

IRB protocol
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Abdominal and Pelvic CT as a screening modality for occult malignant disease in unprovoked Venous Thromboembolism: A randomized, controlled prospective study.

A. Study Purpose and Rationale

Venous Thromboembolism ("VTE") defined as being a pulmonary embolism or a deep vein thrombosis, might be the first manifestation of cancer¹⁻². It has been proven in multiple studies that occult cases of cancer can cause a clinically overt VTE, although the mechanism is yet unclear and there are a few postulated mechanisms. There are a few ways to approach a patient with a new onset of VTE: a patient can have a limited workup to try to screen for occult cancer which includes a meticulous medical history, a physical exam, basic set of labs and a chest X-ray ("limited screening")³⁻⁴. A different and more extensive approach ("extensive screening") is the one that adds an additional screening method, e.g. CT of the abdomen and pelvis, US of the abdomen and pelvis, age appropriate screening tests and tumor markers, to the limited screening method⁵⁻⁶. To date, there have been a number of studies that have shown that a more extensive screening method can diagnose more cases of occult cancer than the limited screening. However, no studies have ever shown a survival benefit for the Extensive screening group. In a recent large Systematic, the most extensive one to date, these two methods were reviewed⁷. Adding a CT of the Abdomen and pelvis to the limited screening showed a statistically significant increase in the detection of occult cancer. However, this review did not show any benefit in survival rate in between the two groups.

There are a few potential benefits to diagnosing a cancer early with a VTE presentation: there is a potential decrease of risk for cancer associated complications such as pathological fractures, hypercalcemia etc. The management of the VTE may change depending on a simultaneous occurrence of cancer- choice of coumadin vs. LMWH (CLOT Trial)⁸. The most important benefit of detecting more cases of cancer in this population is the potential survival advantage in the extensive screening population, as it was shown for mammography or colonoscopy in multiple studies.

The purpose of this current study will be to answer the question of a possible survival benefit in using CT abdomen and Pelvis in addition to the limited screening strategy. If the results of these studies will demonstrate such an advantage, it will then raise more questions prior to setting new guidelines about screening for occult cancer in patients who experienced an unprovoked VTE. Some of these questions will be regarding other screening options such as PET CT, cost-effectiveness analysis of such a move, screening complications, etc.

B. Study design and Statistical Analysis

This study will be conducted as a prospective, randomized controlled study of patients with a new diagnosis of unprovoked VTE, comparing the use of limited screening in one arm of the study, and a CT abdomen and Pelvis in addition to the limited screening on the other study arm. The primary outcome measured will be the overall mortality.

From previous studies it has been shown that about 10% of patients with a recent unprovoked VTE were found to have an occult cancer within one year of the diagnosis⁷. When limited screening is initially applied to these patients, about 4.8% of the patients or 48% of the total cases of cancer are detected. When an additional extensive screening is applied (CT abdomen and pelvis has been shown the only statistically significant modality)- 7% of the patients or 70% of total cases of cancer are detected. From the systematic review it was shown that the cases of cancer diagnosed were diverse- and included pancreatic, colorectal, gastric, breast, prostate cancers as well as others. Taking leading cancers of this list and analyzing the 5 years survival rate shows the following: Colon cancer- 90% survival if found as an early stage, 10% if metastatic⁹. Breast cancer- 97% survival if diagnosed at a local stage vs. 25% survival if diagnosed at a distant stage¹⁰. It is assumed that cases of cancer which are missed and therefore late diagnosis of overt cancer is made, the 5 years survival rate is about 5%. For pancreas cancer patients with advanced disease, the overall 5-year survival rate of all stages is less than 1%. For those patients with small and localized disease that can be completely resected surgically, 5-year survival rates improve to 18% to 24%. For patients with gastric cancer in an early stage 0/1A the 5 years survival rate is 78%-89%. For advanced stages of gastric cancer 3B/4, the 5 years survival rate is 7-8%¹¹. Looking at the over-all survival from cancer, it is assumed that for cases of cancer that are detected at an early stage and treated accordingly, the 5 years survival will be about 75%. The over-all survival from cancer detected at an advanced stage is about 10%. For these estimations, Chi squared analysis revealed that 4690 subjects must be enrolled in Each group to detect a 1.3% difference in mortality. The primary outcome will be defined as death due to a malignant disease itself, or death due to complications of diagnostic or surgical procedures performed to diagnose or treat cancer. Secondary outcomes measured include comparison in early-stage cancer detection and analysis of the different types of cancer.

C. Study Procedure

This will be a randomized multi center clinical study in apparently cancer-free patients with acute idiopathic venous thromboembolism to compare the strategy of extensive screening for occult malignant disease with no limited testing.

Patients who are admitted to the ER with a finding of a VTE will be referred to the study.

They will then have an initial medical interview, physical exam, and labs to see if they meet the inclusion/exclusion criteria of the study.

After patients will be consented, they will be randomized to the study arm and to the control arm. Patients randomized to a the control arm will be going through a limited screening process which includes a combination of medical history, physical examination, routine laboratory blood tests, and chest radiography.

patients randomized to the study arm, will have a CT of abdomen and pelvis as an additional imaging modality to the limited screening.

Once cancer is found, patient will be referred to an oncologist. They will be treated by the oncologist in a conventional way for their specific type of cancer, which will include surgical options, chemo or radio therapies.

The follow up of this study will be 5 years. There will be a median follow up point at 2.5 years. As we are interested in the 5 years survival rate, We will locate all of the patients at that time. We will check the mortality rate and other outcomes such as types of cancer and stage of the cancer at diagnosis.

D. Study Drugs

N/A

E. Medical Devices

Pts on the study arm will be exposed to a CT of abdomen and Pelvis, with IV contrast.

F. Study Questionnaires

N/A

G. Study Subjects

Inclusion criteria:

- * new diagnosis of a VTE
- * absence of known malignant disease, trauma of the leg, surgical procedures or immobilization within 6 months, confirmed spontaneous venous thromboembolism in a first degree relative, estrogen use, pregnancy or childbirth.
- * absence of thrombocytosis (platelet count $>600 \cdot 10^9/L$), deficiency of antithrombin, protein C or S or presence of circulating lupus anticoagulant.

Exclusion criteria

- * Any present or past cancerous condition.
- * Age < 25 years

H. Recruitment of Subjects

Once patient is included in the study (see inclusion and exclusion criteria above), they will be consented to the study. Prior to signing, they will be informed about the VTE and a possible association to cancer. They will also be informed that it has been suggested but

not shown in any studies that there might be a benefit of an additional CT to the basic cancer screening. Additionally, they will be told that CT of abdomen and pelvis will expose them to a certain dose of radiation. This will be an intention to treat study and there will be no cross over in between the groups. This is raised as there is the possibility that people in the limited screening group will eventually decide to get a CT as they might be anxious from the possibility of a cancerous process.

I. Confidentiality of Subjects

All data will be stored in a secure location and password protected. All materials containing identifying information will be discarded after the study identifying number is issued.

J. Potential Conflict of Interest

The investigators have no proprietary interest in any of the screening modality under investigation in this study and they will not benefit financially in any way from the results of this investigation.

K. Location of the Study

The study will be performed within the ER or medicine floor of several hospitals as a multicenter clinical study. A list of hospitals participating has still not been established.

L. Potential Risks

The major risks associated with this study are related to radiation of an additional CT radiation exposure. There is no risk at preventing a CT as a screening modality as there have been no survival benefits shown to date for patients screened with a CT of abdomen and pelvis.

M. Potential Benefits

The potential benefit to patients enrolled in the study arm is a potential improvement in mortality in the face of a potential malignant disease.

N. Alternative Therapies

This study is not studying therapies for neither cancer nor VTE. As above, patients that will be found to have a malignant condition will be treated for their condition appropriately by their Oncologist.

O. Compensation of Subjects

No compensation will be provided to study participants.

P. Costs to Subjects

The subjects will not incur any further hospital-related costs due to being enrolled in the study.

Q. Minors as Research Subjects

N/A

R. Radiation and Radioactive Substances

See potential risks

S. References

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