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CHAPTER 9

Decision analysis for cancer screening in idiopathic venous thromboembolism.

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Summary

Background
The SOMIT trial randomized patients with idiopathic venous thromboembolism (IVTE) and without signs of cancer at routine medical examination, to extensive screening for cancer plus 2 years of follow-up or to just 2-year follow-up.

Methods
The data of the SOMIT trial were used to perform a decision analysis. The screening tests were divided in several possible strategies. The number of detected cancer patients and the number of patients investigated further for an eventually benign condition were calculated for each strategy. The total costs for the screening strategy and for each detected cancer patient were determined. Based on the tumor type, stage, age and gender of the individual cancer patient, the difference in live years gained (LYG) was calculated between the two study groups.

Results
Computed tomography (CT) of the abdomen combined with sputum cytology and mammography detected 12 of the 14 patients with cancer and had one false-positive result. In general, screening strategies including abdominal/pelvic ultrasonography (US) or tumor markers yielded a higher number of patients needed to screen in comparison with those using abdominal/pelvic CT. Furthermore, the strategies which included colonoscopy, tumor markers, and abdominal/pelvic US were significantly more costly, had inferior LYG and higher costs per LYG when compared with strategies using abdominal/pelvic-CT.

Conclusions
Despite the limitations of this analysis, the screening for cancer with a strategy including abdominal/pelvic CT with or without mammography and/or sputum cytology appears potentially useful for cancer screening in patients with IVTE. The cost-effectiveness analysis of this strategy needs confirmation in a large trial.

Introduction
The first report about the relationship between venous thromboembolism (VTE) and occult cancer was published in 1935 (1). Only recently, however, the incidence of malignancy in the 2–3 years after the first VTE event has been determined and was shown to be 7.5% in patients with idiopathic VTE (IVTE) vs. 1.6% in patients with a secondary VTE (2–10). When the doubling time of cancer cells and the minimal tumour volume necessary for detection are taken into account, it is likely that the cancers were indeed occult at the time IVTE was diagnosed (11). The usefulness and the extension of the screening for cancer in patients with IVTE have been long debated. Several investigators advise only a basic screening by means of a thorough clinical history, physical examination, simple laboratory tests and a chest X-ray (3,12,13). Others advocate a more extensive screening with computed tomography (CT) scans, ultrasound (US) and the determination of circulating tumor markers (5,6,10,14). Recently, the results of the Subsequent Diagnosis Of Malignancy in patients presenting with Idiopathic venous Thromboembolism (SOMIT) trial comparing an extensive screening procedures with a basic screening in patients with IVTE have become available (15). Unfortunately, the SOMIT study was terminated prematurely because of slow recruitment and logistic problems. In spite of this, the results remain useful. In the present analysis, the available data from the SOMIT trial were used to determine, for each of the evaluated screening strategies, the number of patients needed to screen (NNTS) to detect one additional case of cancer and the number of patients harmed. Finally, the costs of the various strategies were calculated and a cost-effectiveness analysis was performed.
Methods

Study population

The analyses are based on the data from the SOMIT study (15). Only patients over the age of 25 years, with a first IVTE event were included. VTE was defined as idiopathic if it occurred in the absence of known malignant disease, trauma of the leg, surgical procedures or immobilization within 6 months prior to presentation, confirmed spontaneous VTE in a first degree relative, thrombocytosis, circulating lupus anticoagulant, pregnancy, childbirth, or deficiency of anti thrombin, protein C or S. The basic screening for malignant disease had to be completed and without abnormal results. When allocated to the extensive screening group patients were offered to undergo US of the abdomen and the pelvis, followed by CT scan of these areas, gastroscopy or double contrast X-ray of the stomach, colonoscopy or sigmoidoscopy followed by barium enema X-ray of the colon, fecal occult blood tests (FOBT), sputum cytology and tumormarkers including carcinoembryonic antigen (CEA), a-fetoprotein (α-FP), and cancer antigen CA-125. In addition, mammography and PAP-smear were performed in women and trans-abdominal US of the prostate and prostate specific antigen (PSA) plasma levels in men. The cut-off values for all tumor markers were twice the upper limit of the normal range. All screening procedures were performed on an out-patient basis. The patients in the control group were not additionally investigated, but were just followed up for 2 years, as in the screening group. During the follow-up visits, scheduled at 3, 12 and 24 months after the IVTE, special attention was paid to the recent medical history by means of a standardized form. Tumors were staged according to the system of the American Joint Committee for Cancer and comparison for tumor stage was performed with the Fischer exact test (16).

Decision Model

A decision model was developed representing 19 possible strategies for the diagnostic work-up of patients with IVTE (Table 1). There were 8 diagnostic strategies with abdominal/pelvic CT, 8 similar strategies using abdominal/pelvic US instead of CT, and 3 strategies with tumor markers. Since a normal basic evaluation was the prerequisite for inclusion, this standard basic assessment was left out of the decision model. Sigmoidoscopy followed by barium enema X-ray of the colon was not considered in any model, because this combination is more expensive than colonoscopy and it lacks the possibility of taking biopsies proximal from the sigmoid. A common sense approach was used to determine the strategy for further evaluation after an abnormal test result. An elevated CEA led to colonoscopy and abdominal/pelvic CT, an elevated CA-125 to a consultation of a gynecologist and abdominal/pelvic CT, and an elevated α-FP to abdominal/pelvic CT. An elevated PSA was followed by a US and a biopsy of the prostate, a positive FOBT by colonoscopy and if negative also by gastroscopy. The detection of a mass resulted in a biopsy, unless the suspicion of cancer was high enough to perform surgery (i.e. in the patients with renal or ovarian cancer). Number needed to screen analysis. All cancers detected by the extensive screening were considered as new cases. The NNTS to detect one additional case of cancer was calculated by dividing the total number of patients in the extensively screened group, by the number of detected cases ND). This calculation was performed for each of the diagnostic strategies. When a diagnostic test had an abnormal result, the patient was evaluated further. If cancer was suspected by more than one diagnostic procedure within a specific strategy, it was counted once. The number of patients evaluated further, eventually because of a benign condition, was calculated for each strategy and was defined as the number harmed (NH).

Costs

Costs were calculated from the perspective of the health insurance system and were determined according to the Committee Tariffs Healthcare in 2001 (This Committee regulates the maximum fees to be charged by healthcare workers/institutes in the Netherlands). To calculate
the costs of the screening strategies, the costs of the initial treatment of VTE, of the basic screening, and of follow-up were not taken into account as these were considered necessary and standard for every patient with VTE. Moreover, the costs related to the treatment of the cancer patients were excluded from the calculations, as these were inevitable for any cancer patient and not part of the screening procedure. Thus, the analyses focused on the incremental costs of screening for cancer patients with IVTE. The costs of the screening tests and the subsequent evaluations were added up to calculate the total costs for each strategy, and were multiplied by the number of patients who underwent that particular (set of) investigation(s). Patients with an abnormal test result were evaluated further. If a test was used that already had been part of the initial strategy, the cost of that test was counted only once. The costs to detect or to rule out a diagnosis of malignancy were calculated dividing the total cost of the screening procedure by the number of patients with cancer detected by that specific strategy. All costs were calculated in Euro.

Cost-effectiveness

Overall life expectancy was estimated, adjusted for age and excusing the figures of the Dutch Bureau of Statistics (17). For all cancer patients, the likelihood of curative treatment was determined, based on the type of tumor and its stage, according to current cancer treatment (18). Based on the data of life expectancy in stage IV cancers, patients with incurable malignancies were assumed to live (median) for another year (18). Life expectancy of patients with a potentially curable cancer was calculated by multiplying the overall life expectancy with the chance of a curative treatment. If the time between the index IVTE and the detection of the cancer was more than 1 month, it was added up to the life expectancy. The Live Years Lost (LYL) for the screened and control patients were determined by the subtraction of the life expectancy with malignancy from the life expectancy without malignancy. If in a certain strategy a cancer was not detected, the mean LYL of the control group was assigned to this case. In case a life expectancy was less than the mean LYL of the control group, the latter was conservatively considered to be the LYL. The mean LYL per strategy was calculated by dividing the total LYL by the number of patients in the group (14 and 10 for the screened and control group, respectively). The Live Years Gained (LYG) per strategy were calculated subtracting the LYL of the screened group from the LYL of the control group. Total LYG were then calculated for each strategy by multiplying the LYG per the ND of the specific strategy. Furthermore, the costs per LYG and incremental costs (the additional cost per additional LYG) were calculated for all strategies. Sensitivity analysis was performed by varying the costs (50% increase) and LYG (50% decrease) of the most attractive strategies. Scenario analysis was performed to evaluate the potential role of the chest CT.

Results

The median age of the 99 patients in the extensive screening group was 66 years and 45 were women. Within this group, the screening detected 13 of the 14 patients who had a histological confirmed malignancy within 2 years from the IVTE. In the control group, the median age was 67 years and 56 were women. The mean time between the IVTE and the detection of the cancer in this group was 370 days (120–628 days). In the extensive screening group, five patients were diagnosed with stage I and seven with stage II tumors whereas in the control group no stage I and four stage II tumors were detected. All other malignancies (two in extensive screening group and six in control group) were more advanced at the time of detection. In total, nine out of 14 patients with cancer in the extensive screening group vs. two of the 10 patients in the control group had T1–T2 disease without signs of local or distant metastasis. (P ¼ 0.047) (15).

Number needed to screen analysis

As most cancers were detected by means of abdominal/pelvic CT with a low number of false-positive results, abdominal/pelvic CT was combined with most of the other diagnostic tests. The
lowest NNTS (7.6) was achieved by the combination of abdominal/pelvic CT, mammography, sputum cytology and tumour markers, but for every cancer patient detected two patients were evaluated further for an, eventually, benign condition. This problem was observed in all strategies that included the determination of circulating tumor markers. The NNTS of the combination abdominal/pelvic CT and colonoscopy was 9.0 with a NH of 4. As the addition of abdominal/pelvic US or a gastroscopy to abdominal/pelvic CT yielded no additional detected cases, these test combinations were not evaluated. However, because of the radiation exposure associated to the CT, an abdominal/pelvic US may be preferred over an abdominal/pelvic CT. For this reason, the abdominal/pelvic US was assessed in combination with other tests. The strategies that used abdominal/pelvic US, as well as those using only tumor markers, yielded higher NNTS in comparison with those using abdominal/pelvic CT. However, the NH by the strategies involving tumormarkers were 2–6.6 times the ND of cancer patients.

**Costs analysis**

The costs per strategy varied between €10547 for tumormarkers without PSA and €61607 for abdominal/pelvic US combined with colonoscopy. The lowest costs per detected cancer patient was achieved with the abdominal/pelvic CT (€1974), whereas the highest costs were reached by the combination of abdominal/pelvic US with colonoscopy (€10268). These high costs were due to the low number of detected cancer patients and the high costs of the investigations. The costs per detected cancer patient for strategies that included abdominal/pelvic US were at least €4262. All strategies using FOBT showed a substantial increase in costs due to the high rate of false-positive results and the subsequent (expensive) investigations. The strategies that included colonoscopy were substantially more costly, whereas those including abdominal/pelvic CT instead of US were substantially less costly per ND. Abdominal/pelvic CT combined low costs with a low NH and the addition of mammography or sputum cytology did not result in a substantial increase of the costs per ND (€2085 and €2258, respectively).

**Cost-effectiveness analysis**

The life expectancy of all cancer patients would have been 214 years (15.3 years per patient) and 112 years (11.2 years per patient) in the absence of cancer, in the extensively screened and in the control group, respectively. Due to the malignant disease and taking into account the chance of curative treatment, the life expectancy declined to 128 years (9.1 per patient) in the extensively screened group and to 40.6 (4.1 per patient) in the control group. The main determinants of the life expectancy were the age and the stage of the cancer. To bypass the effect of age, the life expectancy was determined for all patients to be equal by dividing the life expectancies of the two groups by 24. The LYL per cancer patient for the various strategies in the extensively screened group varied between 5.7 and 7.8 compared with 8.6 in the control group. The LYG varied for the different strategies between 4 and 38 years. The strategies that included abdominal/pelvic CT yielded the highest LYG (mean 28, range 20–38) whereas the LYG was generally lower for strategies in which US was used (LYG mean 9.6, range 5–17). The costs per LYG varied between €870 (abdominal/pelvic CT plus mammography) and €6603 (abdominal/pelvic US plus colonoscopy). Strategies that included US, FOBT and/or colonoscopy were inferior in terms of LYG and costs per LYG when compared with strategies using the abdominal/pelvic CT and thus were dominated by them. The determination of tumor markers appeared not to be cost-effective and was accompanied by a high rate of false-positive results. The most attractive strategies seemed to be the abdominal/pelvic CT-mammography combination with or without the sputum cytology given the associated costs per LYG (€974 and €870, respectively) and the low NH.

**Additional analysis**

For these two latter strategies, an additional analysis was performed. Hypothesizing a 50% increase in the total costs because of false-positive test results, the cost-effectiveness
ratio(costs per LYG) would have been € 1450 and € 1323, respectively. Furthermore, a 50% decrease in LYG due to a lower incidence of cancer in the population, to a lower sensitivity of the screening test used or due to co-morbidities caused by false-positive test results, or any combination of these, would lead to a cost-effectiveness ratio of € 1934 and € 1764, respectively. Strategies that included US, FOBT or colonoscopy were always dominated by those including abdominal/pelvic CT. The determination of tumormarkers did not seem to be cost-effective and was accompanied by a high rate of false-positive results. Replacing the sputum cytology by CT chest in the strategy combining abdominal/pelvic CT plus mammography would increase the cost-effectiveness ratio from € 974 to € 1427.

Discussion

The current decision analysis suggests that extensive screening for cancer in patients with IVTE has the potential to be cost-effective. In particular, the abdominal/pelvic CT, with or without mammography and/or sputum cytology, seems an unattractive combination. All other screening strategies, and especially those including US, FOBT or colonoscopy performed less because of higher NNTS and/or NH. The costs for abdominal/pelvic CT plus mammography with or without the sputum cytology would be € 974 and € 870, respectively, in order to achieve one LYG in this population. Compared with the costs per LYG in other cancer screening programs (median approximately $ 15 000 ¼ € 19500), these costs seem very reasonable (19–21). The addition of the CT of the chest to abdominal/pelvic CT and mammography could be an alternative to the sputum cytology. Indeed, the CT-chest is likely to be more sensitive and specific for the detection of lung cancers than sputum cytology, although this has not been adequately investigated (22). Moreover, the CT of the chest has the potential advantage of detecting other malignancies than lung cancer in the area of the thorax. The obvious disadvantage will be the increasing number of false positive (i.e. due to lymphadenopathy). Assuming that CT-chest would have the same sensitivity and specificity as the sputum cytology, the costs per LYG would be € 1427. Some important limitations of the present analysis have to be acknowledged. Firstly, the SOMIT study was stopped prematurely and included only a total of 201 patients. Although there was a difference in mortality in favour of the screening group, this difference was not statistically significant. Secondly, the sensitivity of the screening method(s) was based on a limited number of patients with detected cancer. Hence, the true sensitivity for any of the evaluated strategies remains uncertain. However, even with a decrease of sensitivity to 50% and an increase of the costs of 50%, the cost-effectiveness ratio of the abdominal/pelvic CT combined plus mammography with or without sputum cytology remains within acceptable margins (€ 1934 and € 1764). The estimates of LYGs used for the analysis were based on chances of curative treatment and life expectancy without cancer that were longer than the time-frame of the SOMIT study (2 years). Moreover, several additional assumptions were made in the analysis. Based on recent data from the literature, patients with stage IV cancer were assumed to live another year. The life expectancy of patients in the extensive screening group whose cancer was not detected was considered to be the mean life expectancy of those in the control group. Therefore, the results of this decision analysis should be considered exploratory. However, the results of the 2-year follow-up of the SOMIT study are in line with those of the LYG per patient in the present analyses, especially for patients with a high chance(>75%) of curative treatment. It has been suggested that the life expectancy of cancer patients with a concomitant VTE may be shorter than in cancer patients without VTE (23). However, the overall life expectancy of cancer patients with IVTE remains unknown, so adjusted estimates could not be used for the present analysis. Finally, in this analysis the costs to diagnose a malignancy in the cancer patients and in the control group were not assessed. The use of diagnostic resources was based on clinical practice, whereas these costs were calculated based on standard fees rather than real-life costs. However, using real-life costs rather than standard fees is unlikely to change the conclusion on the cost analysis. In summary, this decision analysis indicates that extensive screening for cancer in patients with IVTE, in particular strategies combining CT and mammography, results in a high yield of detected cancer patients with a low number of patients harmed, at acceptable cost per life-years gained. However, the cost-effectiveness and the
possible impact on survival of the strategy including abdomen/pelvis CT plus mammography warrant further evaluation in a large trial. Considering the difficulties because of the randomized design of the SOMIT study, the study would have to be a large prospective, cohort follow-up project.
References


