Cancer Screening in Patients with Idiopathic Venous Thromboembolism – a Position Paper of the German Society of Hematology and Oncology Working Group on Hemostasis

Axel Matzdorf\textsuperscript{a} Hanno Riess\textsuperscript{b} Frauke Bergmann\textsuperscript{c} Guido Bisping\textsuperscript{d} Steffen Koschmieder\textsuperscript{e} Stefani Parmentier\textsuperscript{f} Petro E. Petrides\textsuperscript{g} Markus Sosada\textsuperscript{h}

\textsuperscript{a}Clinic for Internal Medicine II, Dept. of Hematology, Oncology, Asklepios Clinic Uckermark, Schwedt/Oder, Germany;\textsuperscript{b}Medical Clinic Hematology/Oncology, Charité Campus Virchow-Clinic, Berlin, Germany;\textsuperscript{c}Ambulatory Healthcare Center (MVZ) Wagnerstibbe for Laboratory Medicine and Pathology GmbH, Hanover, Germany;\textsuperscript{d}Mathias-Spital, Clinic for Internal Medicine I, Rheine, Germany;\textsuperscript{e}Dept. of Hematology, Oncology and Stem Cell Transplantation, University Hospital RWTH Aachen, Germany;\textsuperscript{f}Rems-Murr Hospital, Dept. of Hematology, Oncology, and Palliative Care, Waiblingen, Germany;\textsuperscript{g}Hematology Oncology Center, Munich Isartor, Munich, Germany;\textsuperscript{h}Siloah Hospital, Clinic for Internal Medicine III, Dept. of Hematology and Oncology, Hanover, Germany

\textbf{Keywords}
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\textbf{Summary}
Cancer can trigger thromboembolism. There is a 4–10\% chance of finding an asymptomatic occult cancer in patients with idiopathic venous thromboembolism (VTE). Current guidelines recommend limited cancer screening with history, physical examination, and screening examinations according to age after idiopathic VTE. Recent studies found that a more extensive screening program, including endoscopy and computed tomography, may increase the cancer detection rate. The Hemostasis Working Group of the German Society of Hematology and Oncology recommends a more extensive screening program after idiopathic VTE.

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\textbf{Introduction}
Venous thromboembolism (VTE) is a common complication of cancer. The high incidence is due to numerous risk factors typical for cancer patients, including frequent surgeries, immobility, advanced age, and prothrombotic medication. Another less obvious reason is that tumors can activate the coagulation system creating a tumor-friendly environment. Activated coagulation factors and activated platelets support the growth and spread of tumor cells. It is not uncommon that the thromboembolic event occurs before the diagnosis of cancer. Current guidelines recommend a limited cancer screening for patients with unprovoked idiopathic VTE, including history taking, physical examination, chest X-ray, complete blood count, liver and renal function tests, urinalysis, and cancer surveillance examinations according to age. More extensive screening with computed tomography (CT), mammography, and endoscopy was not previously recommended [1–5], the main arguments being cost-effectiveness and physical and psychological consequences.

In 2012, the National Institute for Health and Clinical Excellence (NICE) changed its policy by recommending also abdominal CT and mammography [6]. The Working Group on Hemostasis of the German Society of Hematology and Oncology (Arbeitsgruppe Hämostaseologie in der Deutschen Gesellschaft für Hämatologie und Onkologie, DGHÖ) therefore decided to review and amend the 2011 Onkopedia guideline on VTE in tumor patients [7]. The new recommendations are based on scientific evidence and, in the case of lacking study data, on expert opinion and clinical practicability. Since the risk of VTE is not only increased in patients with solid tumors but also in those with hematologic malignancies, the terms ‘malignancy’, ‘tumor’, or ‘cancer’ will be used below for both types.
Malignancy and VTE

The incidence rate of VTE in the general population ranges from 0.9 to 1.9 per 1,000 persons per year [8–10]. Cancer patients have an approximately 7-fold higher risk of VTE, and 15–25% of all VTE are associated with cancer [11–14]. Thus, cancer is the most common trigger of VTE, more common than surgery or immobilization. Cancer patients with VTE also have a poorer prognosis than those without [15–19].

In 25–50% of VTE there is no obvious trigger [17]. With the association between VTE and malignancy being so common, the question frequently arises whether an underlying occult tumor could be responsible.

Occult Malignancy and Idiopathic VTE

Patients with idiopathic VTE have a high risk of being diagnosed with cancer [13, 17, 20–29]. This also applies to superficial thrombophlebitis [24, 30]. Incidence numbers range from 1.5 to 10% newly diagnosed tumors after idiopathic VTE [22, 31–35]. This wide range can be explained by differences in study methods and patient groups (e.g. study duration, year of study, patient age, utilization of routine cancer screening prior to VTE). The high cancer incidence rate in patients with VTE contrasts with a rate of 0.4% in the non-VTE population [36–38]. The cancer risk is higher in young patients with VTE (e.g. < 60 years) than in the elderly [21, 26, 27, 29] because the latter have more competing risk factors. It is also higher with bilateral or recurrent VTE [39–41].

Cancer Screening after Idiopathic VTE

The high risk of occult cancer in patients with idiopathic VTE leads to the practical question whether screening at the time of VTE could lead to earlier detection of cancer with a better chance of cure. A meta-analysis of non-randomized studies suggested that screening identifies cancer in 6% of patients with idiopathic VTE [22]. Extensive screening (table 1) yields even higher detection rates [20, 23, 35]. A supplemental analysis of the SOMIT trial [20] estimated the number of patients needed to screen with abdominal/pelvic CT, mammography, sputum cytology, and tumor markers to find 1 additional cancer to be 7.6. The cost of life years gained was €936 [42]. Many of the detected occult cancers are at an early stage and potentially curable [20, 43]. The most common cancers associated with VTE are lung, gastrointestinal, breast, and prostate cancer [13, 19, 20, 25, 26, 35], which reflects the relative frequency of these cancer types among all cancers.

Cancer Screening after Non-Spontaneous VTE and Thrombophilia-Associated VTE

Current guidelines do not recommend thrombophilia screening after VTE, except for patients with a strong family history, young patients, atypical thrombus location, or recurrent VTE despite adequate anticoagulation [1, 6]. It is the experience of the authors that in contrast to the recommendations many patients with VTE undergo thrombophilia screening, and not unexpectedly a considerable percentage comes back positive. This leads to the practical question as to whether a patient with thrombophilia and no other triggering factors for VTE should undergo tumor screening. Most studies on cancer screening after VTE excluded patients with risk factors such as thrombophilia [20, 23, 35]. The decision to offer cancer screening to a patient with thrombophilia and VTE but no other triggers should be individualized and discussed with the patient. In all other clinical situations where there are obvious risk factors such as homozygous thrombophilia, immobilization, or surgery, one will most likely refrain from screening.

| Table 1. Limited versus extensive screening after idiopathic venous thromboembolism |
|---------------------------------|---------------------------------|
| Limited screening program       | Extensive screening program     |
| Piccioli et al. [30], Carrier et al. [32] | limited screening plus: |
| History taking                  | Hemoccult test                  |
| Physical examination            | sputum cytology                 |
| Chest X-ray                     | tumor markers (CEA, αFP, CA-125) |
| Laboratory (complete blood count, electrolytes, liver and renal function tests, urinalysis) | abdominal ultrasound |
| | computed tomography (CT) abdomen/pelvis |
| | gastroscopy or contrast radiography of stomach |
| | colonoscopy or sigmoidoscopy plus contrast radiography of colon |
| | 9 mammography, pelvic exam and Pap smear |
| | further diagnostic testing if a screening test is positive |
| Kleinjan et al. [43], van Doormaal et al. [45] | limited screening plus: |
| History taking                  | chest CT                        |
| Physical examination            | CT abdomen/pelvis               |
| Chest X-ray                     | 9 mammography                   |
| Laboratory (complete blood count, electrolytes, liver and renal function tests, urinalysis) | further diagnostic testing if a screening test is positive |
Cancer Screening, Cost-Effectiveness, and Patients’ Expectations

While extensive cancer screening detects more cancers, it has not yet been shown to reduce mortality. An argument against this is that all screening studies were conducted at a time when most of the new cancer therapies were not yet available, and today results could be much better. In addition, it is not clear whether reduction of cancer-related mortality is the most relevant parameter to gauge the utility of cancer screening. Many patients want to know whether or not they have cancer, and so do their physicians. Piccioli et al. [20] found in their study that after the identification of more cancers in the extensive screening group many participating physicians started to offer extensive screening. This led to the premature termination of that study. Knowing whether or not he/she has cancer, may be more relevant to a patient than knowing what consequences this might eventually have. It seems counterintuitive to explain to VTE patients that malignancies are a possible cause of the condition and to then deny them the opportunity to find out whether or not a cancer is present.

Another argument against extensive cancer screening is the increased risk of false-positive results which lead to additional diagnostic interventions with more side effects and complications. The studies by Piccioli et al. [20] and Kleinjan et al. [33] looked at additional morbidity from screening procedures and found none.

Cost has become a relevant parameter in medical decision-making, and extensive screening of course costs more. 2 studies calculated the additional cost at €160–503 per patient and €900–6,600 per life year gained [33, 42]. These estimates have to be regarded in the context of the costs of cancer treatment. Early detection of a small and resectable cancer could spare the patient and the healthcare system the expenses for chemotherapy, antibodies, or one of the novel and extremely expensive targeted agents. The 2 available cost-effectiveness analyses were calculated on the basis of healthcare tariffs from 2001 and 2006. There is a lack of more recent cost-effectiveness data, but with many of the new targeted agents being priced at €100,000 (or more) it makes intuitively more sense to offer extensive screening and detect cancer earlier.

With regard to cost-effectiveness, screening after VTE needs to be compared with already established cancer screening programs. General mammography screening achieves an absolute risk reduction of 0.04% cases over 10 years [44]. Lung cancer screening with CT prevents 0.6% lung cancer deaths [45]. The benefit of prostate cancer screening is in the same range with 1 life saved for approximately 1,500 patients screened [46]. With such low numbers of lives saved by established cancer screening programs, the benefit of screening after idiopathic VTE appears much more acceptable.

An additional argument pro cancer screening is that the detection of cancer alters the VTE treatment. The treatment of cancer-associated VTE is different in that low-molecular-weight heparins should be given initially and long-term because of improved efficacy over vitamin K antagonists. The use of direct oral anticoagulants is currently not recommended for patients with malignancy and VTE [47]. In addition, cancer patients are usually anticoagulated as long as the cancer is active which could be more than 3–6 months.

The health and well-being of his/her patients is a physician’s first priority. However, today conflicts often arise when deciding between the appropriateness of a new diagnostic approach or treatment while trying to keep healthcare expenditures at a certain level. Patients are often willing to accept even very aggressive therapies and severe toxicities for small gains in cure rate or survival time [48, 49]. Limiting diagnostic procedures and treatments for cost reasons is hard to communicate in oncology. The patient expects his physician to be his advocate and not the steward of healthcare resources. The decision to limit screening is counterintuitive in an era when minimizing the risk of cancer has become a major societal goal.

Recommendations

Current guidelines recommend limited cancer screening plus cancer surveillance according to age. Extensive screening that includes CT and endoscopy can detect hidden malignancies with a high degree of sensitivity, but it has not been shown to improve overall survival. It is highly unlikely that there will be another randomized study on limited versus extensive cancer screening large enough to show an effect on mortality or cost-effectiveness.

When discussing with a patient the possible reasons of his idiopathic VTE, one cannot omit to mention cancer, and the patient will ask what will be done about this risk even if it is small. The absence of evidence does not justify the absence of opinion. Considering the frequent requests of physicians for advice and guidance on this topic and the risks and consequences of a cancer diagnosis for the patient, the Working Group on Hemostasis of the German Society of Hematology and Oncology suggests to discuss the pros and cons of screening and if requested offer the following program:

i) Medical history including risk factors for cancer,
ii) Physical examination including rectal exam,
iii) Complete blood count, electrolytes, liver and renal function tests, urinalysis, and in the case of atypically located thromboses (e.g. abdominal vein thromboses) also JAK2 and CALR mutation screening.
iv) Women: breast exama, mammographya, pelvic exama, Pap smeara,

v) Men: prostate exama, transrectal ultrasounda, prostate-specific antigen (PSA)a (PSA never alone, always combined with the aforementioned exams),
vi) Tumor marker screening (CEA, CA-125, αFP, never alone, only after positive findings from other studies to narrow down the differential diagnosis),
vii) New recommendation: gastroscopy and colonoscopya,
viii) New recommendation: CT or, if available, magnetic resonance imaging of the abdomen and pelvis,
ix) New recommendation: low-dose chest CT.

aIf not already received as part of prior routine cancer screening.

Studies on the utility of FDG-positron emission tomography/CT are too limited to give a recommendation.
**Conclusion**

Extensive cancer screening after idiopathic VTE detects more cancers than limited staging. In the absence of solid data on mortality reduction and cost-effectiveness, one has to discuss both strategies with the patient. Considering the high risk and the grave consequences of a cancer diagnosis for the patient, it is very likely that the majority will ask for an extensive screening strategy. The Working Group on Hemostasis of the German Society of Hematology and Medical Oncology therefore recommends an extensive screening program that besides history taking, physical examination, basic laboratory tests, and cancer surveillance examinations according to age also includes endoscopy of the upper and lower gastrointestinal tract and CT.

**Addendum**

Recently, another study on extensive cancer screening including abdominal/pelvic CT was published [50]. It found a non-significantly higher cancer detection rate during the initial staging with abdominal/pelvic CT but no difference in the rate of cancers that were missed. However, the patient population was young, and the overall cancer rate very low. This study does not solve the problem of what to offer to patients with idiopathic VTE after explaining to them that occult cancer could be the cause of their VTE.

**Disclosure Statement**

The authors declare no conflicts of interest.


