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Incidental Venous Thromboembolism in Oncology Patients

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Cancer-associated thromboembolism is a frequent clinical complication, particularly in the context of anti-neoplastic therapy. The introduction of multidetector CT (MDCT) scanner technology has led increasingly to the identification of venous thromboembolism (VTE) on scans ordered primarily for staging or restaging of malignancy. Such incidentally discovered VTE are variously referred to in the literature as "incidental", "asymptomatic", "unexpected" or "unsuspected" VTE. There are emerging data describing the prevalence, prognostic implications and treatment options for such incidentally discovered VTE events.

The overall prevalence of incidental VTE among cancer patients undergoing routine staging MDCT scans varies, depending on the study population. Studies have reported incidental findings of both pulmonary embolism (PE) as well as deep venous thrombosis (DVT) identified on CT scans of abdomen and pelvis as well as splanchnic or visceral vein thrombi. In a recent large systematic review and meta-analysis of 12 studies including over 10,000 patients, cancer patients had a weighted mean prevalence of incidental PE of 3.1% (95% CI, 2.2–4.1%)[1]. In a large retrospective cohort analysis of scans in cancer patients, Douma et al reported a prevalence of an incidental abdominal deep vein thrombosis of 1.1% (95% CI 0.6–2.0), similar to that of a PE or lower extremity DVT (1.3%, 95% CI 0.7–2.3)[2]. A higher prevalence of abdominal DVT [2.50% (95% CI 1.78–3.48)] was observed by Ageno et al in a subgroup of cancer patients[3]. In higher-risk cancer patients, prevalence can be much higher. Singh et al evaluated consecutive gastrointestinal malignancy patients undergoing routine staging scans and found that 7.3% had unsuspected deep vein and visceral venous clots with incidental PE in 2.3% of patients[4]. The most recent reports suggest that a high proportion of cancer-associated VTE are incidentally discovered. In a retrospective cohort analysis by Moore et al, 44% of all thromboembolic events were incidental[5]. In the cohort study of Singh et al discussed earlier, 50% of DVTs and over 35% of PE were incidentally discovered[4].

Consequences of incidentally diagnosed VTE appear not to differ significantly from those associated with suspected VTE. In a recent analysis, rates of VTE recurrence, bleeding, and mortality were similar in cancer patients with incidental VTE compared to cancer patients with symptomatic VTE[6]. In a case-control study, cancer patients with incidental VTE had

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significantly worse survival (HR=1.51, 95% CI 1.01–2.27, P = 0.048) when compared to matched cancer patients without VTE[7]. In patients with pancreatic cancer, DVT (HR 25, 95% CI 10–63, p <0.0001), PE (HR 8.9, 95% CI 2.5–31.7, p = 0.007) and incidental visceral events (HR 2.6, 95% CI 1.6–4.2, p =0.0001) were all independently associated with mortality[8]. Furthermore, the pulmonary distribution of incidental emboli is no different than symptomatic emboli, with nearly half being in major pulmonary vessels[9]

Thus, incidentally discovered PE and DVT is a prevalent clinical problem amongst cancer patients and contributes significantly to the burden of cancer-associated VTE. However, there remains considerable confusion amongst investigators regarding appropriate nomenclature and definitions of such events and whether such events should be included in endpoints of prospectively designed cohort and interventional studies. In addition, there is confusion amongst clinicians regarding appropriate reporting and treatment choices for individual patients. The objective of this ISTH statement is to propose a standardization of the nomenclature, definition and reporting of incidentally discovered VTE. Such standardization is necessary to ensure consistency in reporting and to facilitate summary of results across studies.

Recommendations

1. **Nomenclature**. We recommend the use of the term “incidental” and recommend against the use of the term “asymptomatic”. Chart reviews of patients incidentally diagnosed with VTE suggest that many of them are in fact symptomatic, with symptoms possibly attributed to the underlying malignancy rather than to VTE[10]. Thus, in the majority of patients, these events are not truly asymptomatic. “Unsuspected” VTE may also be used; however, the majority of reports in this field have used the term “incidental” and this is concordant with the use of the term in other such diagnoses in medicine (e.g., incidental lung nodules or incidental adrenal adenomas). We recommend using the term “symptomatic” VTE to indicate cases where patients were investigated specifically for VTE based on signs and symptoms.

2. **Radiologic issues**. Radiology-related factors including slice thickness and sensitivity of the reader impact incidental VTE prevalence. In a meta-analysis of studies including patients with and without cancer, Dentali and colleagues reported a weighted mean prevalence of incidental PE of 3% with CT scans utilizing less than 5 mm slice thickness as opposed to 2% with scans utilizing at least 5 mm slice thickness[1]. Browne and colleagues reported that 5 mm slice thickness CT scans missed 39% of PE identified by thinner slices in CT pulmonary angiography scans[11]. Engelke evaluated the accuracy of PE diagnosis in patients with and without suspicious symptoms and found that PE was more likely to be missed when clinical suspicion was low (89.5% false negative rate among routine staging scans for esophageal cancer) and when the clot burden was low[12]. Indeed, little data are available regarding the prevalence and accuracy of isolated subsegmental pulmonary emboli, the detection of which may be heavily influenced by the expertise and threshold of suspicion among individual radiologists[13]. Isolated subsegmental PE constituted 6% of incidental PE identified in the series reported by Gladish et al and 24% in the series reported by O’Connell et al[10, 14]. We urge cancer providers in multidisciplinary teams to discuss these issues with their radiology colleagues and to ensure awareness of incidental VTE within their institutions, given the known clinical consequences of such diagnoses.

3. **Reporting of events**. We recommend, where possible, that retrospective and prospective studies (including clinical trials) separately report rates or proportion of

VTE that are incidental or symptomatic. We strongly encourage identifying the regional vessel involved (e.g., “portal vein thrombus” rather than “abdominal vein DVT”) as well as known information regarding the extent of the burden (e.g., isolated subsegmental PE). Where known, investigators should also report radiological factors such as slice thickness, which can influence the sensitivity of VTE detection.

4. **Reporting of outcomes**. We urge, where possible, that retrospective and prospective studies (including clinical trials) report outcomes including recurrent VTE, other synchronous or metachronous VTE, failure rates on anticoagulation and survival separately for incidental and symptomatic VTE.

5. **Study endpoints**. We leave to individual research teams the decision regarding whether or not to include incidental VTE as part of primary endpoints for studies of prophylaxis or treatment of VTE in cancer. We note, however, that the preponderance of evidence suggests that outcomes for patients with incidental PE are not significantly different than for symptomatic PE (with the possible exception of isolated subsegmental PE for whom additional imaging with lower extremity compression ultrasonography may be beneficial[10]) and that most clinicians do in fact anticoagulate patients with incidental PE[15].

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