PICO question:
In outpatients with cancer, what is the predictive value of the D-dimer on patient overall mortality?

Objectives
The primary objective of this pooled proportion analysis is to determine the correlation, if any, between the D-dimer and mortality in cancer outpatients. If a group of outpatients can be reliably identified as being at high risk of death (from cancer-associated venous thromboembolism [VTE] or any other cause), then a D-dimer may be an important prognostic marker that can help guide patient care.

Criteria for Considering Studies for This Review

Type of studies:
We will include all randomized control trials, prospective and retrospective studies in which outpatient D-dimer studies were performed in cases of solid tumour or haematologic malignancies.

Types of participants:
Adults (18 years and older) diagnosed with cancer (any solid tumour or haematologic malignancy) that had any type of D-dimer testing performed in the outpatient setting, with subsequent follow-up to document outcomes.

Types of outcome measures:
We will analyze all studies that reported on at least one of the following outcomes:

Primary: Overall survival in cancer outpatients.

1. Overall survival is defined as the time from enrolment into the study to death from any cause.

Secondary:

1. Cancer-related mortality, defined as the cumulative incidence of death from cancer.
2. Fatal pulmonary embolism (PE), defined
    a. As per the definitions found within the individual studies, or
    b. By radiographic confirmation (of an intra-luminal filling defect in a segmental or larger artery on invasive or computed tomographic pulmonary angiography, or a high probability ventilation/perfusion scan [V/Q scan]), or
    c. By hypotension, hypoxia, or cardiac arrest with no other explanation other than PE, or
    d. By autopsy.
3. Fatal bleeding complications in cancer patients.

Search Methods for Identification of Studies

An electronic search using Ovid MEDLINE (including in-process and other non-indexed citations, 1946 to present), EMBASE (1980 to 2012 week 17), and the Cochrane Register of

Controlled Trials (April 2012) will be performed, without restrictions on language, using the following terms (Appendix 1a):

Neoplasms (MeSH) or cancer* (keyword) or malignanc* (keyword)

Venous Thromboembolism (MeSH) or Venous Thrombosis (MeSH) or Thromboembolism (MeSH) or Pulmonary embolism (MeSH) or PE (keyword) or deep vein thromb* (keyword) or DVT (keyword) or thromb* (keyword)

Fibrin fibrinogen degradation products (MeSH) or D-dimer (keyword)

A second electronic search for abstracts only from the past 5 years (2007-2013) will be done through the Blood and Journal of Thrombosis and Haemostasis (JTH) website search engines, using the following terms (Appendix 1b):

D-dimer, cancer

Adjustments will be made to the search strategy to account for the differences in indexing between databases. Complete references of all articles will be imported into RefWorks and duplicates will be removed from within the RefWorks program.

Data collection and Analysis

Selection of trials

Two authors will independently screen the title and abstract of identified records for potential eligibility. Full text of articles judged potentially eligible will be retrieved. Discrepancies will be resolved by discussion between reviewers.

The two authors will then independently assess the full text of the selected article for inclusion into the present review. Any disagreements will be resolved by consulting a third party. In order to be included the trial will have to meet the following criteria:

Inclusion Criteria

1. Adults (18 years and older) with any solid tumor or hematologic malignancy who had D-dimer testing as an outpatient for any reason
2. Randomized control trials, prospective studies of consecutive patients, and retrospective studies
3. One or more primary or secondary outcome measures is reported

Exclusion Criteria:

1. Individuals less than 18 years of age
2. Case report studies
3. Prospective studies not following consecutive patients

A flow diagram/chart will be used to tract included or excluded studies at each step of the search process.

Data extraction

Both authors will independently extract the data from the retrieved articles. The primary authors of any articles with inadequate or missing information will be contacted. Any discrepancies will be resolved by consensus.

A standardized data collection form will be used to collect data pertaining to:

Participants:

- Population characteristics (age, gender, co-morbidities)
- Number of patients in study group
- Number of patients followed-up in or withdrawn from study group
- Duration of follow-up in study group
- Type of cancer
- Stage of cancer
- Time since cancer diagnosis
- Interventions including radiotherapy, chemotherapy, and hormonal therapy (type and duration)
- Patient overall survival
- Number of patients in which cancer was the cause of death
- Number of patients in which fatal PE was the cause of death
- Number of patients in which fatal bleeding was the cause of death

Statistical analysis

We will determine whether the D-dimer is predictive of overall and VTE-associated mortality in cancer outpatients.

Results will be stratified by:

- Type of cancer
- Stage of cancer
- Cancer interventions including radiotherapy, chemotherapy, and hormonal therapy (type and duration)

Individual study rates will first be transformed into a quantity using Freeman-Tukey variant of the arcsine square root transformed proportion. The pooled proportion will then be calculated as the back-transform of the weighted mean of the transformed proportions, using a random effects model. The weighting of outcomes accounts for differences in sample size and length of follow-up periods between the individual studies.

Potential Conflict of Interest: None known

Appendix 1a:

Search strategy, Ovid MEDLINE/EMBASE/ Cochrane Register of Controlled Trials:

1	exp neoplasms/
2	cancer*.ti,ab,mp,tw.

3	malignanc*.ti,ab,mp,tw.
4	1 or 2 or 3
5	exp Venous Thromboembolism/ or exp Pulmonary Embolism/ or exp Thromboembolism/
6	exp Venous Thrombosis/
7	PE.ti,ab,mp,tw.
8	deep vein thromb*.ti,ab,mp,tw.
9	DVT.ti,ab,mp,tw.
10	thromb*.ti,ab,mp,tw.
11	5 or 6 or 7 or 8 or 9 or 10
12	exp Fibrin Fibrinogen Degradation Products/
13	D-dimer.ti,ab,mp,tw.
14	12 or 13
15	4 and 11 and 14

Appendix 1b:

Search strategy, Blood:

- Annual Meeting Abstracts Jan. 2007-Jan. 2013
- Text/Abstract/Title with all of the following words: D-dimer, cancer

Search strategy, JTH:

- Abstracts from the XXI (2007), XXII (2009), and XXIII (2011) ISTH Congress
- Any presentation, abstract title: D-dimer

Appendix 2:

Data extraction form:

1) Verification of eligibility
    - Adults (18 years and older) with any solid tumor or hematologic malignancy who had D-dimer testing as an outpatient for any reason
    - Randomized control trials, prospective studies of consecutive patients, and retrospective studies
    - One or more primary or secondary outcome measures is reported
        i. Overall survival
        ii. Cancer-associated mortality
        iii. Fatal PE
        iv. Fatal bleeding complications

2) Document Identification

Refwork ID #	
Title of article	
Lead Authors	
Journal and year of publication	
Language of publication	
Countr(ies) of study origin	

Sources(s) of funding (if available)	
Type of study (RCT, prospective, retrospective)	
Type of document (full journal article, published abstract, conference proceeding)	

3) Results
    - Demographics and Outcomes

Population characteristics (age, gender, co-morbidities)	Age: Gender: Co-morbidities:
Number of patients in study group	
Number of patients followed-up in or withdrawn from study group	
Duration of follow-up in study group	
Type of cancer	
Stage of cancer	
Time since cancer diagnosis	
Interventions including radiotherapy, chemotherapy, and hormonal therapy (type and duration)	○ Radiotherapy: ○ Chemotherapy: ○ Hormonal therapy:
D-dimer (context, and types thereof)	
Patient overall survival	
Number of patients in which cancer was the cause of death	
Number of patients in which fatal PE was the cause of death	
Number of patients in which fatal bleeding was the cause of death	