

Limitations of screening for occult cancer in patients with idiopathic venous thromboembolism

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ABSTRACT

Background: Idiopathic venous thrombosis (IVT) is associated with occult malignancy in 10% of patients. The Trousseau study investigated whether extensive screening using abdominal and chest computed tomography (CT) scans and mammography in women would decrease mortality, compared with limited screening. Here, the costs and test characteristics of these screening strategies are presented, including true- and false-positive findings, sensitivity and specificity.

Methods: All investigations performed because of a suspicion of malignancy in the limited or extensive screening groups were collected. Costs were calculated using Dutch healthcare tariffs.

Results: A total of 342 and 288 patients with IVT were included in the extensive and the limited screening group, respectively. The prevalences of malignancy and mortality were comparable between these two groups, as were the abnormal findings during routine screening. In 30% of the extensively screened patients, the CT scans or mammography showed abnormalities necessitating further diagnostic work-up; this yielded six malignancies and resulted in a positive predictive value of 6.6%, sensitivity of 33% and specificity of 70%. Mean costs per patient were € 165.17 for the routine and € 530.92 for the extensive screening.

Conclusion: Screening using CT scans and mammography results in extra costs due to the high percentage of false-positive findings for which a further diagnostic work-up is indicated.

KEYWORDS

Whole body CT screening, costs, occult cancer, idiopathic venous thromboembolism

INTRODUCTION

In 1935, the first case of a patient presenting with an idiopathic venous thromboembolism (IVT) as a sign of an occult cancer was reported by Illtyd James and Matheson. The incidence of malignancy within the first years after an IVT is approximately 10%. The benefit of screening for cancer in patients with IVT is intensely debated.^{1,5} In today's clinical practice, the approach to a patient with IVT varies widely, ranging from no screening to extensive screening using invasive tests. Only one randomised controlled trial has been performed.⁶ In this prematurely terminated study 201 patients were included and were randomised to a limited screening strategy or an extensive screening strategy, consisting of a large number of imaging, invasive and laboratory tests. This trial suggested a beneficial effect of extensive screening, based on a less advanced cancer stage at the time of diagnosis. An additional analysis showed that the combination of computed tomography (CT) of the abdomen and a mammography in women had the potential to be the most cost-effective.⁷ The design of the Trousseau study was based on these data. In this multicentre concurrently controlled cohort study a limited cancer screening strategy was compared with an extensive screening strategy consisting of CT of the chest and abdomen and additionally in women mammography. As reported recently, no difference in overall survival was observed between the two groups.⁸

The present study analyses the costs and test characteristics (i.e. false- and true-positive findings, sensitivity and specificity) associated with screening using CT scans and mammography in a population at high risk for cancer.

METHODS

Study population

The analysis is based on the previously reported Trousseau study, performed between 2002 and 2008 in the Netherlands after approval by the institutional review boards of all participating hospitals.⁸ Briefly, 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 factors for venous thromboembolism were potentially eligible. Informed consent was obtained prior to performing any study-related procedures.

Cancer screening strategies

In both the limited and extensive screening groups a history was taken and a physical examination was performed with a focus on signs and symptoms of malignancy with the use of a standardised data collection form. Furthermore, blood was drawn for determination of the erythrocyte sedimentation ratio, whole blood count with leucocyte differentiation, creatinine, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase and calcium; also a chest X-ray was routinely obtained. This screening, which was done in both groups, is referred to as the routine screening. In case of abnormal findings indicating a possible underlying malignant process, appropriate problem-targeted testing to detect the cancer was required. Patients in the extensive screening group underwent an additional CT of the chest and abdomen and a mammography was also performed in women, provided no cancer was identified at baseline screening. Follow-up visits were planned at 6, 12, 24 and 36 months. The last study visit was scheduled for April 2008. At each contact information regarding vital status and malignancy was obtained with a standardised questionnaire. In case of death or newly diagnosed malignancy all available relevant clinical information was collected and adjudicated by an independent and blinded adjudication committee.

All the extra tests to detect cancer, which were performed because of abnormalities at routine screening, extensive screening or follow-up, were recorded. Additionally, the medical records of all patients were searched for examinations additionally to the registered data.

Costs

Costs in euros were calculated using the data of the 2006 Committee of Tariffs for Healthcare; this committee regulates the fees to be charged by healthcare workers or institutions in the Netherlands. The 2006 tariffs were used because the study was conducted at that moment in time, and the declaration system in the Netherlands changed afterwards. One euro is currently approximately 1.30 dollar; in 2006 it varied between 1.20 and 1.32 dollar

(average currencies per month). Costs were multiplied by the specific surcharge percentage of the specialist involved in the diagnostic procedure. Costs per procedure were multiplied by the frequency by which this specific test was done in a certain patient. Finally, all costs were added up to arrive at the total costs per individual patient. The total costs were calculated excluding and including costs for the screening X-ray, laboratory measures, CT scans and mammographies. Furthermore, a subdivision was made between costs made to evaluate abnormalities found by routine screening, extensive screening and during the follow-up period. Costs related to treatment for cancer or hospitalisations were excluded from these calculations. Statistical analyses were executed using SPSS 16. The Mann-Whitney test was used to evaluate whether costs were statistically significantly different between the two groups. Alternative diagnoses (i.e. diseases other than malignancy, found during the screening) and the tests used to evaluate these were scored and divided into alternative diagnoses for which treatment was initiated and those for which no treatment was needed. Also, alternative diagnoses which have an effect on prognosis or on future treatment were considered clinically relevant and taken into account.

Exploratory sensitivity analysis

Information on overall mortality and mortality among patients diagnosed with cancer was used to calculate the amount of life years gained (LYG) by the implementation of extensive screening.

A cost-efficacy limit of 50,000 US dollars or approximately € 30,000 per LYG is commonly used.⁹ Using the costs for extensive screening and defining the hypothetical costs per LYG (€ 30,000), an exploratory fixed sensitivity analysis was performed. The observed costs were used to determine the minimum of LYG needed to remain within cost-efficacy limits.

RESULTS

Main results of Trousseau study

The results of the Trousseau study are presented in the original paper.⁸ Briefly, 630 patients with IVT were included, 342 in the extensive screening and 288 in the limited screening arm. The baseline clinical characteristics were comparable between the two groups, except for smoking and the percentage of patients with pulmonary embolism. In both groups routine screening procedures were performed in 98% of the patients, with the exception of the chest X-ray which was performed in only 72% of the patients in the extensive screening group. 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. The median time of follow-up was 2.6 years (IQR 1.6 to 3.7) in the routine screening group compared with 2.5 years (IQR 1.5 to 3.9) in the extensive screening group.

During the total study period a malignancy occurred in 21 of the 288 patients undergoing limited screening (7.3%), vs 30 out of 342 extensively screened patients (8.8%) (adjusted OR 1.25; 95% confidence interval (CI) 0.66-2.38). Overall, 50 patients died during follow-up, 24 (8.3%) in the limited screening group and 26 (7.6%) in the extensively screened group, for an adjusted hazard ratio of 1.22 (95% CI 0.69-2.22). The mortality rate among patients diagnosed with cancer during the study was 38% (8 out of 21) for the routine screening group and 57% (17 out of 30) in the extensive screening group (adjusted OR 2.22; 95% CI 0.63-8.33). The study was terminated prematurely at a planned interim analysis because of the low yield of extensive screening. Therefore, the effect of screening was expected to be very small, also after inclusion of the planned number of patients.

Diagnostic procedures performed after suspicion of malignancy

In the limited screening group, baseline routine screening prompted further investigations in 21.5% of the patients, which is not significantly different from the percentage of abnormalities after routine screening in the extensive screening group (16.7%, table 1). The routine screening performed in the limited as well as the extensive screening group identified 19 malignancies in 119 patients with a suspicion of malignancy at routine screening (positive predictive value (PPV) 16%, table 2).

Extensive screening resulted in 91 patients - 30% of all patients who underwent at least one extensive screening test - with an indication for further investigations. In six patients, cancer was confirmed, which yields a PPV of 6.6%. Abdominal CT findings prompted further tests in 16.7%, chest CT in 14.2% and mammography in 10.6% of all patients who underwent these tests. CT of the chest and abdomen together resulted in four identified malignancies, after 84 patients had to undergo further diagnostic procedures (PPV 4.8%). Screening using CT of the chest and abdomen only would have a sensitivity of 22% and a specificity of 72%. Mammography identified two malignancies in 94 women. Eight patients had abnormalities on mammography which ultimately turned out to be benign. This yields a sensitivity of 100%, a specificity of 91% and a PPV of 20%.

During the follow-up period further diagnostic tests were performed in 14.2% in the routine screening group and 17.3% in the extensive screening group (p=0.39).

The diagnostic procedures which were ordered because of abnormalities in routine or extensive screening are quite diverse and are listed in tables 3 and 4. From table 3 it can be

Table 1. Frequency of the suspicion of malignancy in the two study populations

	Limited screening group (number of patients with abnormalities / total number of patients)	Extensive screening group (number of patients with abnormalities / total number of patients)	P value (Chi square)
Routine screening	62/288 (21.5%)	57/342 (16.7%)	0.42
History	22/288 (7.6%)	24/342 (7.0%)	
Physical examination	14/288 (4.9%)	18/342 (5.3%)	
Laboratory measures	26/288 (9.0%)	24/342 (7.0%)	
Chest X-ray	11/270 (4.1%)	5/260 (1.9%)	
Extensive screening		91/302 (30.1%)	NA
Chest CT		43/302 (14.2%)	
Abdominal CT		50/299 (16.7%)	
Mammography		10/94 (10.6%)	
Follow-up	40/281 (14.2%)	56/324 (17.3%)	0.39
Total study period	97/288 (33.7%)	171/342 (50%)	<0.05

Proportion of the patients, per part of the study and further subdivided in individual screening modalities, with abnormalities necessitating further diagnostics. Multiple abnormalities could be present in one patient.

Table 2. Test characteristics of the screening methods

	Sensitivity	Specificity	Positive predictive value
Routine screening	37% (19/51)	83% (479/579)	16% (19/119)
Extensive screening	33% (6/18)	70% (199/284)	6.6% (6/91)
Chest and abdominal CT scans	22% (4/18)	72% (204/284)	4.8% (4/84)
Mammography	100% (2/2)	91% (84/92)	20% (2/10)

Sensitivity, specificity and positive predictive values of the routine, extensive screening and subdivisions of the extensive screening, i.e. chest and abdominal CT and mammography. For the routine screening, the routine screening in the limited and the extensive screening group were combined.

Table 3. Frequency and description of performed diagnostic procedures

Diagnostic procedure	Limited screening group		Extensive screening group	
	Number of procedures	Number of patients	Number of procedures	Number of patients
Laboratory measurements	49	23	142	56
Imaging tests	157	77	282	134
Invasive techniques	60	40	131	85
Pathology	56	39	97	70
Consultation other specialist	25	17	106	53
Total	347	97*	758	171*

* Multiple abnormalities could be found in one patient.

Table 4. Overview of diagnostic procedures

Laboratory measures		Imaging techniques		Invasive diagnostics	
<i>Tumour markers</i>		<i>Nuclear</i>		<i>Scopy</i>	
Alpha-fetoprotein	10.69	Skeletal scintigraphy	90.70	Bronchoscopy	422.14
CA125/CEA	21.38	PET scan	1359.33	Broncho-alveolar lavage	422.14
Prostate specific antigen	10.69	Thyroid gland scintigraphy	135.82	Coloscopy	449.90
BetaHCG2	14.26			Cystoscopy	118.41
		<i>Ultrasonography</i>		Oesophageal endoscopic ultrasound	47.59
<i>Clinical chemical lab</i>		Abdomen	40.39	Endoscopic retrograde	245.14
Anaemia lab	53.34	Thyroid gland / neck	40.39	Cholangiopancreatography	
Complete blood count	7.13	Vaginal	49.76	Gastroscopy	449.90
Calcium	7.13	Prostate	46.55	Hysteroscopy	171.69
Kidney function	7.13	Breast	52.67	Sigmoidoscopy	449.90
Parathyroid hormone	10.69				
Adrenal gland function	24.95	<i>Radiodiagnosics</i>		<i>Surgery</i>	
Liver function	8.91	CT brain	164.16	Exploratory surgery	941.87
LDH isoforms	1.19	CT thorax	200.77	Uterus extirpation	1596.13
Leucocyte differentiation	1.78	CT abdomen	164.16	Thoracotomy	1484.24
Thyroid function	19.25	CT neck	46.53	Mediastinoscopy	422.14
Prolactin	8.27	Mammography	66.14	Low anterior resection	2918.71
Albumin	1.78	X-ray rib detail	46.53		
		Chest X-ray	46.53	<i>Other</i>	
<i>Other laboratory measures</i>		Abdominal X-ray	46.53	Cervical smear	20.20
Protein spectrum	20.62	X-ray oesophagus	139.36	X-ray colon	155.74
Inhibin/oestrogen	51.92	X-ray small intestines	139.36		
Kahler measurements	21.38	X-ray spinal column	46.53		
Plasma/erythrocyte volume	883.39	Kahler series	325.72		
Plasma viscosity	7.13				
<i>Punctures/biopsies</i>		<i>MRI</i>		Consultation specialists	
Punctures		MRI pelvis	200.77	All consultations	185
CT-guided puncture	127.55	MRI leg	200.77		
Bone marrow puncture	115.28	MRI spinal column	455.20		
Pleura puncture	57.42	MRI neck	200.77	Pathology	
Ascites puncture	99.79	MRI brain	200.77	Pathology	38.34
Other puncture	99.79			Urine cytology	37.08
Ultrasound-guided puncture	66.53				
<i>Biopsies</i>					
Liver biopsy	139.36				
Skin biopsy	168.10				
Kidney biopsy	139.36				
Prostate biopsy	118.41				
Excision biopsy	909.02				
Breast biopsy	139.36				
Ultrasound-guided biopsy	66.53				
Wedge excision	2187.66				

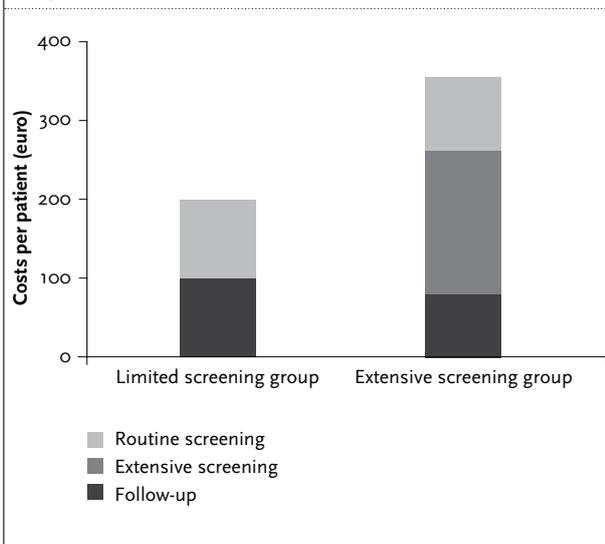
Overview of all the different diagnostic procedures undertaken after abnormal findings in routine, extensive screening or during follow-up. Costs in euro per procedure, multiplied by surcharge for personal costs. Some laboratory measures (e.g. complete blood count) are a combination of different measures.

appreciated that the largest number (69%) of all diagnostic procedures were ordered in the extensive screening group. In this group, 758 diagnostic procedures were carried out in 171 patients, compared with 347 procedures in 97 patients in the routine screening group. None of the diagnostic procedures resulted in morbidity or mortality.

Mean costs per patient

The diagnostic procedures detailed above resulted in costs specified in figure 1. Costs for diagnostic procedures performed after suspicious findings following routine screening and during follow-up were comparable ($p=0.77$) between the two groups. Routine screening itself, i.e. chest

Figure 1. Mean costs per patient in euros; of the resulting diagnostic procedures in case of abnormalities during screening, divided between the limited and the extensive screening group. The costs of performing the screening itself are excluded



X-ray plus laboratory tests, costs € 71.48 per patient. After the routine screening the additional tests ordered cost € 93.69 per patient in the limited group. In summary, costs for baseline screening itself and the tests subsequently ordered because of abnormalities were € 165.17 and comparable for the two strategies. From *table 4* it can be calculated that the costs for CTCA were € 364.93 and € 431.07 for CTCA plus mammography. In this study, the extensive screening itself costs € 349.37 per patient, due to the fact that mammography was not performed in all women and the CT scans were sometimes performed incompletely. Another € 181.55 (range 0-3710) per patient was spent on further tests, due to abnormalities seen on the CT scans and/or mammography. The sum of costs for extensive screening, including costs from the screening tests themselves and costs to exclude malignancy after observed abnormalities, was € 530.92 per patient.

Alternative diagnoses found

Routine screening resulted in the detection of 36 alternative diagnoses, of which 77% were considered relevant. In total, 24 alternative diagnoses were found after extensive screening, of which 25% were considered relevant (*table 5*).

Cost-efficacy

Total costs including the costs for the screening itself were € 47,659 for the routine screening (in the limited screening group) and € 181,574 for the extensive screening. The routine screening performed in the limited screening

Table 5. Alternative diagnoses

Alternative diagnoses and frequencies			
Routine screening	36	Extensive screening	24
Renal insufficiency	6	Abdominal CT	11
Liver toxicity due to alcohol	4	Haemangiomas/cysts liver	5
Liver steatosis	1	Liver steatosis	1
Nodus thyroid gland	2	Neuroendocrinal pancreatic cyst	1
Anaemia due to myoma	4	Benign adrenal gland tumour	3
Aanemia of unknown origin	3	Asymptomatic retroperitoneal fibrosis	1
Pernicious anaemia	3	Chest CT	12
Hernia diaphragmatica causing anaemia	1	Nodus thyroid gland	8
Diverticle bleeding	1	Chronic obstructive pulmonary disease	1
Polycythemia vera	1	Tuberculosis	1
Uterus myoma	3	Aortic aneurysma	2
Intestinal polyp	1	Mammography	1
Haemorrhoids	1	Cyst breast	1
Asymptomatic gall stones	1		
Benign prostate hyperplasia	2		
Diabetes mellitus de novo	2		

Alternative diagnoses found by the routine screening (performed in the limited and extensive screening groups) and the extensive screening strategy.

group found seven malignancies at the cost of € 6796 per malignancy (€ 47,659/7). Using the extensive screening strategy, six additional malignancies were discovered, at the cost of € 30,262 per malignancy (€ 181,574/6).

Extensive screening did not result in LYG for total mortality. The mortality rate among patients diagnosed with cancer during the study was 38% (8 out of 21) for the limited screening group and 57% (17 out of 30) in the extensive screening group. Hence, LYG for mortality due to cancer could not be computed. To exclude that the higher rate of mortality due to cancer in the extensive screening group was mainly caused by a difference in cancers found by routine screening, we excluded the malignancies diagnosed by routine screening in both groups. When the malignancies diagnosed by routine screening are excluded, 14 malignancies remain in the limited screening group (only follow-up) and 18 in the extensive screening group (i.e. malignancies identified by extensive screening and during follow-up). Mortality among these patients was 14% (2/14) in the limited screening group and 44% (8/18) in the extensive group.

Sensitivity analysis

The minimal mortality difference needed to stay within cost-efficacy limits was calculated, using the mean costs per patient of extensive screening using CT scans and

mammography (€ 530.92) divided by the commonly used upper cost-efficacy limit of € 30,000. We should have found a minimum mortality difference of 0.0177 LYG (€ 530.92/30,000) to remain within this limit. Extensive screening detected six of 18 malignancies, resulting in a sensitivity of 33.3%. In the power calculation, a sensitivity of 80% was assumed; in that case 14.4 malignancies would have been identified by extensive screening. Cost per malignancy would then shift from € 30,262 (€ 181,574/6) to € 12,609 (€ 181,574/14.4).

DISCUSSION

We compared the costs and test characteristics of extensive screening to routine screening for the detection of an underlying malignancy in patients with IVT. The extensive screening is three times more expensive compared with the routine screening. These additional expenses for the extensive screening did not save lives or costs spent in the follow-up period. When the costs for the extensive screening itself were not taken into account, costs resulting from extensive screening were still €181.55 on average per patient. These costs were mainly caused by the high proportion of patients with false-positive results. As a consequence, in a quarter of all patients in the extensive screening group invasive procedures were performed, which is twice as often as in the limited screening group. These invasive procedures did not result in additional morbidity or mortality. The minimal LYG that should have been reached by extensive screening to remain under the accepted limit of € 30,000 was 0.0177. The costs for screening would probably have been considered acceptable if there had only been an effect on mortality.

Several limitations of this study have to be acknowledged. Most important, due to the lack of effect of extensive screening, we could only perform a very limited and exploratory sensitivity analysis whereas a formal cost-effectiveness analysis was not possible. Although the study was terminated prematurely, it seems unlikely that continuation of recruitment would have resulted in a higher sensitivity. All costs were calculated using the 2006 Committee of Tariffs for Healthcare; these costs vary in time and could be different for other countries. Furthermore, the low sensitivity could be a result of the quality of the radiological assessment. However, the radiologists completed a standardised form with a predefined list of abnormalities suggestive for malignancy.

The low PPV is in line with that of CT of the chest in patients with a high risk for lung cancer. In two large lung cancer screening programs, more than 20% of all patients screened with one single CT scan had false-positive

results.^{10,11} This is comparable with the 27% of patients in our study with false-positive findings on a single CTCA. The sensitivity of screening using CT scans will deteriorate in low-risk populations, while the number of false-positive findings will probably be equal or higher in these individuals. Therefore the use of whole body CT scans as a screening modality in asymptomatic low-risk populations is likely to lead to a negative benefit-risk ratio.¹² This is important as there is a worldwide tendency to an increase in screening of asymptomatic patients, in some cases initiated by the 'patients' themselves. Alternative or non-cancer diagnoses were rarely (7.6%) found in our patient group. Furthermore, of these diagnoses, the majority did not lead to a change in treatment or prognosis. Therefore, screening for cancer using whole body CT scans in low-risk patients should be discouraged as long as no randomised or otherwise comparative trials have proved beneficial effects on mortality or morbidity. Also, further study of psychosocial effects of these false-positive findings is needed, as current literature suggests that false-positive findings strongly influence people's well being.¹³

In summary, although the prevalence of occult cancer in patients with idiopathic venous thrombosis is sufficiently high to justify screening and at least the costs of the screening strategy used in this analysis do not seem to be very high, screening for cancer using CT scans should not be implemented due to the low sensitivity and specificity and the high number of false-positive findings.

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