Approach to the Management of Incidental Venous Thromboembolic Events in Patients With Cancer

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Abstract
Venous thromboembolism (VTE) is a frequent clinical complication of cancer and its treatment. Although much of the epidemiologic data regarding this complication have been based on symptomatic events, the use of multidetector row CT scanner technology has led to increased identification of VTE on scans ordered primarily for staging or restaging of malignancy. These incidentally discovered VTEs are variously referred to in the literature as incidental, asymptomatic, unexpected, or unsuspected VTE. A recent guidance paper by the Hemostasis and Malignancy Subcommittee of the International Society on Thrombosis and Haemostasis provided recommendations regarding this terminology (now termed incidental) and reporting of incidental VTE for clinical trials. A growing number of retrospective and case-controlled reports have described the prevalence, prognostic implications, and treatment options for these incidentally discovered VTE events, and have reported similar clinical outcomes for patients with incidental and symptomatic VTE. Because most reported patients with incidental VTE have been treated in a manner similar to those with symptomatic events, the present recommendations, except in rare circumstances, support the use of standard anticoagulation in the management of incidental deep vein thrombosis and pulmonary embolism. (J Natl Compr Canc Netw 2014;12:1557–1560)

Venous thromboembolic (VTE), inclusive of deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication of cancer and its treatment. Patients with cancer have a 4- to 7-fold increased risk of VTE and a 5- to 7-fold increased risk of bleeding on anticoagulation compared with patients without cancer.1–6 The development of VTE in patients with cancer is strongly influenced by tumor type, stage, and treatment modality.4 Thrombotic events contribute significantly to morbidity and mortality among patients with cancer, and VTE is the fourth leading cause of death among ambulatory patients.7 Available guidelines all recommend use of low-molecular-weight heparins (LMWHs) as opposed to warfarin among patients with VTE.8–11 However, anticoagulation for primary prophylaxis of VTE among patients with cancer is only recommended for those who are hospitalized, those who have multiple myeloma and are receiving lenalidomide and dexamethasone, and most patients postoperatively.8–11 Most available treatment guidelines using published clinical trial data do not recommend prophylactic anticoagulation for ambulatory patients receiving chemotherapy; however, one set of international guidelines suggests that primary pharmacologic prophylaxis “may be considered” for patients with a low bleeding risk who are receiving chemotherapy for locally advanced or metastatic pancreatic (strong recommendation) or lung cancer (weak recommendation).10 Current knowledge of the incidence, demographics, and outcome of cancer-related VTE is generally based on reported symptomatic events. However, the unsuspected finding of PE, DVT, or intra-abdominal thrombosis in the splanchic or visceral veins is not uncommon on routine staging CT scans of chest, abdomen, and pelvis.12 Studies addressing the clinical significance of these findings have been retrospective and are reviewed herein. Unfortunately, clinical trials involving patients undergoing cancer treatments have not consistently distinguished between incidental and symptomatic or suspected VTE, and therefore limited prospective data are available on patients with incidental VTE. Thus no high-grade recommendations can be made regarding their treatment. This problem was addressed in a set of

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recommendations by the Scientific Subcommittee of the International Society on Thrombosis and Haemostasis in 2012, which tackled the issues of proper nomenclature, reporting of radiographic techniques, notation of clot location, and distinction between symptomatic and incidental VTE in cancer clinical trials.12 This group advocates use of the term incidental rather than unsuspected, although they acknowledge that the PE-related symptoms may frequently be overlooked or misattributed in these patients.

The prevalence of incidental PE (IPE) is approximately 3%,13 with incidental DVT (IDVT) involving the lower extremities or abdominal vessels occurring in 1% to 3% of unselected patients with cancer.14,15 However, an analysis restricted to patients with gastrointestinal malignancies revealed a much higher prevalence of IDVT (7.3%), including lower extremity and visceral vein thromboses,16 highlighting the distinct impact of cancer type on the epidemiology of VTE. Retrospective studies suggest that as many as half of all cancer-related VTEs are incidentally detected.17 The pulmonary distribution of incidental emboli is different from that of symptomatic emboli, with nearly half occurring in major pulmonary vessels.18,19 Moreover, most patients with IPE actually have PE-related symptoms, such as shortness of breath or fatigue.19–21

Although no prospective data exist regarding the outcome of IPE among patients with cancer, retrospective studies suggest that these thromboses cause significant morbidity and have an impact on mortality that is comparable to that of symptomatic PE.20–24 Although some of these data may be flawed by the inclusion of various cancer types, stages, and treatment modalities known to impact survival, the general conclusion of nearly all published studies is that no significant difference in clinical outcome exists between patients with incidental versus symptomatic DVT and PE.

Abdel-Razeq et al25 performed a retrospective review of 34 patients with cancer and IPE, among whom 60.0% were symptomatic, and reported that 26.5% experienced sudden death within 30 days, not necessarily because of PE; 5.9% experienced pulmonary hypertension; and 5.9% developed recurrent PE. In the single study that used a control group of patients with cancer without PE matched for age, sex, cancer histology, and stage, patients with IPE complained of fatigue and shortness of breath significantly more frequently than did matched controls unaffected by VTE.19,21 Median overall survival was 8 months for the IPE cohort compared with 12 months for the matched controls;21 moreover, among the patients with IPE, those with symptoms had poorer survival than those who were truly asymptomatic.21 In 2 additional retrospective analyses of heterogeneous groups of patients with cancer, IPE conferred a similar adverse impact on survival than symptomatic PE, with death rates just less than 50% at 6 months22 and just more than 50% at 12 months.23 In addition, the report by den Exter et al23 found a similar incidence of VTE recurrence between the patients with symptomatic VTE and those with IPE (16.9% vs 13.3%; P=.77).

Two reported studies that included more homogeneous cohorts of patients with cancer also evaluated the clinical impact of IPE. In a small series of patients with non-Hodgkin’s lymphoma diagnosed with IPE, median survival was only 2 months, whereas median survival among the patients without thromboses was not reached.24 Sun et al26 compared a large cohort of patients with lung cancer and IPE (n=113) with similar patients with suspected symptomatic PE (n=67), and although no differences were seen in the distribution of thromboses between the groups, the median overall survival was significantly better in the group with IPE (9.3 vs 4.2 months; P=.001). These findings are contrary to those of other studies, and could be because only truly asymptomatic patients were assigned to the IPE group. As previously noted, one report found that the survival of patients with symptomatic IPE was worse than that of patients who were truly asymptomatic.24

The American College of Chest Physicians (ACCP) guidelines currently provide a grade 2B recommendation for the treatment of IPE and IDVT with anticoagulation.6 Unfortunately, the occurrence of these thromboses among patients with cancer was not specifically addressed within the recently published international clinical practice guidelines for the treatment of cancer-related VTE.10 In the study by Sun et al,26 anticoagulation therapy was used to treat only 45% of the patients with IPE, and these patients had a higher thrombotic burden than those who were not treated. Nonetheless, the median survival was significantly better in the treated group (30.9 vs 6.1 months; hazard ratio, 4.1; 95% CI, 2.3–7.6; P=.001). Most surveyed physicians self-report the use of anticoagulation to treat patients with cancer and in-
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Incidental VTE. ASCO guidelines suggest that the appropriate treatment of IPE identified proximal to the subsegmental pulmonary is not different from the standard treatment recommendation for cancer-associated VTE. Unfortunately, patients with cancer have a higher risk of major bleeding than those without when treated with anticoagulation. Pooled analysis of 3 studies including 154 patients with IPE treated with LMWH demonstrated major bleeding in 5.2%, with fatal bleeding in 1.3%, 23,25,27 The incidence of major bleeding was similar to that reported in the dalteparin-treated patients from the CLOT study (6%), which also included 1 fatal bleed. 28

The incidental identification of isolated subsegmental PEs (SSPEs) on staging CT scans can be a particularly vexing problem for oncologists, especially in light of the suggestion that these may not be clinically significant in a noncancer population. 29,30 In a recent meta-analysis by Carrier et al, 29 the rate of SSPE among patients presenting with symptoms suggestive of PE was 9.4% in patients who underwent multidetector row CT pulmonary angiography (CTPA) compared with 4.7% in patients who underwent a single-detector row CTPA. Nonetheless, the VTE risk at 3 months in patients with suspected PE who were left untreated based a negative result was 0.9% (95% CI, 0.4–1.4) and 1.1% (95% CI, 0.7–1.4) for single- and multidetector row CTPA, respectively. The authors imply that, despite the high likelihood that SSPEs were missed on single-detector CTPA, untreated patients did as well in terms of subsequent VTE development as those who had a negative result on the more sensitive screening test. Carrier et al 29 therefore suggest that the diagnosis of SSPE in an unselected group of patients presenting with PE-related symptoms may not be clinically relevant. However, the study population did not consist predominantly of patients with cancer, whose subsequent risk of VTE may be higher.

Furthermore, the risk of VTE recurrence may not outweigh the bleeding risk associated with anticoagulation given the favorable short-term outcome in unselected patients with untreated symptomatic SSPE. In a retrospective cohort study of 93 patients found to have SSPE on multidetector row CTPA, no recurrent VTE, hemorrhages, or deaths were reported at 3 months among the 22 untreated patients. 29 Among the 76% of patients who were treated with anticoagulation, however, 5 major bleeding complications, 1 VTE recurrence, and 2 deaths occurred (neither from PE). Because the decision to treat or to withhold anticoagulation was left to the treating physician and the study was conducted retrospectively, the impact of other factors, such as cancer, concomitant medications, or comorbidities, could not be analyzed.

The retrospective, matched cohort study by O’Connell et al 19,21 included the largest cohort of patients with cancer and incidental SSPE (ISSPE) published to date for whom survival data are available. Of the 70 patients identified to have IPE, 24% had ISSPE. The authors found no significant difference in survival between the 17 patients with ISSPE and their age-, histology-, and stage-matched controls. 21 Despite data suggesting that SSPE may not impact survival in the general population or among patients with cancer, most patients are treated when the diagnosis is known. 31 A survey of 47 physician members of the Thrombosis Interest Group of Canada indicated that the physicians were more likely to treat ISSPE if metastatic cancer was present. 32 Few data are available regarding the presence of coincident DVT among patients with cancer diagnosed with IPE, suggesting that it is not routine practice to test. However, ultrasonography to detect DVT may help determine whether to treat a patient with IPE confined to the subsegmental pulmonary arteries; in one study, half of patients with SSPE in whom ultrasound was performed demonstrated an unsuspected DVT. 19 Therefore, the detection of SSPE in patients with cancer can sometimes reflect a thrombosis in other sites, such as the lower extremities.

Incidental intra-abdominal and visceral VTE are also detected with increasing frequency in cancer staging CTs. Douma et al 15 reported a prevalence of incidental abdominal VTE of 1.1% (95% CI, 0.6–2.0). An even higher frequency of incidental visceral thrombi has been reported by other investigators. 14,17 However, ACCP guidelines currently do not recommend treating patients with asymptomatic visceral thrombi. Clinical data are lacking on outcomes in patients with cancer who have this problem and on the impact of anticoagulation.

Despite the limitations presented by the paucity of prospective treatment trials involving the management of patients with cancer who have IDVT and IPE more proximal than the subsegmental pul-
monary arteries, the weight of evidence strongly suggests that these patients have a clinical outcome similar to that of symptomatic patients. These patients frequently have symptoms that are likely PE-related but overlooked or misattributed to other factors. Therefore, several expert advisory groups have favored treating patients with IDVT and IPE similarly to patients with symptomatic DVT and PE, with extended use of LMWH.9–11 Controversy remains regarding the management of ISSPE in patients with active cancer. Because they may have a greater probability of concurrent DVT and a higher risk of recurrent thrombosis than noncancer patients, additional diagnostic studies for DVT detection and treatment may be justified in this group. Further research is needed to characterize the clinical relevance and outcome of ISSPE among patients with cancer, because these may differ from those of unselected patients reported in the literature. Although most of the research published to date suggests that IPE identified proximal to the subsegmental pulmonary arteries is clinically indistinguishable from IPE identified in patients with symptoms suggestive of PE, these data are largely retrospective in nature. Cancer clinical trials should report the incidental identification of VTE, including location, biomarkers, and treatment outcomes separately from suspected VTE.

References