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Review

Recurrent venous thromboembolism in anticoagulated cancer patients: Diagnosis and treatment

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ABSTRACT

Patients with cancer are at significantly increased risk of venous thromboembolism (VTE), due both to the impact of malignant disease itself and to the impact of certain anticancer drugs on haemostasis. This is true both for first episode venous thromboembolism and recurrence. The diagnosis and management of VTE recurrence in patients with cancer poses particular challenges, and these are reviewed in the present article, based on a systematic review of the relevant scientific literature published over the last decade. Furthermore, it is uncertain whether diagnostic algorithms for venous thromboembolism, validated principally in untreated non-cancer patients, are also valid in anticoagulated cancer patients: the available data suggests that clinical decision rules and D-dimer testing perform less well in this clinical setting. In patients with cancer, computed tomography pulmonary angiography and venous ultrasound appear to be the most reliable diagnostic tools for diagnosis of pulmonary embolism and deep vein thrombosis respectively. Options for treatment of venous thromboembolism include low molecular weight heparins (at a therapeutic dose or an increased dose), fondaparinux or oral direct factor Xa inhibitors. The choice of treatment should take into account the nature (pulmonary embolism or VTE) and severity of the recurrent event, the associated bleeding risk, the current anticoagulant treatment (type, dose, adherence and possible drug-drug interactions) and cancer progression.

1. Abbreviations

bid	twice daily
CAT	cancer-associated thromboembolism
CDUS	colour Doppler ultrasonography
CI	confidence interval
CT	computerized tomographic
CTPA	computed tomography pulmonary angiography
DVT	deep vein thrombosis

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DXI	direct oral factor Xa inhibitor
HR	hazard ratio
IU	international unit
IVCF	inferior vena cava filter
LMWH	low-molecular weight heparin
MRI	magnetic resonance imaging
MRDTI	magnetic resonance direct thrombus imaging
PE	pulmonary embolism
qd	once daily
SPECT	perfusion scintigraphy and CT
VKA	vitamin K antagonist
VTE	venous thromboembolism

2. Introduction

Patients with cancer are at significantly increased risk of venous thromboembolism (VTE), due both to the impact of malignant disease itself and also to the impact of certain anticancer drugs on haemostasis [1]. In consequence, the risk of VTE recurrence is also elevated [2,3]. The diagnosis and management of VTE recurrence in patients with cancer poses particular challenges, and these are reviewed in the present article, based on a systematic review of the relevant scientific literature published over the last decade.

3. Epidemiology of recurrent VTE in anticoagulated cancer patients

In non-cancer patients, the risk of recurrent VTE on full-dose anticoagulant treatment reported in prospective trials and registries is less than 2% at six months. It was recently estimated at 1.4% at one year in the relatively high-risk population of patients treated for a first unprovoked VTE [4]. In contrast, the VTE recurrence rate while on anticoagulants in patients with active cancer has consistently been shown to be significantly higher, ranging from 4 [5] to 17% [6] at six months in prospective trials and registries. Recurrent VTE has been reported to be associated with a 52% increase in the risk of death in patients with active cancer (95% confidence interval [CI] 1.16–2.00) [7]. A systematic review and meta-analysis estimated the case-fatality rate of recurrent VTE in such patients to be 14.8% [8]. However, this rate is likely to be an overestimate, since it is mainly explained by one large outlier in which 39 of 76 (47.4%) recurrent VTE events were considered fatal by the independent adjudication committee [9]. Of note, these uncertainties have led to the exclusion of fatal events from the primary endpoint of recurrent VTE in a recent pragmatic randomised trial of cancer-associated thromboembolism (CAT) treatment [10]. Using a common (recommended) and more restrictive definition of fatal PE could prove useful to obtain more homogeneous and reliable values for the case-fatality rates across studies [11].

The main factor influencing the rate of recurrent VTE in cancer patients appears to be the anticoagulant treatment regimen: vitamin K antagonists (VKAs) are associated with the highest rates, up to 17% at six months [6], whereas low-molecular weight heparins (LMWHs) reduce this risk by about 40% (hazard ratio [HR] 0.60, 95%: CI 0.45–079) when compared to VKAs [12]. Direct oral factor Xa inhibitors (DXIs) have been shown to be associated with the lowest VTE recurrence rates, ranging from 4% to 7.9% at six months, with a significant 37% risk reduction (95% CI: 0.47–0.86) when compared to dalteparin in non-inferiority randomised trials [5,13–15].

The search for other factors that may influence VTE recurrence despite therapeutic anticoagulation in patients with active cancer has been largely unsuccessful. The Ottawa score, developed in a retrospective cohort of 543 patients, took into account sex, cancer stage (Stage I vs. others), certain cancer types and a history of VTE, and appeared promising in a meta-analysis [16]. However, the first prospective study designed as an external validation cohort failed to show any significant prognostic value of this score [17]. Nevertheless, patients with metastatic disease [18], cancer progression, or with certain cancer types, such as pancreatic or lung cancer, have been shown to be at highest risk of recurrence in most studies. However, until more robust data is collected, such observations cannot translate into any therapeutic recommendations for routine practice either for initial anticoagulant treatment or, for example, for treatment intensification in case of cancer progression. Finally, apart from potential drug-drug interactions, whether cancer treatments themselves affect the risk of recurrent VTE while on anticoagulants remains largely unknown and poorly studied.

4. Diagnosis of recurrence of pulmonary embolism

4.1. Clinical suspicion

Even if treated with appropriate doses of anticoagulants, any new symptoms evocative of PE in cancer patients should trigger further diagnostic investigations. However, cancer patients frequently have symptoms evocative of PE, such as chest pain, dyspnoea or haemoptysis, which may be explained by the cancer itself, and the emergent symptoms that trigger further investigation must be evaluated carefully, looking for simple alternative diagnoses in order to avoid repeated tests that may be unnecessary. Furthermore, it is uncertain whether the recommended diagnostic algorithms for PE, validated principally in untreated non-cancer patients, are also valid in anticoagulated cancer patients [19].

As in first episode PE, recurrent PE in cancer patients may be only diagnosed incidentally through the findings of tests, such as chest CT with contrast, ordered for reasons other than clinically-suspected VTE recurrence, principally for cancer evaluation. The proportion of asymptomatic incidentally identified recurrent PEs in cancer patients has been reported in only one of the prospective trials comparing dalteparin and DXIs [5]. In this study, the independent blinded adjudication committee identified 7 of 13 recurrent PE events (54%) as being asymptomatic.

4.2. D-dimers

The diagnostic performance of D-dimer tests for VTE diagnosis is known to be much lower in cancer patients than in non-cancer patients [20]. Furthermore, recent data suggest that, even in non-cancer patients on anticoagulant therapy for a previous VTE episode, normal D-dimer levels might be insufficient to safely rule out recurrent VTE with confidence [21,22]. Therefore, the exact place, if any, of D-dimer testing in the diagnostic work-up of a clinically-suspected recurrent VTE event in cancer patients is likely to be extremely limited, and imaging tests may be required even in patients with a low clinical probability of PE.

4.3. Chest CT and CT pulmonary angiography

Chest computed tomography pulmonary angiography (CTPA) is the most reliable diagnostic tool for diagnosis of PE [23]. In addition, unlike lung scintigraphy, this test is able to diagnose alternative or associated conditions that may explain emergent symptoms, such as pleural or pericardial effusion, pneumonia, or cancer progression involving large vessels, the proximal airways or the chest wall.

Regarding incidental PE, the diagnosis is often made or suspected on CT scans with contrast that are not as informative as CT pulmonary angiograms dedicated to diagnose PE. In case of any doubt, reinterpretation or reinjection should be performed in a timely manner (as soon as possible) in order to ascertain or to rule out the diagnosis.

Table 1
Common diagnostic criteria for recurrent pulmonary embolism.

In patients with new symptoms of PE:
– One or more new filling defects observed in segmental or more-proximal arteries with CTPA or pulmonary angiography[a]
– A new intraluminal filling defect, or an extension of an existing defect, or a new sudden cut-off of vessels more than 2.5 mm in diameter observed on pulmonary angiogram[a]
– A new perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) observed on ventilation/perfusion lung scan (VQ scan)
– If CT pulmonary angiography, pulmonary angiography or VQ scan is inconclusive or cannot be performed, demonstration of a new or recurrent proximal DVT in the lower extremities by colour Doppler ultrasonography, venography or MRI allows a diagnosis of recurrent PE to be made
In unsuspected PE:
– One or more new filling defects in a segmental or a more-proximal artery observed with CTPA
– Visible on a follow-up image but not identifiable on previous images
– Or an interval study clearly showing resolution of emboli

Adapted from the Supplementary appendix of Agnelli et al., 2020 [15].
[a] Pulmonary angiography is no longer available in most centres.

The criteria required for the diagnosis of recurrent PE, as used in virtually all prospective clinical trials and registries, and as recommended in everyday practice, are listed in Table 1. Whether symptomatic or not, the most important step is a comparison with a previous similar imaging test, showing the presence of new defects. In the absence of previous imaging tests, or if similar tests cannot be compared (for example, comparing CTPA and lung scintigraphy), the diagnosis of recurrent PE should be considered with extreme caution.

4.3.1. Lung scintigraphy and venous imaging

When CTPA is unavailable or unfeasible (for example, in severe renal insufficiency), clinicians must rely on other imaging techniques. Lung scintigraphy, whether using the classical planar technique or more recent SPECT technology, is a non-invasive test that has virtually no contraindication and a sensitivity approaching 100% for the diagnosis of PE. However, this test is not readily available in all centres. Furthermore, many patients with cancer have conditions not related to PE (for example, pleural effusion, emphysema or thoracic tumour masses) that may complicate the interpretation of abnormal lung scintigraphy findings. Therefore, the criteria for diagnosing recurrent PE on lung scintigraphy are rather restrictive and, as for CTPA, a comparison with previous imaging tests is required (Table 1). Whether a newer technique that combines perfusion scintigraphy and CT images (SPECT) could improve the specificity of the test and its performance in the diagnosis of recurrent PE should be considered currently uncertain and its results interpreted with caution [24,25].

Finally, when CTPA and lung scintigraphy cannot be performed or are inconclusive, venous imaging (colour Doppler ultrasonography [CDUS], venography, CT venography, magnetic resonance imaging) may prove helpful if they show new venous clots in proximal veins. However, again, strict criteria including comparisons with previous imaging must be applied (Table 1). These criteria remain consistent with the ISTH guidance published in 2013 [19]. Of note, upper-limb DVT, particularly in the case of placement of a central venous catheter, may be a source of PE and should be considered in this context.

4.3.2. Diagnostic challenges

In cancer patients, clinicians must be aware of a number of imaging "red herrings" that can be misinterpreted as recurrent VTE and lead to unnecessary therapeutic measures.

4.3.3. Tumour "thrombi"

Tumour thrombi (endovascular masses that contain mainly or exclusively tumour cells, rather than coagulated blood) may be difficult to distinguish from "real" PEs. Such tumour thrombi are common in lung cancer patients with invasion of proximal pulmonary arteries, but may also represent a form of endovascular lung metastasis. An example is shown in Figs. 1 and 2. Although pathological confirmation is difficult to obtain (and rarely necessary), such tumour thrombi have been demonstrated mainly in sarcoma patients (including primary sarcomas of pulmonary arteries), renal-cell carcinoma and urothelial carcinomas. The real frequency of this phenomenon is difficult to determine [26,27]. In a case series of four patients with renal cell carcinoma and pulmonary "embolism" who had follow-up CT scans, one (25%) patient was shown to have thrombus growth consistent with tumour thrombi [28]. In case of doubt, a PET scan may be helpful to distinguish blood clots from tumour thrombi, and endovascular biopsies may be performed in specialised centres [26,27]. Of note, these macroscopic tumour thrombi must be distinguished from pulmonary tumour microembolisms and pulmonary tumour thrombotic microangiopathy, which are not usually visible on CTPA (whereas perfusion lung scintigraphy is abnormal). Such diagnoses are often suspected late, at the stage of pulmonary hypertension, and too often confirmed only at autopsy [29], but they may also occur in the absence of pulmonary hypertension [30].

4.3.4. Stasis clots

The pathophysiology of PE (i.e., the passage of free venous clots through the right cardiac cavities and their embolisation in the pulmonary arteries) indicates that "true" embolisation can only occur in pulmonary arteries with a blood flow. Therefore, clots seen in arterial stumps after surgery, or in chronically atelectatic lobes or lungs, cannot be emboli *stricto sensu* and are instead clots formed in situ due to stasis (Fig. 2). Whether such clots need anticoagulant treatment is unknown but, at least, the risk of extension or "recurrence" is likely to be limited, even if left untreated (Figs. 1 and 2).

4.4. Proposals of the expert group

Proposals of the expert group:

- we suggest directly ordering imaging tests in cancer patients with clinically-suspected recurrent PE, and not using clinical prediction rules and D-dimer testing beforehand;
- in patients with suspected recurrent PE, we recommend carefully considering simple alternative diagnoses (for example, dyspnea due to massive pleural effusion or thoracic pain due to chest wall invasion) in order to avoid repeated tests that may be unnecessary;
- as a general rule, when incidental (symptomatic or asymptomatic) PE is diagnosed on an imaging test in cancer patients, we recommend that the new images be compared to baseline images to confirm or rule out recurrent PE;
- in cancer patients with suspected recurrent PE, we recommend CTPA as the preferred imaging technique, with comparison to baseline CTPA images, to confirm or rule out recurrent PE;

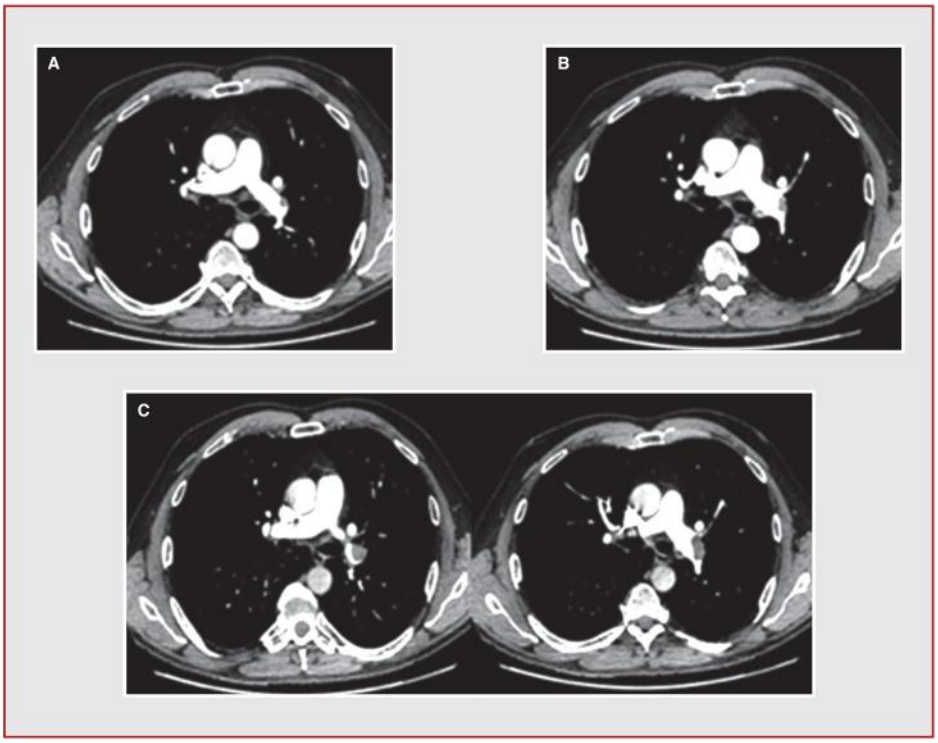


Fig. 1. Not pulmonary embolism recurrence: tumour thrombi. Asymptomatic left-sided lobar pulmonary "embolism" diagnosed on a routine CT scan after resection of renal-cell carcinoma with venous invasion (A). After 6 months of anticoagulants, the endovascular "thrombus" looks larger (B). A new CT scan 3 months later confirms thrombus growth (C). Solitary endovascular metastasis of the renal carcinoma was confirmed pathologically by pulmonary endarterectomy.

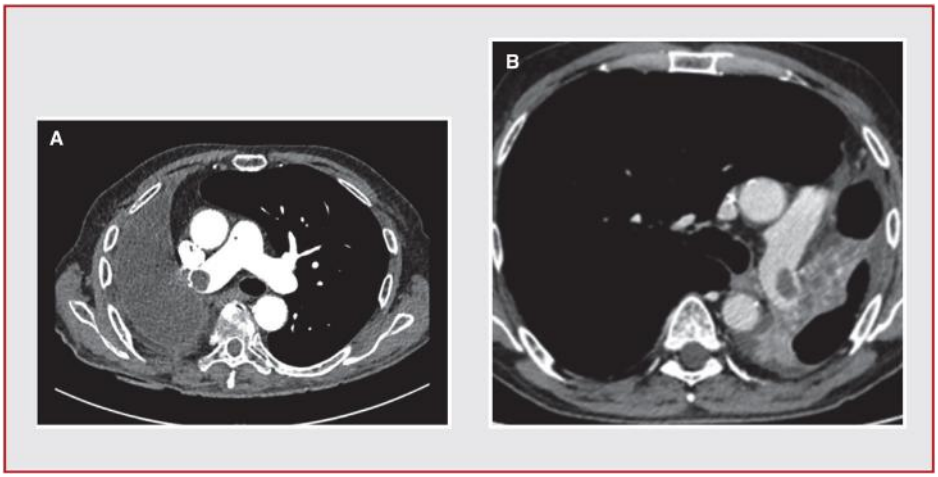


Fig. 2. Not pulmonary embolism recurrence: stasis clots. Stasis clots (i.e., not pulmonary emboli) in the right pulmonary artery stump after pneumonectomy (A), and in the left pulmonary artery trunk of a chronically atelectatic lung (B).

- in cancer patients with suspected recurrent PE, when CTPA is unavailable or unfeasible, we suggest performing V/Q lung scintigraphy only if a previous similar imaging test (planar scintigraphy or SPECT) is available for comparison;
- in cancer patients with suspected recurrent PE, when CTPA and lung scan are unavailable, infeasible or inconclusive:
  - we suggest performing CDUS of the lower extremities; recurrent VTE should be confirmed only if CDUS shows new proximal venous clots (this implies that a baseline CDUS should be available for comparison);
- in cancer patients with suspected recurrent PE and positive findings on CTPA, we recommend considering alternative diagnoses such as tumour thrombi or stasis clots before confirming the diagnosis of recurrence.

5. Diagnosis of recurrent deep vein thrombosis

5.1. Clinical presentation

As with first episodes of PE and DVT, recurrent DVTs may be asymptomatic. When the patient is symptomatic, the clinical symptoms and signs are similar to those of a first episode, such as pain, oedema, erythema, superficial collateral circulation or increase in skin temperature. As with the first episode, severe clinical presentation (indicated by entire leg or calf swelling, pitting oedema or collateral superficial veins) might be more frequent in cancer than in non-cancer patients. Moreover, the prevalence of recurrent DVT is at least two-fold higher in cancer patients [31].

5.2. Clinical probability assessment and D-dimer testing

Given the severity of the clinical presentation, the presence of cancer and the prior history of DVT, the proportion of patients who are classified as being at low risk of recurrence by the Wells rule should be very low. The same applies to D-dimer testing which is expected to be positive in the vast majority of cases. It thus seems pointless to rely on the combination of clinical probability assessment and D-dimer testing to rule out DVT recurrence in this context.

5.3. Diagnostic imaging

The recurrent DVT is a thrombus appearing on the site of a chronic post-thrombotic lesion or a new thrombosis in a normal venous segment in a patient with a former thrombosis episode in the same or the contralateral leg [32–35]. In the former case, it is not easy to recognize a new acute thrombus occurring on a chronic post-thrombotic lesion [32,36,37]. Therefore, recurrence of DVT must always be confirmed by imaging. If a thrombosis occurs in a previously normal vein segment, symptomatic diagnosis of recurrence is certain. Nonetheless, if symptoms occur with the presence of endovenous images in a previously involved territory, it is important to characterise the acute nature of the thrombosis by comparison with previous imaging and rigorous image analysis. No dedicated imaging study on the specific criteria for recurrence of VTE in patients with cancer has been reported. The data presented are extrapolated from studies of DVT recurrence in the general population.

5.3.1. Contrast venography

Venography was the conventional 'Gold Standard' for the diagnosis of a first episode of acute DVT. The venographic findings may be inconclusive in patients with previous disease [38]. Due to patient discomfort, bleeding complications, as well as contrast-related adverse event and accessibility issues, venography is rarely performed nowadays.

5.3.2. Venous ultrasound

The diagnosis of a first episode of acute DVT on venous ultrasound relies on vein incompressibility and direct visualisation of the thrombus on B-mode or CDUS, and abnormal flow patterns within or distal to the thrombosis location on CDUS.

A diagnosis of DVT recurrence can be made on venous ultrasound if at least one of the following two features are present: either a new non-compressible vein segment or an increase in diameter in transverse section of more than 4 mm in a previously thrombosed vein segment of the common femoral or popliteal vein. In contrast, an increase in diameter of < 2 mm in a previously thrombosed vessel enables recurrence to be ruled out. An increase between 2 and 4 mm is considered equivocal: repeating the measure after 5–7 days has been proposed, especially if symptoms persist, with the absence of changes in ultrasound scans being used to rule out recurrent DVT [19].

5.3.3. Magnetic resonance imaging (MRI)

MRI can be used for diagnosis of DVT, but it is rarely performed. Visualisation of deep venous structures can be improved with IV gadolinium. A venous filling defect is diagnostic of DVT. Alternatively, magnetic resonance direct thrombus imaging techniques (MRDTI) can diagnose DVT without the use of IV contrast agents. In a diagnostic management study of patients with clinically-suspected recurrent DVT and a negative baseline MRDTI in whom anticoagulant treatment was withheld, the incidence of VTE at three months was 1.7% (95% CI: 0.20–5.9) [39]. The low power in this study leads to imprecision and it is thus difficult to base any strong recommendations on such data. In addition, the limited access to MRDTI and high associated cost may limit its use in clinical practice. Furthermore, although some recently described refined MRI techniques may appear promising in helping distinguish recent from established DVT [40–42], the diagnostic value of MRI for diagnosing recurrent DVT is still a subject of research, and its implementation in routine practice cannot be recommended at the moment.

5.3.4. CT venography

In order to confirm DVT recurrence, computerized tomographic (CT) venography can be performed, but it is rarely used as a first-line imaging method because of its lack of availability, relative invasiveness and cost. The intravenous contrast is injected though a peripheral vein without cannulation of the lower extremity and CT images are obtained with a timed protocol coinciding with the filling of a lower extremity vein. Using this technique, acute DVTs have higher Hounsfield unit values than chronic (bland) thrombi at CT venography [43]. Although the literature regarding the diagnostic value of CT venography for diagnosing recurrent DVT is virtually non-existent, it may be assumed that criteria similar to those used for diagnosing recurrent PE on CT (for example, the presence of new intravenous filling defect(s) when compared to a previous test) could be considered reliable and clinically useful.

5.4. Differential diagnosis

Concerning the differential diagnosis of recurrent venous thrombosis in cancer patients, some patients present with tumour thrombosis, defined by endovenous tumour tissue invasion. Tumour thrombosis is particularly common in renal and digestive cancers with extension to the suprahepatic veins, but can also be found in germ cell tumours [44,45]. More rarely, they are primary tumours of the venous wall, such as leiomyosarcomas [46]. The distinction between these different types of cruciate or tumour vein thrombosis can be difficult with CDUS, and is most often made using MRI, CT with contrast or PET, or a combination of these techniques.

5.4.1. Proposals of the expert group

Proposals of the expert group:

- in cancer patients with suspected recurrent DVT, we suggest not using the Wells rule or D-dimer testing, either solely or in combination, to rule out DVT recurrence;
- in cancer patients with suspected recurrent DVT, we recommend that new images be compared to baseline images to confirm or rule out recurrent VTE:
  - we suggest that a diagnosis of recurrent DVT be retained only in case of a new non-compressible vein segment, or an increase of more than 4 mm in diameter under compression of the common femoral or popliteal veins,
  - in case of an increase in vein diameter under compression of 2 to 4 mm, we suggest repeating venous ultrasound evaluation, within 5 to 7 days;
- in cancer patients with suspected recurrent DVT, we suggest performing CT venography as available if repeat venous ultrasound is still inconclusive;
- in cancer patients with suspected recurrent DVT, we suggest performing MRDTI, CT venography or a PET scan (or combinations of these) in case of suspected tumour thrombosis.

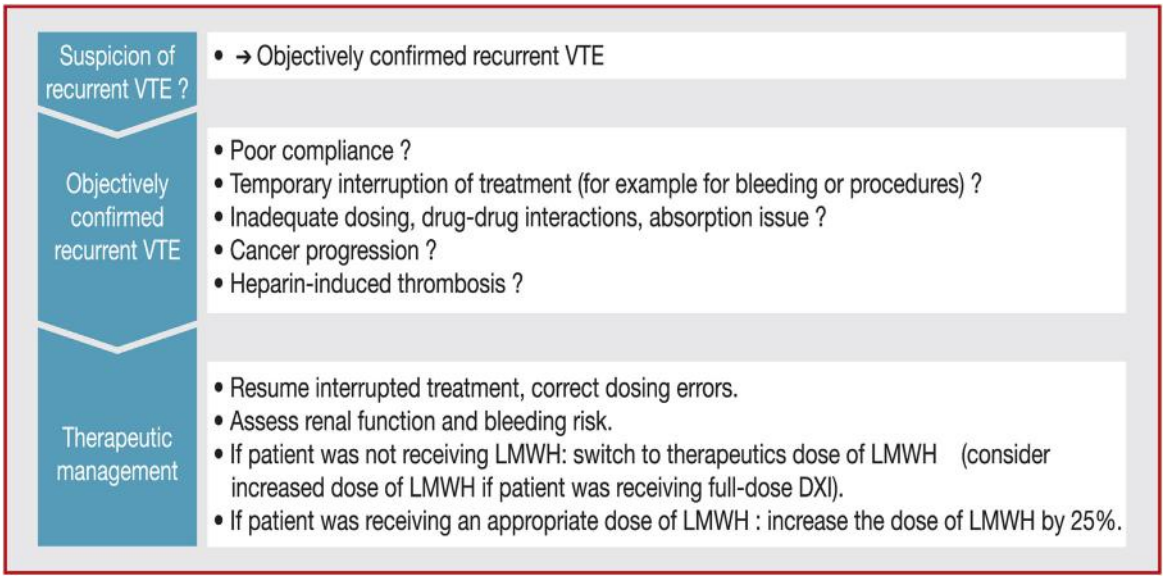


Fig. 3. Proposed management strategy for recurrent VTE in patients with CAT. LMWH: low molecular weight heparin; DXI: direct Factor Xa inhibitor; VTE: venous thromboembolism.

6. Treatment of recurrent VTE in patients anticoagulated for CAT

6.1. Pharmacological approaches

A first study evaluating management of VTE recurrence under anticoagulant treatment was reported by Carrier et al. in 2009 [47]. This single-centre retrospective series reported on three-month follow-up of 70 patients with VTE recurrence on anticoagulant therapy, who had been managed with one of two strategies. If the event occurred in patients taking VKAs, a relay to full-dose LMWH implemented. If the event occurred in patients taking weight-adjusted full-dose LMWH, the dose of LMWH was increased by 20–25% for at least four weeks. Within three months, six patients (8.8% [95% CI: 4.0–17.5]) had a second recurrence, and three (4.3% [95% CI: 1.5–11.9%]) a bleeding complication. A few years later, the same team reported similar results in another monocentric retrospective cohort of 55 patients, again managed in the same way [48].

Under the aegis of the ISTH, an international registry has produced prospective data describing the management of recurrent VTE in 212 patients with CAT [49]. Both the treatment received at diagnosis of recurrence and the management of recurrence were very heterogeneous, limiting any therapeutic interpretation. However, outcome was poor: within three months of the index VTE recurrence, 11% of patients had experienced a second VTE recurrence and 8% had experienced a major haemorrhage and 27% had died.

Since then, a number of practice guidelines [50–53] all propose a relatively consensual approach to management, illustrated in Fig. 3. In summary, if the recurrence occurs while the patient is taking VKA, a switch to full-dose LMWH is suggested. If the patient is taking reduced dose LMWH, a dose increase to full dose is suggested. If the recurrence occurs on full-dose LMWH, a dose increase of 20–25% (depending on the recommendations) is suggested.

More recently, two other situations have been identified where management strategies need to be defined. The first is VTE recurrence in patients taking an increased dose of LMWH (25% higher than the standard full dose). Although several management options have been suggested [54–56], the level of evidence for any of them is weak to very weak. These include adjusting the dose of LMWH based on peak anti-Xa [57] in order to target 1.0–2.0 units/mL for once-daily and 0.8–1.0 units/mL for twice-daily dosing (even though it this is not routinely recommended, since the correlation between anti-Xa activity and clinical outcomes is weak), switching to fondaparinux [58], insertion of a vena cava filter [59–61] (especially in case of high haemorrhagic risk [62]) and fibrinolysis in case of haemodynamic deterioration [63].

The second situation is VTE recurrence in patients receiving DXIs. Current proposals converge towards a switch to LMWH [54–56]. There is still uncertainty about which dose of LMWH should be proposed. Meta-analyses of data from pivotal trials suggest better efficacy with DXIs than with LMWH [64]. Therefore, it would seem logical to propose an increased dose of LMWH. However, as the LMWH in most trials was dalteparin used with a 25% reduction in dose (from 200 to 150 anti-Xa IU/kg/day) after the first month of treatment, a case could be made for resuming the higher dose of dalteparin.

6.2. Use of vena cava filters

In the setting of preventing VTE recurrence in patients with CAT, the evidence for the utility of Inferior vena cava filters (IVCF) is scarce. Only one randomised trial has evaluated anticoagulant treatment (fondaparinux for 90 days), with or without the addition of an IVCF, in 64 patients with DVT (86%) or PE (55%) or both [65]. Two patients experienced an asymptomatic PE (one in each treatment group), and two patients (7%) in the IVCF group presented major complications from the filter. Therefore, as in non-cancer patients, the real therapeutic benefit of IVCF on top of anticoagulation to prevent recurrent VTE in cancer patients remains uncertain at best, and this technique should not be proposed routinely in patients who can receive therapeutic doses of anticoagulants, and who have not experienced a recurrent VTE event [51,52,66].

In patients with confirmed VTE recurrence despite appropriate anticoagulant therapy, inserting an inferior vena cava filter (IVCF) is often proposed as a management strategy, particularly in cancer patients with a perceived high risk of bleeding [56]. Again, the evidence base for this strategy in the specific setting of CAT is limited. Epidemiological studies suggest that IVCF insertion may be associated with reduced mortality in patients presenting with recurrent VTE (with around 40% of them having cancer) [67], if the index event was PE. However, filter placement may result in a high rate of complications [68], as well as an increased risk of recurrence

Table 2
Approved treatment regimens for cancer-associated venous thromboembolism.

	Loading dose	Full dose	Reduced dose[a]
Dalteparin	200 IU/kg/d (first 30 days)	150 IU/kg/d	–
Enoxaparin	200 IU/kg/d (first 5–10 days)	150 IU/kg/d	–
Tinzaparin	175 IU/kg/d		–
Apixaban	10 mg bid (first 7 days)	5 mg bid	2.5 mg bid[a,b]
Rivaroxaban	15 mg bid (first 21 days)	20 mg qd	10 mg qd[a,b]
Edoxaban	–	60 mg qd[c] (after LMWH for 5 days)	–

LMWH: low molecular weight heparins; *bid*: twice daily; *qd* once daily; IU: international unit.
[a] Efficacy of a reduced dose not demonstrated beyond six months.
[b] These doses are currently not validated in cancer-associated thromboembolism.
[c] 30 mg/day in case of creatinine clearance 30–50 mL/min, body weight ≤ 60 kg or drug-drug interactions.

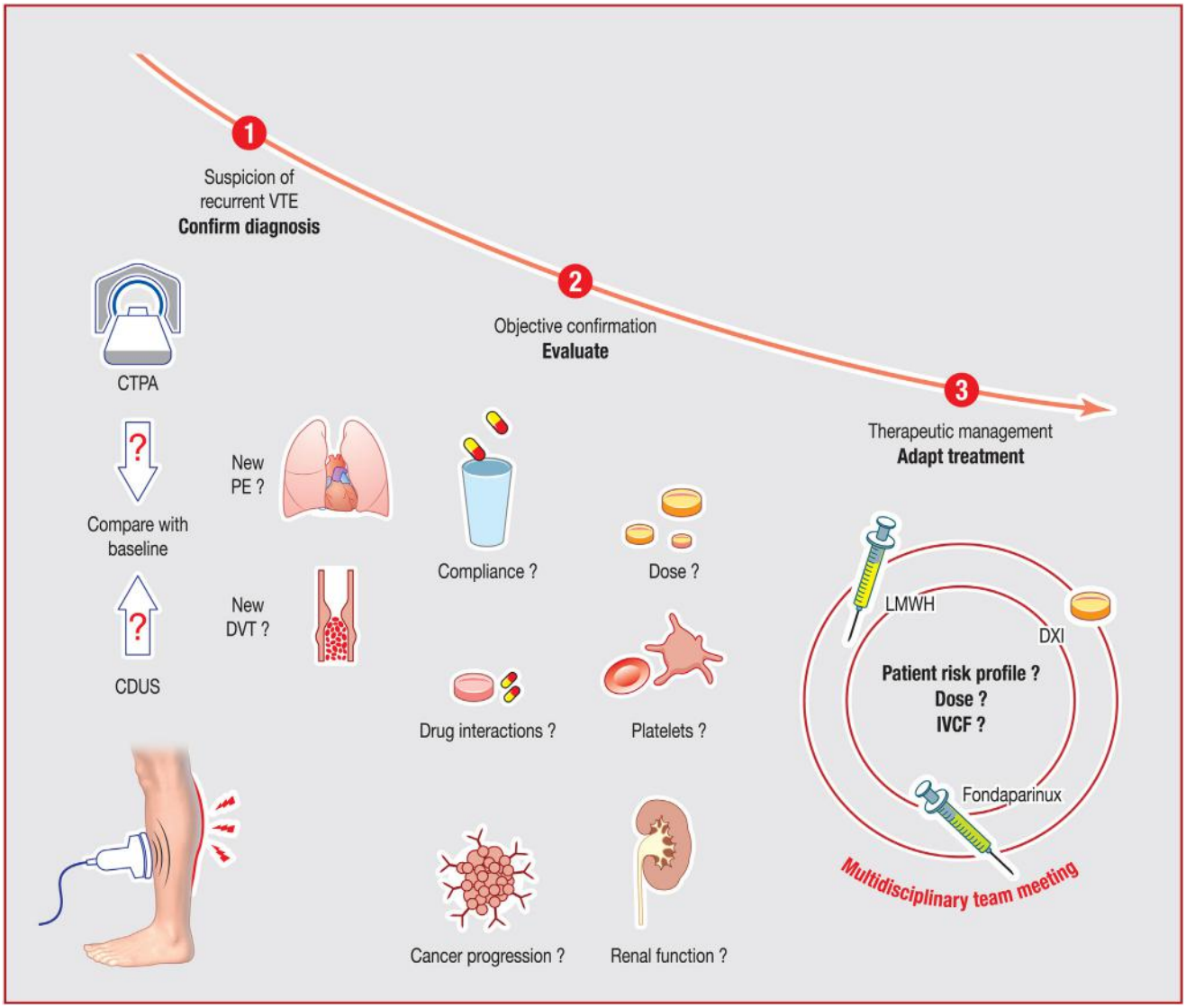
when the anticoagulant therapy is stopped [69]. Moreover, filters are more frequently not retrieved in patients with cancer [70].

Given the limited information available, the decision to insert an IVCF should be taken on a case-by-case basis, preferably by a multidisciplinary team, taking into account the risks and benefits of the intervention, as well as alternative or associated therapeutic options, such as increasing the dose of anticoagulant. Whether recent proximal venous clots persist at the time of recurrence should also be taken into account in these decisions.

6.3. Proposals of the expert group

Proposals of the expert group:

- in order to decide anticoagulant options for individual patients with recurrent VTE, we recommend evaluating and taking into account the following modulators:
  - the type of recurrent VTE (DVT or PE), its severity and the bleeding risk,
  - the current anticoagulant treatment (molecule, dose),
  - adherence to current anticoagulant treatment and possible drug-drug interactions;
- on the basis of the individual patient's modulator profile, we suggest discussing (ideally with a dedicated multidisciplinary thrombosis team) the following options for anticoagulation: LWMH (therapeutic dose or increased dose), fondaparinux or DXI (therapeutic dose with or without initial loading dose). Approved dose regimens for anticoagulants are listed in "In case of objectively-confirmed proximal extension of DVT with or without associated PE while on adequate anticoagulation, we suggest considering the insertion of a vena cava filter, especially in patients with a high risk of bleeding (Table 2)";
- for patients on a reduced therapeutic dose of dalteparin (150 UI/kg day beyond the first month of treatment) or enoxaparin (150 UI/kg day beyond the first 7 days of treatment) or an inappropriate dose of LMWH, we suggest a full-therapeutic dose of LMWH. As an alternative, we propose a switch to a therapeutic dose of DXI (with or without initial loading dose – see Table 2);
- for patients on a full-therapeutic dose of LMWH (200 UI/kg of dalteparin during the first month, 175 UI/kg of tinzaparin or 100 UI/kg bid of enoxaparin), we suggest an increased dose of LMWH, with a dose increased by 20–25%. As an alternative, we propose a switch to a therapeutic dose of DXI (with or without initial loading dose);
- for patients on a loading dose of DXI (rivaroxaban 15 mg bid during the first 21 days or apixaban 10 mg bid during the first 7 days), we propose a switch to a higher dose (+20–25%) of LMWH;
- for patients on full dose of DXI (rivaroxaban 20 mg, apixaban 5 mg bid or edoxaban 60 mg), we propose a switch to therapeutic (with or without increased) dose of LMWH;
- for patients on reduced or inappropriate dose of DXI (rivaroxaban 10 mg, apixaban 2.5 mg bid or edoxaban 30 mg), we propose a switch to full-dose LMWH or a switch to therapeutic (with or without initial loading dose) dose of DXI;
- for patients on VKA, we suggest a switch to full-dose anticoagulation with LMWH;
- in case of objectively-confirmed proximal extension of DVT with or without associated PE while on adequate anticoagulation, we suggest considering the insertion of a vena cava filter, especially in patients with a high risk of bleeding (Central Illustration).



Central Illustration. Proposed management of recurrent VTE.

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Appendix C. Supplementary material

Supplementary material associated with this article can be found in the online version available at https://doi.org/10.1016/j.acvd.2023.11.006.

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