The diagnosis of venous thromboembolism on the basis of clinical signs and symptoms is notoriously inaccurate and, therefore, mandates confirmatory diagnostic testing. Unfortunately, all diagnostic tests for deep venous thrombosis (DVT) and pulmonary embolism have clinical or practical limitations. Contrast venography and pulmonary arteriography are usually regarded as the reference standards for the diagnosis of DVT and pulmonary embolism, respectively. However, even contrast venography may be impossible to perform in 9% to 14% of patients, may fail to visualize 10% to 30% of venous segments, and may be associated with postvenography thrombosis in up to 8% of patients.[1]

Both venography and pulmonary arteriography are often perceived as too invasive and impractical for routine use. This has led to the use of a variety of less invasive screening tests. Venous duplex ultrasonography is now the most widely used diagnostic test for acute DVT, while helical (spiral) computed tomography (CT) pulmonary angiography is replacing ventilation/perfusion scintigraphy for the diagnosis of pulmonary embolism at many institutions. However, rather than serving as diagnostic end points, the limitations of these noninvasive studies require their use in validated algorithms that limit but do not eliminate the number of angiographic studies required.

Diagnostic Pitfalls

The cancer patient exemplifies many of the pitfalls in the diagnosis of venous thromboembolism. In their review, Gomes and Deitcher note that the appropriate diagnosis of venous thromboembolism in cancer patients is especially critical, as these patients have autopsy rates of venous thromboembolism as high as 50%, are at high risk for a recurrence of the condition, and are at a three- to sixfold increased risk of treatment-related complications. The risks of failing to make a timely diagnosis and of inappropriate anticoagulation are high in this patient population. Unfortunately, some features of the cancer patient's underlying disease may make diagnosis particularly difficult. Diagnostic algorithms that are useful in healthy outpatients may have limited utility in the patient hospitalized with cancer. As the authors note, although potentially useful in excluding venous thromboembolism in symptomatic outpatients, D-dimer testing has relatively little value in the cancer patient.

Similarly, limitations in imaging the iliac veins and differentiating thrombus from extrinsic compression may limit the utility of duplex ultrasonography in patients with bulky pelvic tumors or adenopathy. Venous duplex ultrasonography also has well-recognized shortcomings in differentiating acute from chronic thrombus-a concern in cancer patients at high risk for recurrent DVT. Bronchial or pulmonary arterial obstruction by tumor may similarly cause false-positive studies for pulmonary embolism. Although initial noninvasive evaluation is appropriate in the cancer patient, further workup with other imaging modalities, such as CT or magnetic resonance imaging to evaluate for extrinsic compression by tumor, or invasive contrast studies may be necessary to establish a definitive diagnosis.

Clinical Context
Commentary (Meissner): Diagnosis of Venous Thromboembolic Disease in Cancer Patients
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The importance of understanding both the technical and local limitations of any diagnostic test, as well as their role in validated diagnostic algorithms, is perhaps the most important point of Gomes and Deitcher's review. A thorough understanding of these limitations has been made more difficult by the rapid proliferation of diagnostic technology, the occasional introduction of new diagnostic tests prior to clinical validation, and the frequent disconnection between the specialist interpreting a study and the clinician caring for the patient. Without understanding the implications of a nondiagnostic or indeterminate noninvasive test, physicians are often unwilling to consider further studies such as contrast venography or pulmonary angiography.

The authors make a valid point that essentially all cancer patients with clinical signs or symptoms should be regarded as having a high probability of venous thromboembolism in algorithms that rely on an assessment of pretest probability. Indeterminate studies mandate more definitive evaluation. Perhaps of even greater concern is the casual acceptance of a positive or negative study without considering the limitations of the diagnostic test in the context of the patient's clinical presentation. A negative compression duplex ultrasound does not exclude isolated iliac venous thrombosis, while a positive study may not eliminate the possibility of extrinsic compression by tumor.

Institutional Variations

It is also important to recognize that diagnostic tests vary considerably across centers. Clinicians must therefore have a basic understanding of how a given test is performed at their institution. Although duplex ultrasonography is now widely used in the diagnosis of acute DVT, there is considerable variability in the extent of the examination. Many departments routinely perform only compression ultrasound of the proximal lower-extremity veins without imaging the pelvic or calf veins. This approach has been validated in prospective management trials,[2,3] but provides only a partial evaluation of the venous system and requires serial testing to exclude propagation of isolated calf vein thrombosis. Although more technically challenging, adequate visualization of the iliac veins is possible in up to 47% of patients,[4] and the sensitivity of technically adequate studies for symptomatic calf vein thrombosis may be as high as 95%.[5] Still others limit studies to the symptomatic extremity. However, given the difficulty in differentiating acute from chronic thrombus,[2,3] the authors are correct in recommending that cancer patients undergo bilateral lower extremity duplex ultrasound to establish a baseline in the event of recurrent symptoms. This recommendation should probably be extended to any patient who is at significant risk for recurrent venous thromboembolism.

Helical CT pulmonary angiography is now widely used in the diagnosis of pulmonary embolism and appears to have some utility in the detection of central and segmental pulmonary embolism. However, the reported sensitivity has varied from 53% to 100%, and accuracy is highly dependent on equipment, scanning parameters, and reader experience.[6,7] Furthermore, although the importance of detecting subsegmental pulmonary embolism remains controversial, it is difficult to discount the potential of a missed subsegmental pulmonary embolism in the cancer patient at risk for recurrent venous thromboembolism if not treated appropriately. Use of multidetector spiral CT with thin (1-mm) collimation appears to improve both the detection of subsegmental pulmonary embolism as well as interobserver variability.[8] However, the accuracy of such tests in specialized centers with well-defined protocols and late-generation equipment may not be universally applicable.

Validation Standards

Finally, with the rapid evolution of technology, new diagnostic tests are increasingly incorporated into clinical practice prior to rigorous validation. The standards for validation of a new diagnostic test have been well established and require first that accuracy be established in consecutive patients who prospectively undergo both the new diagnostic test and an established gold standard test, with independent blinded interpretation of the results according to explicitly defined criteria.[9] Once sensitivity and specificity are established, the safety of managing patients according to the results of the test must be confirmed. In the case of venous thromboembolism, such trials establish the safety of treating or withholding anticoagulation based upon a positive or negative test respectively. Although recurrent pulmonary embolism has been reported in as few as 0% to 3% of patients after a negative helical CT pulmonary angiogram,[10] rigorous prospective management trials are still lacking. The current evidence suggests that a negative CT pulmonary angiogram should not constitute a diagnostic end point in the evaluation of pulmonary embolism.[7] Similarly, despite advances in
imaging technology and the expense and inconvenience of serial exams limited to the proximal lower-extremity veins.[11] the safety of withholding anticoagulation after a single, complete, technically adequate duplex scan including the calf and iliac veins has not been demonstrated.

Conclusions

Gomes and Deitcher review most of the currently available diagnostic tests for acute DVT and pulmonary embolism. Their recommended algorithms for evaluating venous thromboembolism in the cancer patient begin with venous duplex ultrasonography and CT pulmonary angiography for the evaluation of DVT and pulmonary embolism, respectively. These algorithms are appropriately designed to limit but not eliminate the need for contrast venography and pulmonary arteriography. As the authors imply, it is incumbent on all of us caring for patients at risk for thromboembolism to understand the diagnostic tests upon which treatment is based. This includes a thorough understanding of the limitations of the study, particularly the circumstances that may lead to indeterminate, false-positive, or false-negative studies in a given patient population.

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