Prevalence of Upper Extremity Deep Venous Thrombosis Diagnosed by Color Doppler Duplex Sonography in Cancer Patients With Central Venous Catheters

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Objective. The purpose of this study was to review the literature concerning upper extremity deep venous thrombosis (UEDVT) diagnosed by color Doppler duplex sonography (CDDS) in cancer patients with indwelling central venous catheters (CVCs). ***Methods.*** From computerized databases (MEDLINE and Ovid), relevant publications regarding CDDS of the upper limb veins in cancer patients with CVCs were reviewed. ***Results.*** Patients with malignancy have a higher rate of thrombosis, which is increased by the presence of CVCs. Screening CDDS in asymptomatic patients showed CVC-related UEDVT in 11.7% to 44% of patients. In symptomatic cancer patients, the range was similar to the asymptomatic ones, 6.7% to 48%. The presence of a CVC almost doubled the incidence of UEDVT in symptomatic patients. Color Doppler duplex sonography is an accurate examination for the diagnosis of UEDVT, with sensitivity ranging from 78% to 100% and specificity ranging from 82% to 100%. The main obstacle for the diagnosis of UEDVT is the presence of overlying bones, making it difficult to visualize and impossible to directly assess by compression techniques. Color and spectral Doppler sonography and the use of small transducers aid in the diagnosis. When several parameters are evaluated in combination, CDDS is a reliable method for diagnosing CVC-related thrombosis. ***Conclusions.*** Great variability in the prevalence of catheter-related thrombosis in cancer patients has been reported, although it is uniformly higher compared with patients without cancer. Color Doppler duplex sonography is the modality of choice for the diagnosis of CVC-related UEDVT in symptomatic cancer patients and for screening for asymptomatic thrombosis in this specific population. ***Key words:*** central venous catheter; color Doppler sonography; embolism; extremities; venous thrombosis.

Abbreviations
CDDS, color Doppler duplex sonography; CVC, central venous catheter; DVT, deep venous thrombosis; PE, pulmonary embolism; SVC, superior vena cava; UEDVT, upper extremity deep venous thrombosis; VTE, venous thromboembolism

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Cancer patients have an increased predisposition for the development of thrombosis because of an inherent and acquired hypercoagulable state, initiated by tumor cells and increased by stasis secondary to tumoral mass compression and by different therapeutic regimens, including chemotherapy, hormonotherapy, and radiation. Venous thromboembolism (VTE) is one of the most common complications seen in cancer patients.[1,2] The incidence based on the analyses of controlled trials varies from 1% for limited stage breast cancer treated with tamoxifen to 60% for patients with any type of cancer who undergo orthopedic surgery and do not receive prophylactic therapy.[3] Patients with cancer have a 6-fold increased risk of VTE compared with those

without cancer. Among internal medicine hospitalized patients, the relative risk among cancer patients for development of VTE is 10-fold compared with patients without cancer.[4] The calculated incidence of VTE in cancer patients overall is 15%.[5]

The increasing use of indwelling central venous catheters (CVCs) for chemotherapy administration and parenteral feeding or any fluid administration may result in an increased prevalence of upper extremity deep venous thrombosis (UEDVT) in cancer patients. Pulmonary embolism (PE) is not unusual; it is sometimes a lethal complication of UEDVT, and prevalence comparable with that of lower extremity thrombosis has been reported.[6,7] Other notable complications of UEDVT are loss of vascular access, superior vena cava (SVC) syndrome, and post-thrombotic venous insufficiency.[8,9] The extent of VTE associated with CVCs in cancer patients remains unclear. Central venous catheter–associated upper venous thrombosis may be asymptomatic, or its presenting symptoms may include swelling or pain of the ipsilateral arm or neck. The clinical manifestations of UEDVT are not specific, and in more than 50% of cases, objective methods of examination yield negative findings for UEDVT. Venography is the standard method for the diagnosis, although because of its invasive nature and the risk of nephrotoxicity and allergic reactions to iodinated contrast agents, it cannot be used as a screening tool in asymptomatic patients at high risk for deep venous thrombosis (DVT). Color Doppler duplex sonography (CDDS) is an accurate examination for the diagnosis of UEDVT, with sensitivity ranging from 78% to 100% and specificity ranging from 82% to 100%.[9,10] Sensitivity of 100% and specificity of 94% for compression sonography and color Doppler sonography for UEDVT with venography as the reference test were reported by Prandoni et al.[7] Color Doppler duplex sonography allows an early and safe diagnosis of thrombosis without straining the patients. The incidence of clinically overt CVC-related UEDVT in different studies varies between 0.3% and 28.3%; the incidence assessed by venography ranges between 27% and 66%; and PE is reported to occur in 15% to 25% of patients, with an autopsy-proven PE rate of up to 50%.[11] A 13% incidence of PE was described in a total population of 406 patients with UEDVT in 9 studies.[12] In another study, PE was reported to complicate UEDVT in 36% of patients and may even have been the presenting manifestation.[13]

We review the prevalence of UEDVT in patients with indwelling catheters, specifically, in a cancer population with diagnosis by CDDS. The incidence of CVC-associated thrombosis of the upper limb diagnosed by CDDS, venography, or both in symptomatic and asymptomatic cancer patients is given in Table 1.

Color Doppler Duplex Sonography for the Diagnosis of UEDVT in Symptomatic Cancer Patients With CVC

In a retrospective study, among 573 examinations in cancer patients with symptoms of UEDVT, sonographically evident thrombosis was present in 40% of the patients. In 57% of the cases, a CVC had been inserted. In this specific population, the frequency of thrombosis was 48% versus 28% in patients without CVCs.[14] The 28% frequency of UEDVT in cancer patients without central lines suggests that malignancy alone is a considerable risk factor for the development of UEDVT. With a strict protocol examination, the authors of that study found 90% adequate visualization of the vessels, 9% limited visualization, and 1% inconclusive findings.

In a prospective registry of 592 patients with UEDVT confirmed by venous sonographic examination, 324 patients had CVC-associated UEDVT; an indwelling CVC was the strongest independent predictor factor for UEDVT (odds ratio, 7.3; 95% confidence interval, 5.8–9.2); the presence of a central line was statistically significant for the prediction of UEDVT ($P < .001$).[25] In a study of peripherally inserted central catheter–related thrombosis in 76 upper extremities examined by CDDS for different indications, including symptomatic and asymptomatic patients, the overall rate of thrombosis was 3.9%; for cancer patients, the rate was 6.7%, significantly higher when compared with the benign diagnoses ($P = .011$).[20] Baarslag et al[22] reported UEDVT in 43% of symptomatic patients diagnosed by venography, sonography, or both; malignancy, central venous lines, or both were present in 74% of the patients with thrombosis. Survival for patients with known malignancy was significantly worse than for patients without malignancy ($P < .001$). In a prospective study of 246 cancer patients with CVCs, 24 occlusions (9.7%) were shown by sonography, 13 with catheter dysfunction and 11 with symptoms of phlebitis.[21] In a recently published multicenter

Table 1. Incidence (%) of CVC-Associated Thrombosis of the Upper Limb Diagnosed by CDDS, Venography, or Both in Symptomatic and Asymptomatic Cancer Patients

Report	Symptomatic	Asymptomatic	CDDS	Venography	Patients, n	UEDVT, %
Horattas et al[8]	+	+		+	539	28
Giess et al[14]	+		+		573	48
van Rooden et al[15]	+	+	+		105	28.6*
Bonfils et al[16]		+	+		78	14.1
Male et al[17]		+	+	+	66	29
Ruud et al[18]		+	+		41	44
Luciani et al[19]	+	+	+		145	11.7
Grove and Pevec[20]	+	+	+		76	6.7
Labourey et al[21]	+	+	+		246	9.7
Baarslag et al[22]	+		+	+	116	43
Couban et al[23]	+			+	255	4.3
Lordick et al[24]		+	+		43	30

*Total of patients with UEDVT, 30 (28.6%); 26 asymptomatic for DVT.

study, 255 cancer patients suspected of having CVC-associated thrombosis were investigated first by sonography; venography was performed in patients with negative or equivocal sonographic findings but a high suspicion of thrombosis. The overall incidence of thrombosis diagnosed was 4.3%; in the 11 symptomatic patients, the diagnosis was made by sonography alone in 7, and in 4, venography confirmed the sonographic diagnosis.[23] According to this study, symptomatic CVC-associated thrombosis in patients with cancer, although significant, was less common than previously reported. Whether measured clinically or radiographically, the rate of catheter-associated thrombosis was relatively low. Improvements in biocompatibility and insertion and maintenance techniques may be responsible for the reduction in the thrombosis rate in recent years.[26]

Color Doppler Duplex Sonography for the Diagnosis of UEDVT in Asymptomatic Cancer Patients With CVC

The true incidence of UEDVT in the cancer population is higher than reported. To determine the true incidence of venous thrombosis, a prospective per-protocol study of sequential venous duplex sonography in all patients with CVCs would be required. The use of CDDS in the diagnosis of catheter-related DVT has been debated. Phlebography has been the diagnostic method used for screening asymptomatic DVT in several prospective studies of patients with CVC,[27–29] although phlebography is not an accepted method for screening asymptomatic patients because it is invasive and carries risks of contrast media toxicity, allergy, and exposure to ionizing radiation. Only a few investigators have used prospective CDDS screening for catheter-related DVT.[15,19,30,31] A 28% rate of catheter-induced UEDVT, often subclinical, was reported in a review of the literature.[8] Sonographic screening for internal jugular vein catheter-related thrombosis detected UEDVT in 13 (30%) of 43 patients.[24] Luciani et al[19] reported an 11.7% frequency of catheter-related UEDVT in 145 patients with oropharyngeal tract cancer, usually asymptomatic; the incidence rate for asymptomatic patients with DVT was 76%. Incorrect catheter positioning was found as a major risk factor for thrombosis. Correct positioning of the catheter tip at the SVC or at the junction between the right atria and the SVC lowered the risk. In a previously published study, the authors reported a 14.1% rate of catheter-related DVT in asymptomatic cancer patients.[16] The authors concluded that because the incidence of catheter-related DVT is not low, and CVCs are widely used in cancer patients, careful monitoring and screening for catheter-related complications are highly recommended. Regarding catheter material and diameter, polyurethane and silicon catheters and a catheter diameter of 2.8 mm were associated with a lower rate of catheter-related DVT.[20] In a study by Cheong et al,[32] the complication rate for peripherally inserted central catheters in patients with solid tumors was 40.7%, including sepsis, thrombosis, blockage, and leakage, higher than the complication rate for nononcologic patients. By screening with Doppler sonography,

van Rooden et al[15] found an overall cumulative incidence of CVC-related thrombosis of 28.6% in 105 hematology patients receiving intensive chemotherapy, 26 of them with subclinical thrombosis, with a 7-fold increased risk of development of symptomatic disease. Koskoy et al[33] reported sensitivity of 94% and specificity of 96% for Doppler sonographic screening for catheter-related DVT when several parameters for DVT were assessed together.

Longitudinal studies performed for longer periods will be necessary to show infraclinical adverse events (DVT and PE) in patients with CVCs.[19] Larger study populations will also be needed to find out whether preventive anticoagulant regimens are effective in patients undergoing placement of CVCs, as have been suggested by some reports.[34,35] According to 2 recently published multicenter studies, the efficacy and, therefore, the need of thromboprophylaxis for CVC-related thrombosis in cancer patients were not proven.[23,36] Technical improvements in catheter insertion lowered the rate of thromboembolic complications.[26] Recent recommendations from Geerts et al[37] are to withhold anticoagulants in patients with CVCs, although antithrombotic prophylaxis should be considered for selected subgroups of patients with cancer at high risk for VTE.[38] Doppler sonographic examination may identify patients with subclinical DVT in this specific population and may play a role as a screening procedure and an aid in therapeutic decisions.

Regarding the pediatric population, in contrast to adults, approximately two thirds of DVT cases occur in the upper extremity and are secondary to the placement of a CVC. In a prospective study comparing phlebography and sonography in a population of 66 asymptomatic children with acute lymphoblastic leukemia, UEDVT occurred in 29% of them. The sensitivity of venography was higher than that of sonography regarding the proximal subclavian and more central deep veins (79% versus 37%), but sonography was more sensitive than venography for the jugular veins. The authors concluded that a combination of venography and sonography is required for screening UEDVT.[17] In a prospective study of children with cancer and CVCs, CDDS showed UEDVT in 44% of the catheterized veins.[18] Thrombosis develops frequently in pediatric cancer patients with central lines, but the clinical implications of this observation remain to be clarified.

Accuracy of CDDS in Diagnosing UEDVT

A high accuracy rate was found in 6 prospective studies, with sensitivity of 78% to 100% and specificity of 82% to 100%. False-positive results are unusual.[8,10,19,39,40]

Technical Considerations, Limitations, and Pitfalls

The initial test of choice for diagnosis of acute UEDVT is sonography because of its high accuracy, relatively low cost, portability, and lack of ionizing radiation.[41] Color Doppler duplex sonography is a reliable method for diagnosing CVC-related thrombosis, especially if several parameters are evaluated in combination.[33] Color Doppler duplex sonography of the upper limb veins uses a combination of gray scale, compression, color, and spectral Doppler sonography. The examined veins include the deep veins (internal jugular, subclavian, axillary, and both brachial veins) and the superficial veins (proximal cephalic and basilica veins). The main obstacle for the diagnosis of UEDVT is the presence of overlying bones on the medial subclavian vein and on centrally located veins (brachiocephalic vein and SVC confluence), which makes them difficult to visualize and impossible to directly assess by compression techniques. Spectral Doppler abnormalities in the proximal subclavian vein and upper brachiocephalic veins may be predictable for central occlusion in the lower brachiocephalic veins and SVC. Patel et al[42] related a 100% positive predictive value and a 91% negative predictive value for sonography in the diagnosis of complete central occlusions. A small, nonobstructive thrombus may remain undiagnosed, and large collateral veins may be misinterpreted as normal veins, leading to false-negative results.

To overcome some of the limitations of sonographic examination of the upper limb veins, use of a small footprint sector transducer from a supraclavicular or suprasternal approach is required. Useful findings to confirm the absence of thrombosis are a normal color Doppler biphasic spectral display on duplex sonography and a normal response of the vein to respiratory maneuvers such as vein collapse on brief deep inspiration (sniff test) and enlargement on the Valsalva test. Doppler flow analysis of transmitted atrial waveforms substantially improves the sensitivity of sonography; in the presence of a normal polypha-

sic atrial waveform in the subclavian and jugular veins, the possibility of a more central venous occlusion or stenosis greater than 80% is virtually excluded, and successful placement of central access catheters may be predicted.[43]

In the presence of acute thrombosis, pending its age, the clot may not be visualized in the vein lumen, and the diagnosis may be done in the presence of a vein that is enlarged and rigid, without changes on respiratory phases or respiratory maneuvers. Flow void on color Doppler sonography and dampened, nonpulsatile, and nonphasic flow on duplex sonography are diagnostic of central venous thrombosis.[44] Nonpulsatile flow is highly suggestive of a more central obstruction in the brachiocephalic vein or the SVC. Reversed flow in the jugular vein may indicate thrombosis in the brachiocephalic vein, with the internal jugular vein serving as a collateral pathway. Chronic thrombosis in a patient with long-term catheterization is more challenging because enlargement of the vein with a thrombotic lumen is not present. Color Doppler sonography is even more useful in chronic thrombosis, showing collateral veins, and an echogenic, flow-void, small-caliber central vein. Aliasing due to high velocities and high pulsatility in the stenosed areas in comparison to dampened peripheral waveforms are additional diagnostic parameters. Large veins in an unusual anatomic position and without the accompanying artery must be recognized as enlarged collaterals and not be mistaken for the main vein. Frozen valve leaflets and echogenic synechiae may be seen as sequelae of previous thrombosis.[44–47] A particularly different issue is acute-on-chronic thrombosis. The enlarged vein with a hypoechoic lumen represents an acute process. Comparison with a baseline examination may be helpful in these cases. In any case, the diagnosis of catheter-associated DVT may be difficult. Doppler sonography has lower accuracy in this setting than it does in lower extremity venous thrombosis.[48]

Conclusions

Venous thromboembolism is a significant complication of either chest- or neck-inserted or peripherally placed CVCs. Malignancy and central venous lines are major risk factors for upper extremity thrombosis, with predicted poor survival. The reported rate of CVC-related thrombosis varies widely, from 6.7% to 48% of patients. Color Doppler duplex sonography is the modality of choice for the diagnosis of UEDVT in symptomatic cancer patients with CVCs and in screening for asymptomatic UEDVT in this specific high-risk population.

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