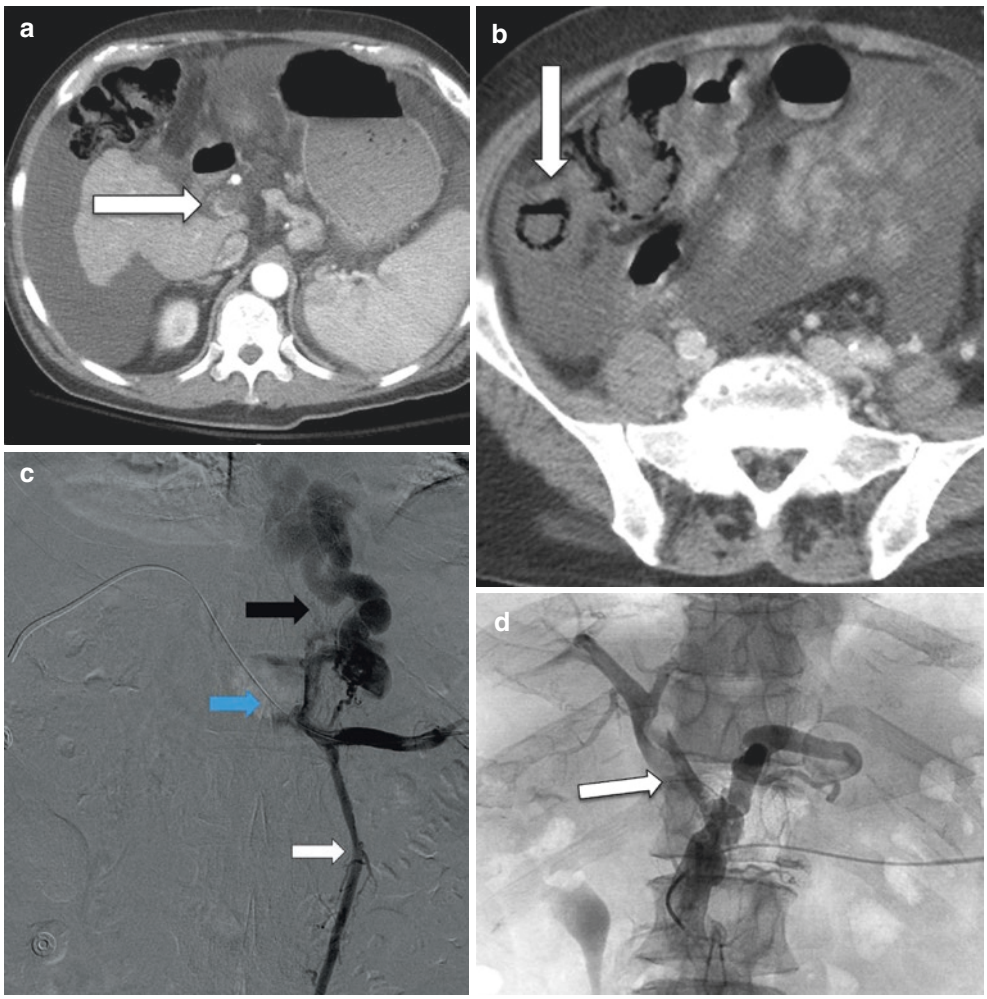

Fig. 11.23 (**a**) A Sixty-six year old male with cirrhosis, ascites presents with worsening abdominal pain. CT Abdomen with IV contrast shows occlusion of the extra-hepatic main portal vein. (**b**) CT Images of the lower abdomen in the same patient shows ileo-cecal pneumatosis, a sign of mesenteric ischemia. (**c**) Digital subtraction angiogram from transplenic venous access. Total occlusion of the portal vein (*blue arrow*) results in diminutive superior mesenteric vein (*white arrow*) and filling of esophageal and gastric varices (*black arrow*) via the coronary vein. Catheter directed thrombolysis was performed. (**d**) Venogram after transplenic catheter directed thrombolysis shows improved filling of the SMV with hepatopetal flow and filling of the portal vein. Filling defect in the portal vein persists (*arrow*), however, there is decreased filling of varices

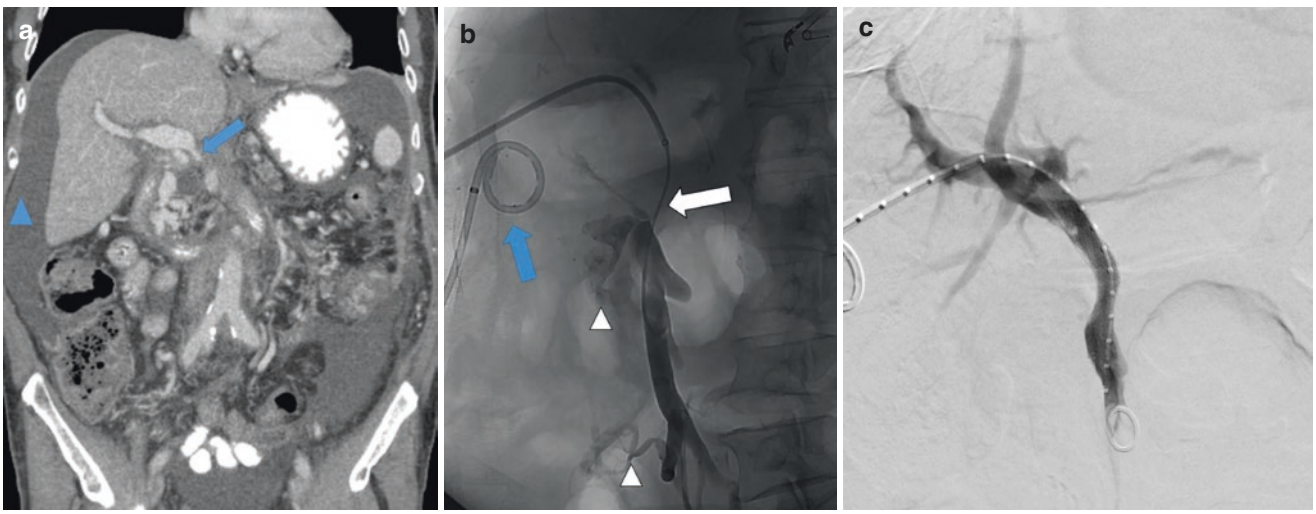

Fig. 11.24 (**a**) A 59 M with locally advanced pancreatic cancer causing occlusion of the main portal vein (*blue arrow*). Patient developed increasing ascites (*blue arrowhead*).(**b**) Transhepatic angiogram from the superior mesenteric vein showing no flow into the portal vein (*white arrow*). Elevated venous pressures result in varices and cavernous transformation of the portal vein (*white arrowheads*). An intraperitoneal drainage catheter (*blue*) was placed prior to transhepatic access. (**c**) Resotration of hepatopedal flow after placement of self-expanding metallic stent. Patients ascites volume decreased substantially

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