Venous thromboembolism, coagulation and cancer
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Citation for published version (APA):

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CHAPTER

Is extensive screening for cancer in patients with idiopathic venous thromboembolism warranted?


Submitted for publication
ABSTRACT

Context
Patients with a first episode of idiopathic venous thromboembolism (IVTE) have an estimated 10% incidence of cancer within 12 months after diagnosis. However, the utility of screening for cancer in this population is controversial.

Objective
To assess the efficacy of extensive cancer screening in patients with an IVTE.

Design, Setting and Patients
Prospective concurrently controlled cohort study of consecutive patients with idiopathic venous thromboembolism, conducted in 10 centers in The Netherlands from December 2002 through April 2008. The study population consisted of 630 patients.

Intervention
All patients underwent baseline screening consisting of history, physical examination, basic laboratory tests and chest X-ray. In the extensive screening group abdominal and chest CT-scan and mammography were added.

The main outcome measures
Incidence and curability of cancer, cancer-related and overall mortality

Results
In 12 of the 342 (3.5%) patients in the extensive screening group malignancy was diagnosed at baseline. In the limited screening group this was 2.4% (7 of 288 patients). Extensive screening detected an additional 6 cancers (2.0%, 95% CI; 0.74-4.3), three were potentially curable. During a median 2.5 years of follow up cancer was diagnosed in 3.7% and 5.0% in the extensive and limited screening groups, respectively. In the extensive screening group 26 patients (7.6%) died compared to 24 (8.3%) in the limited screening group; adjusted hazard ratio 1.22 (95% CI 0.69-2.22). Of these deaths 17 (5.0%) in the extensive screening group and 8 (2.8%) in the limited screening group were cancer-related; adjusted hazard ratio 1.79 (95% CI 0.74-4.35).

Conclusions
The low yield of extensive screening and lack of survival benefit do not support routine screening for cancer with abdominal and chest CT-scan and mammography in patients with a first episode of IVTE.
INTRODUCTION
The incidence of previously undiagnosed cancer in patients with idiopathic venous thromboembolism (IVTE) is approximately 10% in the first 12 months after diagnosis [1]. An intense debate is ongoing whether screening for cancer at presentation of IVTE is a useful strategy [2;3]. Data are limited and results contradictory. This leads, for this common clinical problem, to a wide variation in daily practice. Several cohort studies suggested that a limited cancer screening, consisting of history, physical examination, basic laboratory tests and chest X-ray, suffices [4-8]. Others advocate a more extensive screening [9-12]. The single randomised controlled trial revealed that a very extensive screening strategy was indeed able to detect early cancers, but it remained uncertain whether there was a net clinical benefit [13]. This study was hampered by the fact that after informed consent many patients and physicians did not accept limited screening, which eventually led to premature termination of the trial. Moreover the authors suggested that an extensive screening strategy confined to abdominal and chest CT-scan and mammography would have the highest yield [13;14].

Therefore, in patients with a first episode of IVTE, we compared in a concurrently controlled design, this extensive cancer screening strategy with the limited one. The objectives were to assess the additional value of extensive screening, to compare the incidence of cancer during long-term follow-up and to evaluate whether extensive screening affected mortality.

METHODS
Design
This was a prospective concurrently controlled cohort study in which the participating centres used either a limited or an extensive screening strategy for cancer in patients with IVTE. All 10 participating centres were teaching hospitals in the Netherlands.

Patients
Patients with confirmed symptomatic deep venous thrombosis (compression ultrasound) and/or pulmonary embolism (high probability ventilation-perfusion scanning or CT-angiography) who had no known risk factor for venous thromboembolism were potentially eligible [15;16]. Risk factors were defined as recent (<2 months) fracture of the lower extremity, surgery, immobility for more than 6 days, thrombocytosis
(>1000x10^9/ml), severe dehydration, pregnancy or puerperium, recently started oral contraceptives and presence of a known malignancy. Exclusion criteria were: previous venous thromboembolism, age below 40 years, known presence of antithrombin, protein C or protein S deficiency, known factor V Leiden, prothrombin G20210A mutation or circulating lupus anticoagulant. Eligible patients gave written informed consent before inclusion. The study was approved by the Institutional Review Boards.

**Baseline cancer screening**

In both the extensive and limited screening groups in all patients a history was taken and a physical examination was performed with a focus on symptoms and signs of malignancy according to a standardized format. Furthermore, blood was drawn for determination of the ESR, whole blood count with leukocyte differentiation, creatinin, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase and calcium and a chest X-ray was made. In case of abnormal findings appropriate problem targeted further testing to detect cancer was required.

**Extensive cancer screening strategy**

In patients in the extensive screening group, who had no cancer identified at baseline screening, an additional abdominal and chest CT-scan was performed. In the women of this group also a mammography was made. In case of abnormal findings appropriate further testing to detect cancer was required.

**Follow-up**

All included patients were followed up at 6 and 12 months and yearly thereafter. A last contact with all patients was scheduled in March or April 2008. At these contacts information on the presence of malignancy was elicited. In case of death or newly diagnosed malignancy all available relevant clinical reports and images were collected.

**Outcome definition**

The primary outcomes were overall mortality and cancer related mortality (defined as mortality due to cancer or to any procedure to diagnose or treat cancer). Other outcomes were the occurrence of cancer (histologically or cytologically confirmed) and the prognosis at the time of its diagnosis, defined as potentially curable or non-curabe with a median survival of <1 or >1 year, based on current standards of care, as assessed by an experienced oncologist (JMO).
Analysis
The sample size was based on the assumption that 10% of patients had occult cancer at baseline of which 80% could be detected with the extensive screening strategy [13]. With limited screening it was estimated that the mortality in cancer patients would be 50% after 3 years of follow up. With extensive screening, the earlier detection was assumed to reduce cancer related death by 50 to 75%. Hence, a reduction in cancer-related mortality from 5% to approximately 2.5% was expected, with a resulting sample size of 750 patients in each strategy (type I error, 0.05 two-sided; type II error, 0.20).

An interim analysis was planned after inclusion of 500 patients to review these assumptions. Based on the detection of only 2% (rather than 8%) of malignancies with extensive screening the assumed reduction in cancer related mortality of 2.5% was deemed unlikely to be achieved and estimated to be 0.5 to 0.75% at most. This would lead to sample sizes of more than ten thousand patients. Thus, continuation of the study was deemed futile and inclusion of patients was stopped.

The incidence of cancer-related mortality was compared between the groups using Cox proportional hazards modelling and hazard ratios and their 95 percent confidence interval were calculated adjusting for age, gender, smoking habit and the location of venous thromboembolism. In addition, hazard ratios were calculated for total mortality and malignancies identified during follow up. The assumptions of the Cox proportional hazards model were checked by visual inspection of the log-log survivor function - by time curve. Kaplan Meier curves were generated for overall survival and occurrence of malignancies during follow up.

Other comparisons were made by logistic regression analysis (adjusted for age, gender, smoking habit and the location of venous thromboembolism), chi square test or the Students t-test where appropriate.

RESULTS
Patients
Between December 2002 and December 2007, 630 patients with IVTE were included. Hereafter, inclusion was interrupted, because of futility to continue, based on the results of the planned interim analysis. Centres that used the extensive screening strategy had recruited 342 patients, and centres that used the limited screening strategy had recruited 288 patients (Figure 1). The baseline characteristics of the patients are presented in Table 1.
There were more smokers and more patients who were diagnosed with pulmonary embolism in the extensive screening group. Centres that used limited screening used ventilation-perfusion scintigraphy more frequently to diagnose pulmonary embolism.

**Fig. 1.** Flow diagram of patients in the study
Table 1 - Baseline characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Extensive screening N=342</th>
<th>Limited screening N=288</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Mean (SD)</td>
<td>61 (12)</td>
<td>63 (14)</td>
<td>0.13</td>
</tr>
<tr>
<td>Gender-men n (%)</td>
<td>216 (63%)</td>
<td>168 (58%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Smokers n (%)</td>
<td>184 (54%)</td>
<td>122 (42%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Family history for cancer</td>
<td>124 (36%)</td>
<td>102 (35%)</td>
<td>0.46</td>
</tr>
<tr>
<td>VTE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE only n (%)</td>
<td>91 (27%)</td>
<td>36 (13%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DVT leg only n (%)</td>
<td>236 (69%)</td>
<td>233 (81%)</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>DVT arm only n (%)</td>
<td>5 (1%)</td>
<td>4 (1%)</td>
<td>0.94</td>
</tr>
<tr>
<td>PE+DVT n (%)</td>
<td>10 (3%)</td>
<td>15 (5%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Diagnostic method for PE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VQ scan n (%)</td>
<td>21 (21%)</td>
<td>28 (55%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CT n (%)</td>
<td>71 (70%)</td>
<td>23 (45 %)</td>
<td></td>
</tr>
<tr>
<td>VQ+CT n (%)</td>
<td>9 (9%)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Detection of malignancy by the screening strategies

Baseline screening

Of all patients included in the extensive screening group 98% underwent the baseline screening procedures (history, physical examination, basic laboratory tests). However, the chest X-ray was performed in 72% of the patients. In the limited screening group all tests were performed in 98% of the patients.

Of the 342 patients included in the extensive screening group suspicion of malignancy was raised in 58 patients (17.0%) by baseline screening procedures (Table 2). In the limited screening group a comparable proportion of patients 19.4% (56/288) had a suspicion (p=0.42). All of these patients underwent problem targeted testing to detect malignancy.

In 12 out of the 342 (3.5%) patients in the extensive screening group malignancy was diagnosed. In the limited screening group this was 7 patients out of 288 (2.4%). Cancer types and estimated prognosis were comparable between the two groups (Table 3).
### Table 2 - Detection of malignancy by the screening strategies

<table>
<thead>
<tr>
<th></th>
<th>Extensive screening</th>
<th>Limited screening</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline screening</strong></td>
<td>History, physical examination, laboratory testing, chest X-ray</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspicion of malignancy</td>
<td>58/342 (17.0%)</td>
<td>56/288 (19.4%)</td>
<td>P= 0.42</td>
</tr>
<tr>
<td>Detected malignancies</td>
<td>12/342 (3.5%)</td>
<td>7/288 (2.4%)</td>
<td>Adjusted OR 1.56 (0.53-4.55)</td>
</tr>
<tr>
<td><strong>Extensive screening</strong></td>
<td>Abdominal CT-scan, chest CT-scan, mammography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspicion of malignancy</td>
<td>91/302 (30%; 25 to 35)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Detected malignancies</td>
<td>6/302 (2.0%; 0.74 to 4.3)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>Detected malignancies</td>
<td>12/324 (3.7%)</td>
<td>Adjusted HR 0.86 (0.38-1.96)</td>
</tr>
<tr>
<td></td>
<td>14/281 (5.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total study period</strong></td>
<td>Detected malignancies</td>
<td>30/342 (8.8%)</td>
<td>Adjusted OR 1.25 (0.66-2.38)</td>
</tr>
<tr>
<td></td>
<td>21/288 (7.3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 3 - Cancer - Estimated prognosis based on type of malignancy and extent of disease

<table>
<thead>
<tr>
<th></th>
<th>Extensive screening center</th>
<th>Limited screening center</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline screening</strong></td>
<td>2 colon, prostate</td>
<td>1 lung</td>
</tr>
<tr>
<td>Potentially curable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-curabule&lt;1yr</td>
<td>7 gastric, lung (4), pancreas (2)</td>
<td>4 lung (3), renal</td>
</tr>
<tr>
<td></td>
<td>3 colon (2), ovary</td>
<td>2 colon, Non Hodgkin Lymphoma (low grade)</td>
</tr>
<tr>
<td>Non-curabule&gt;1yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td><strong>Follow up period</strong></td>
<td>3 basal cell, bladder (2), colon (2), lung, NHL high grade, tongue</td>
<td>10 basal cell, breast (2), colon (3), Non Hodgkin Lymphoma (high grade), prostate (2), sarcoma</td>
</tr>
<tr>
<td>Potentially curable</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Non-curabule&lt;1yr</td>
<td>3 bladder, brain, esophagus</td>
<td>3 lung, pancreas, prostate</td>
</tr>
<tr>
<td></td>
<td>1 colon</td>
<td>1 colon</td>
</tr>
<tr>
<td>Non-curabule&gt;1yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total number</strong></td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Potentially curable</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Non-curabule&lt;1yr</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

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Extensive screening
In the extensive screening group an additional abdominal CT-scan was performed in 299 of the 330 patients (91%) and a chest CT-scan in 302 (92%). In 94 out of 119 women (79%) mammography was done. Extensive screening was completed within a median of 5 weeks (IQR 3 to 8) after diagnosis of venous thromboembolism. Reasons for non adherence to the protocol were patient refusal, recent population based screening (mammography), renal insufficiency and logistics.

Of the total number of patients (n=302) who had at least one additional testing procedure (CT-scan or mammography) in 91 patients (30%) suspicion of malignancy was raised. After appropriate work-up malignancy was detected in 6 out of 302 patients (2.0%). Three of these patients had a potentially curable disease. One patient with lung cancer diagnosed by chest CT-scan had no chest X-ray performed at baseline screening.

Follow up
In the limited cancer screening centres the median time of follow-up was 2.6 years (IQR 1.6 to 3.7) compared to 2.5 years (IQR 1.5 to 3.9) in the extensive cancer screening group. Two patients were lost to follow up and one patient withdrew informed consent, all in the extensive cancer screening group.

In spite of the extensive screening strategy the occurrence of malignancy, as well as time to diagnosis, were comparable between groups (adjusted hazard ratio 0.86, 95% CI; 0.38-1.96) (Table 2, Figure 2).

Overall malignancy during study period
In the extensive screening group 30 out of 342 patients (8.8%) had a malignancy, versus 21 of the 288 patients (7.3%) of the limited screening group (adjusted odds ratio 1.25, 95% CI 0.66-2.38). Of the malignancies diagnosed in the extensive screening group 13 were potentially curable versus 11 in the limited screening group.
Fig. 2. Kaplan-Meier curve of the detected malignancies in the extensive and limited cancer screening groups

Mortality

Overall, 50 patients died during follow up, 26 (7.6%) in the extensive screening group and 24 (8.3%) in the limited screening group, for an adjusted hazard ratio of 1.22 (95% CI 0.69-2.22) (Figure 3). Of these deaths 17 (5.0%) in the extensive screening group and 8 (2.8%) in the limited screening group were cancer-related (none due to complication of diagnostic procedures); adjusted hazard ratio for the primary outcome of 1.79 (95% CI 0.74-4.35).

Mortality among patients diagnosed with cancer during the study was 17 out of 30 (57%) in the extensive screening group and 8 out of 21 (38%) in the limited screening group (adjusted odds ratio 2.22, 95% CI; 0.63-8.33). Mortality among patients not diagnosed with cancer during the study was 9 out of 312 (2.9%) in the extensive screening group and 16 out of 267 (6.0%) in the limited screening group (adjusted odds ratio 0.90, 95% CI 0.36-2.27).
In both groups one patient died of pulmonary embolism. In the extensive screening group 8 patients died of other causes versus 15 in the limited screening group. There was no difference in overall mortality between patients with deep venous thrombosis and pulmonary embolism.

**DISCUSSION**

This study demonstrates that additional cancer screening with abdominal and chest CT-scan and mammography in patients with a first episode of IVTE leads to further testing in 30% of them. In only 2.0% (6 of 302 patients) cancer was confirmed, and three patients could be treated with curative intent. During follow-up of approximately 2.5 years, 3.7% of the patients in the extensive and 5.0% in the limited screening group were diagnosed to have cancer (adjusted hazard ratio 0.86, 95% CI; 0.38-1.96) Also, total mortality during follow-up was comparable (Figure 3), whereas the observed cancer related mortality was
higher in the extensive screening group (adjusted hazard ratio 1.79, 95% CI 0.74-4.35) with a 95% confidence interval which makes a benefit of more than 26% unlikely.

Therefore, our results justify a limited cancer screening strategy in patients with IVTE consisting of history, physical examination, basic laboratory tests and chest X-ray. Abnormalities suggestive for cancer with this approach were observed in approximately one fifth of all patients at baseline. Cancer was detected in 3.0%, a rate which is in agreement with previous observations [6;11]. Patients with VTE are presently often managed out of hospital. Therefore, it needs to be emphasized that the limited cancer screening strategy employed here should also be offered to these patients.

Some methodological aspects of this study require comment. This was a non randomized comparison of two screening strategies. We purposely selected a prospective cohort design with concurrent controls to increase feasibility, acceptance and to prevent an ethical dilemma for participating patients. The only randomized controlled trial, the SOMIT study, by Piccioli et al. stranded mainly because of this dilemma [13].

The two patient groups were similar at entry except for smoking and the proportion of PE patients. All analyses were adjusted for this imbalance and we assume they are due to chance and do not constitute an obvious confounding factor. Furthermore, the baseline clinical characteristics of our patients are comparable to those in other studies in IVTE patients [13]. Hence, we believe that our findings are applicable to IVTE patients in general.

Baseline investigations and extensive screening CT-tests were completed in more than 90% of the patients, evaluation of CT-scans was standardized and follow-up was nearly complete, thereby further strengthening the validity of our observations.

Our choice for abdominal and chest CT-scan and mammography was based on several arguments. In earlier studies the distribution of cancer types differed between patients with IVTE and the general population [6;8;17]. The most prevalent cancer types in IVTE patients would be detectable by the aforementioned tests. Based on further analysis of the SOMIT study, the used strategy was found to be more cost-effective and less harmful than other strategies including those using tumour markers. Although, our diagnostic tools proved to be disappointing, novel techniques, such as PET-CT scan, do not seem to outperform CT scan and mammography in this setting [18].

Finally, it should be emphasized that our original hypothesis that screening would be beneficial, was not confirmed. In fact the study was terminated prematurely at a planned interim analysis because of futility due to the low yield of the extensive screening and the relatively low rate of occult malignancy.
The awareness of many physicians that their patients with a first episode of IVTE have an increased risk for occult cancer often leads to concern. This study suggests that those who screen their patients with a careful history, physical examination, basic laboratory tests and a chest X-ray currently follow the most optimal strategy. At present, extensive screening does not seem warranted.

**ACKNOWLEDGEMENTS SECTION**

**Acknowledgements**

We kindly like to thank the following persons for their help with patient inclusion and data collection: Academisch Medisch Centrum, Drs. Iris Wichers, Dr. Clara Klerk, Mrs. Liesbeth van Huizen; Atrium Ziekenhuis Heerlen, Dr. Asiong Jie; Diakonessenhuis Utrecht/Zeist, Mrs. Marianne Deelen, Mrs. Annemieke van Rijissen; Maastricht Universitair Medisch Centrum, Prof. Dr. Hugo ten Cate, Dr. Karly Hamulyák; Medisch Meander Medisch Centrum, Prof. Dr. Mark Kramer, Mr. Jos Krook, Mrs. Linda Zandbergen; Onze Lieve Vrouwe Gasthuis, Mrs. Monique de Boer, Mrs. Lucy Schrijders; Slotervaart ziekenhuis, Mrs. Monique de Rijk; Universitair Medisch Centrum Groningen, Mrs. Patricia Huisman, Mrs. Lucia Kadijk; Westfriesgasthuis, Drs. Peter Nochem. Most important, we thank all the participating patients.

**Author contribution**

The authors WT, RvdG, MHP, MvdR, HB, JvdM and JMO contributed to the design of the study. All authors were responsible for data collection. The analyses were performed by the first author, FFvD and by MHP. The interpretation of the results and the writing of the manuscript were performed by all authors together. The last author, JMO, initiated the study and was study coordinator.

**Conflict of interest statement**

None of the authors do have a conflict of interest. The corresponding author declares that he had fully access to all the data in the study and had final responsibility for the decision to submit for publication.

**Role of funding source**

The study was not sponsored.
REFERENCE LIST


