Published in final edited form as:

Am J Clin Oncol. 2016 June ; 39(3): 294–301. doi:10.1097/COC.0000000000000062.

The Impact of Cancer on the Clinical Outcome of Patients after Inferior Vena Cava Filter Placement: A Retrospective Cohort Study

Anand Narayan, MD/PhD¹, Kelvin Hong, MD¹, Michael Streiff, MD⁴, Russell Shinohara, PhD³, Constantine Frangakis, PhD³, Josef Coresh, MD/PhD^{2,3,4}, and Hyun S. Kim, MD⁵

¹ Department of Radiology, Johns Hopkins School of Medicine, Baltimore, USA

² Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA

³ Department of Biostatistics, University of Pennsylvania Perelman School of Medicine

⁴ Department of Medicine, Johns Hopkins School of Medicine

⁵ Department of Radiology, University of Pittsburgh School of Medicine

Abstract

Objectives—Inferior vena cava (IVC) filters are placed to prevent pulmonary embolism (PE) however some studies have suggested that IVC filters are associated with exacerbated risks of deep vein/IVC thrombosis in cancer patients. The purpose of this study is to determine if cancer patients develop higher than expected rates of venous thromboembolism complications after filter placement compared with non-cancer patients.

Methods—A retrospective cohort study of consecutive patients who received filters (2002-2006) at Johns Hopkins was conducted. Exposures and outcomes were obtained by chart review. Relative risks (RR, 95%CI) for outcomes in cancer versus non-cancer patients were estimated using multistate models.

Results—The cohort included 702 patients – 246 with cancer and 456 without. Cancer patients were older, more likely to be white and have filters placed for contraindications to anticoagulation ($p < 0.01$). The most common cancers were lung (11.8%) and colorectal (10.6%). Cancer patients had an increase in venous thromboembolism (RR 1.9, (1.1,3.2)) due to more DVT/IVC thrombosis (RR 1.7, (1.0,3.0)). Higher PE rates in cancer were not statistically significant (RR 2.2, (0.8,5.8)).

Conclusions—Cancer patients have elevated risks of thrombotic complications compared with non-cancer patients however these risks are not higher than expected based on historical controls.

Keywords

Filter; Venous Thromboembolism; Cancer

Introduction

Cancer patients are at 4-7-fold higher risk of venous thromboembolism (VTE) than patients without cancer[1,2]. While anticoagulation is effective in preventing VTE recurrence in cancer patients, bleeding complications are 2-6 fold more common[3-5]. Although IVC filters have been traditionally used in patients with contraindications to anticoagulation such as bleeding, previous studies have suggested that IVC filters have been associated with exacerbated risks of DVT and IVC thrombosis and decreased survival [6-8] in cancer patients. Although prior studies have suggested increased thrombotic complications associated with filter placement, these studies have been limited by lack of comparison groups and small sample sizes [9,10]. The purpose of the current study is to determine if cancer patients have an increased rate of VTE after filter placement compared with patients without cancer greater than what might be expected based on historical controls.

Materials and Methods

Patients

After obtaining institutional review board approval, we identified patients from a retrospective cohort of consecutive patients at Johns Hopkins Hospital who received an IVC filter between 1/2002-12/2006 [11].

Primary Exposure

The primary exposure of interest in this study was active malignancy. The Johns Hopkins Medical Institutions Electronic Patient Record (EPR) was used to search hospital admissions, clinic notes, laboratory results and radiology reports to determine primary as well as secondary exposures. Patients were classified as having an active malignancy at the time of filter placement if they were noted to have a diagnosis of metastatic cancer, recent (within three months) or ongoing treatment for cancer, or a diagnosis of cancer within 3 months of filter placement. Cancer stage was not uniformly reported but medical reports were searched to determine if patients had metastatic disease prior to or at the time of filter placement. Particular types of chemotherapeutic agents were noted if they have been associated with an elevated risk of VTE[12].

Additional Baseline Exposures

For each filter recipient, the time of filter placement and type of filter were noted along with any procedural complications that occurred during filter placement. Baseline exposures collected included the following variables: age, gender and ethnicity, indications for filter placement, risk factors for venous thromboembolism, and the presence of venous thromboembolism at the time of filter placement.

VTE risk factors included the following: a history of recent surgery, immobilization (no immobilization, short term immobilization, and long term immobilization), trauma, stroke, cardiopulmonary failure, thrombophilia, age, prior venous thromboembolism, current pregnancy or post-partum state (up to six weeks post-delivery), estrogen therapy, nephrotic

range proteinuria (≥ 4 grams per day), leukocyte count, platelet count, hemoglobin and obesity. Definitions of these variables are included in the supplementary material.

Potential Confounders

We hypothesized that most of the covariates in our study would be intermediates instead of confounders with the exception of demographic variables (age, gender, and ethnicity). To take into account potential confounding due to demographic variables, the probability of active malignancy was modeled using propensity scores[13-16].

IVC Filter Placement

Usual clinical practice was followed. Before proceeding with IVC filter placement, informed consent was obtained after a discussion of its potential risks and benefits. Percutaneous access was performed using real-time sonographic guidance, and venograms were performed using iodine contrast. In patients with documented moderate (glomerular filtration rates or $\text{GFR} < 60 \text{ mL/min/1.73m}^2$) to severe ($\text{GFR} < 15 \text{ mL/min/1.73m}^2$) renal insufficiency, gadolinium or CO_2 gas contrast was used. Filters were placed percutaneously via the common femoral vein (CFV) or the internal jugular vein (IJV) in the interventional radiology suite. The attending physician and the primary referring physicians jointly decided on whether permanent (PF) or retrievable (RF) filters were placed. The specific type of RF or PF used was determined by the attending physician based on the clot location, duration of caval filtration anticipated, venous access site availability, caval diameter and operator experience.

When the maximal benefits of a RF were realized and the estimated risk:benefit balance (risk of RF complications versus risk of PE) of continued filtration was judged to be unfavorable; patients were evaluated for possible retrieval by the primary referring service with a consultation with the interventional radiology service. The retrieval decision was made by the attending physician on individual case basis. Each patient was thoroughly evaluated clinically for VTE status, recurrence risk and anticoagulation status. To assess the status of venous thromboembolic disease, bilateral extremity duplex Doppler examinations were performed in all RF retrieval candidates. Patients with evidence of new/progressive VTE were left with RF intact. When VTE was absent or VTE was stable/regressing while on stable anticoagulation therapy, patients were referred for venographic evaluation. Direct venography of both iliac veins and the IVC was performed. RF retrieval was attempted only in patients with absent or minimal thrombus trapped in the RF. Our approach follows the recommendations later set forth by the SIR Multidisciplinary Consensus Conference [17].

Antithrombotic Therapy

Once contraindications to its use were no longer present, anticoagulation was initiated using unfractionated heparin adjusted to achieve an APTT ratio of 1.5 to 2.5 times control or weight-based doses of low molecular weight heparin. In the absence of clinical signs of bleeding, warfarin was started and unfractionated heparin or low molecular weight heparin was continued for a minimum of five days until the INR was at least 2 for 24 hours. In cancer patients, low molecular weight heparin was also used in some instances for long-term

therapy. The duration of therapy and subsequent initiation of therapy for recurrent episodes of venous thromboembolism was dictated by patients' physicians on an individual basis.

Study Outcomes

The primary study outcome was the development of VTE after filter placement. The Johns Hopkins Medical Institutions Electronic Patient Record (EPR) was used to search hospital admissions, clinic notes, laboratory results and radiology reports to determine if patients developed VTE after filter placement. DVT, IVC thrombosis or PE events were defined as any new episode or worsening noted in radiology reports or clinic notes. VTE was defined as any DVT, IVC thrombosis or PE occurring after filter placement. Uniform surveillance was not performed - patients received routine clinical follow up as dictated by their physicians based upon their clinical status.

The principal secondary outcome of interest was death after filter placement. Death was determined by chart review as well as a search of the Social Security Death Index (SSDI) on 9/6/2009.

For VTE, follow up times were determined from the day of filter placement until the time of the event or until the last visit noted in the EPR. For the outcome of death, the duration of follow up was determined from the date of filter placement until the date of death as recorded in the EPR or the most recent date the SSDI was queried[18]. Additional complications of filter placement noted during follow up included filter migration, IVC penetration and major or minor bleeding[19].

Statistical Analysis

Statistical analysis was performed using STATA, version 11.0 (STATA Inc., College Station, TX) and R, version 2.10 (R Foundation for Statistical Computing, Vienna, Austria). Baseline variables were described using means with 95% confidence intervals and analyzed by comparing means using t-tests or proportions using z-tests.

In our analyses, we compared cancer to non-cancer patients and then looked at cancer patients separately.

To compare cancer versus non-cancer patients, we performed 2 different types of analyses – Cox proportional hazards models and temporally multistate models based on propensity scores[14]. The temporally multistate models will be referred to as multistate models for the rest of the paper.

As the competing risk of death constituted informative censoring in the Cox models, we examined the multistate nature of the possible observed combinations of clot events and death. Specifically, we estimated the probability that each individual would be in one of the four states at each time point: those alive without prior clot, those who had experienced a clot but were still currently alive, those who had died without a clot and those who had clotted and subsequently died.

For the multistate model analysis, we considered the time scale from filter installation to 30 days post-procedure. We first estimated the empirical (unadjusted) probability of being in each state and plotted this in cancer and non-cancer patients across time. Relative risks with 95% confidence intervals comparing cancer to non-cancer patients were estimated. To address potential confounding due to demographic variables, we also estimated an adjusted probability of being in each state with 95% confidence intervals using quintiles of propensity scores, after excluding non-comparable patients (min-max criteria). The estimation of the adjusted probabilities involved estimating the probability of being in each state at each time point for both cancer and non-cancer patients. We then averaged these probabilities over the propensity score distribution to get the marginal state probabilities to be compared. The results of this analysis were also plotted (these curves are weighted versions of the empirical curves, with weights based on the propensity scores). Relative risks and 95% confidence intervals were calculated using the delta method; as some of the estimated probabilities were estimated from small samples the coverage probabilities of these intervals might be suboptimal. A complete case analysis was deemed satisfactory due to the low rate of missing data (10.6%).

We also used Cox proportional hazards models to assess the sensitivity of our findings. For the Cox models, we determined the hazard ratios for the time to each of the four events: VTE, IVC/DVT, PE, and death as well as the composite outcome of VTE or death. We first performed these analyses for each outcome in the entire cohort of 702 patients with and without adjustment for demographic variables. Next, we performed these unadjusted and adjusted analyses after excluding cancer and non-cancer patients who did not have overlapping propensity scores (min/max criteria) and patients who did not fall within the 5th to 95th percentile of propensity scores. Proportional hazards assumptions were checked using log log plots as well as tests based on Schoenfeld residuals.

We assessed the sensitivity of our findings in several other ways. To determine if changes in treatment protocol over time introduced bias, we adjusted for procedure year in our Cox models. We also adjusted for quartiles of follow up to determine if patients were more likely to be diagnosed with VTE with longer follow-up. Furthermore, we stratified our Cox models by propensity score quintile to determine if our findings were consistent across propensity score quintiles.

For cancer patients alone, we used Kaplan Meier methods to estimate survival probabilities with 95% confidence intervals in the entire dataset from 30 – 1825 days. We also stratified by cancer status, cancer location/type, presence or absence of metastases, primary or secondary involvement of the brain and clot risk (low risk, high risk and very high risk)[20] and calculated survival probabilities with 95% confidence intervals.

Sample Size Calculations

Based on the PREPIC study, we assumed that 5.6% of subjects on anticoagulation would develop VTE after filter placement within 3 months and that 11.2% of cancer patients would develop VTE (assuming that cancer patients have twice the risk of VTE as non-cancer patients). Although we did not have estimates to allow us to make power calculations based

on a multistate analysis, with a two-proportion z-test, our available sample size of 246 cancer patients and 456 non-cancer patients would yield a statistical power of 70.9%.

Results

Demographics

Between 2002 and 2006, we noted that 702 patients received IVC filters of whom 246 had active cancer at the time of filter placement. Baseline differences were noted between cancer and non-cancer patients in terms of demographics and risk factors for venous thromboembolism (Table 1). Cancer patients were older (62 vs 57 years, $p < 0.01$), more likely to be white (73 vs 56%, $p < 0.001$), more likely to have filters placed due to contraindications to anticoagulation (68 vs 58%, $p < 0.01$), less likely to have filters placed for prophylaxis (8 vs 17%, $p < 0.01$), more likely to present with pulmonary embolus (42 vs 27%, $p < 0.001$). Comparable numbers of cancer patients were female (46 vs 48%, $p = 0.55$) and both groups were comparably likely to have at least 30 days of follow up if they did not experience an episode of venous thromboembolism or death ($p = 0.173$).

Filter Types and Indications

Indications for filter placement differed between cancer and non-cancer patients. Cancer patients were more likely to receive IVC filters for contraindications to anticoagulation (68%) and failures of anticoagulation (13%) while non-cancer patients were more likely to receive filters due to contraindications to anticoagulation (58%) and prophylactic reasons such as trauma (17%) ($p < 0.01$).

Cancer patients were more likely to have permanent filters placed than retrievable filters (46 vs 36%, $p = 0.02$) and the most common filter types were Optease and Trapease filters for cancer patients (35%, 35%) and non-cancer patients (39%, 28%), respectively. In cancer patients who received retrievable filters, filter retrieval was attempted in 15% of patients in which filter removal was successful in 53% of patients with a mean retrieval time of 16.1 days $\pm$ 18.3 days (SD) after implantation. The remainder of the patients did not have their filters retrieved secondary to clot in the filter. No cancer or non-cancer patients experienced symptomatic filter migration or IVC penetration during follow up.

Anticoagulation

Among 246 cancer patients, 38.6% of patients received anticoagulation after filter placement and among 456 non-cancer patients, 33.3% of patients received anticoagulation. Warfarin was the most commonly used anticoagulant in cancer and non-cancer patients with comparable percentages of cancer (81.1%) and non-cancer patients (88.2) were treated with warfarin post filter placement ($p = 0.124$).

Complications were low in both anticoagulated and non-anticoagulated patients. Among the 247 patients who were anticoagulated, 3 patients were noted to have hematomas (1.2%), one patient died due to a retroperitoneal bleed after filter placement (0.4%) and one filter needed to be repositioned (0.4%). Among the 455 patients who were not anticoagulated, 8 patients

were noted to have hematomas (1.8%), 1 patient was noted to have an unsuccessful filter placement (0.2%), 6 filters needed to be repositioned (1.3%), and 1 filter migrated (0.2%).

Cancer Types

Among our 246 patients with active cancer, the most common location was gastrointestinal tract (33.3%) and the most common primary organ sites were lung (11.8%), colorectal (10.6%) and pancreatic (9.4%)(Table 2). Nearly half of the patients (45.9%) were noted to have metastatic cancer at the time of filter placement while 17.1% of cancer patients had brain involvement. Of the 246 cancer patients, 32(13.0%) had cancers that were associated with a very high risk of VTE (pancreatic and gastric) while 92(37.4%) had cancers that were associated with a high risk of VTE (lung, lymphoma, gynecological, and genitourinary cancers excluding prostate).

Venous Thromboembolism and Death after Filter Placement—In the unadjusted analyses with the entire dataset, we noted that 13.4% of cancer patients developed VTE by 30 days compared with 7.7% of non-cancer patients. Using the multistate models, the adjusted percentage of cancer patients who developed VTE was 15.9% (10.5, 21.3) while the adjusted percentage of non-cancer patients developing VTE was 8.0% (5.1, 10.9)(Figure 1). These differences were noted to be statistically significant using multistate models (RR 2.0, 95% CI – 1.2, 3.3) as well as the Cox models (1.9 (95% CI - 1.1, 3.2))(Table 3).

In our sensitivity analyses using Cox models, we adjusted for year of procedure, propensity score quintiles, and quartiles of follow up and noted that cancer was associated with a statistically significantly increased risk of VTE in all of these models (Table 3).

In the unadjusted analyses with the entire dataset, we noted that 10.6% developed DVT or IVC thrombosis by 30 days compared with 6.8% of non-cancer patients. These differences were noted to be statistically significant using multistate models (RR 1.7 (95% CI - 1.0, 3.1)) and the Cox model (HR 1.7 (95% CI – 1.0, 3.0)) (Figure 1)(Table 3). In our sensitivity analyses, Cox models with additional adjustment, exclusion or stratification produced results that were consistent with our main results.

In the unadjusted analysis, we noted that 4.1% of cancer patients developed PE by 30 days compared with 1.8% of non-cancer patients. Using the multistate analysis, these differences were statistically significant using multistate models (RR 2.7 (95% CI - 1.0, 7.5)) but not statistically significant using the Cox model (HR 2.2 (95% CI – 0.8, 5.7)(Figure 1)(Table 3). In our sensitivity analyses, Cox models with additional adjustment, exclusion or stratification produced results that were consistent with our main results.

In our Kaplan-Meier survival analyses, we found that cancer patients had lower survival probabilities compared with non-cancer patients at 30 days (78% vs 86%), 1 year (36% vs 71%), and 5 years (15% vs 52%) (Table 4). The highest survival probabilities were found with genitourinary (prostate, bladder, renal) (82%, 48%, 29%) and gynecologic (uterine, ovarian) cancers (93%, 45%, 11%) and the lowest survival probabilities were found with pancreatic (61%, 17%, 17%) and lung cancers (66%, 24%, 10%) at 30 days, 1 year and 5 years, respectively. Patients with metastatic disease had lower 30 day, 1 year and 5 year

survival probabilities (73%, 27%, 10%) compared with patients without evidence of metastatic disease at baseline (82%, 43%, 20%). We did not note elevated rates of VTE or mortality in patients with high and very high thrombotic risk cancers compared with patients with other cancer types (Table 5). Patients with metastatic cancer or central nervous system cancers did not develop more VTE but did have a higher mortality rates.

Discussion

In this study, we found that cancer patients have elevated risks of thrombotic complications compared with non-cancer patients however these risks are not higher than expected based on historical controls. Comparing cancer to non-cancer patients, a prospective cohort study based out of Olmsted county, Minnesota found that the diagnosis of cancer was associated with a 4.1 fold increased risk of thrombosis (95% CI – 1.9, 8.5) and chemotherapy was associated with a 6.5 fold increase in thrombotic risk (95% CI – 2.1, 20.2) [1]. Similarly, Matsuo et al found elevated risks of distal metastases and decreased survival in ovarian cancer patients with IVC filters [7]. The authors proposed potential explanations in which the placement of an IVC filter triggers a proinflammatory state and activates platelets promoting both venous thromboembolism as well as tumor growth. Given these risks, we may have expected the insertion and ongoing presence of an inferior vena cava filter to exacerbate a hypercoagulable state, leading to magnified risks of VTE in cancer patients compared with non-cancer patients, greater than the 4-7 fold increased risk of venous thromboembolism reported in prior studies.

However, we found that cancer patients with filters had a two-fold increase in thrombotic risk compared with non-cancer patients (95% CI – 1.2, 3.3), a risk which was lower than the four to seven fold rate previously reported [1]. These results are comparable to one of the largest series in which Athanasoulis et al studied 926 patients with underlying malignancies and 827 patients without underlying malignancy [19]. Although DVT rates were not reported, the authors noted that IVC thrombosis occurred approximately twice as often in cancer patients compared with non-cancer patients (4.4% vs 1.8%, $p = 0.002$). Overall proportions of PE were 5.6% and the authors noted no differences in PE between cancer and non-cancer patients. Although they did not compare cancer to non-cancer patients, comparable cumulative incidence rates of DVT, IVC thrombosis and PE were also reported by Wallace [9] and Schwarz [10]. These results suggest that IVC filters do not confer any additional thrombotic risks in cancer patients and that elevated risks of distal metastases and decreased survival in cancer patients may reflect increased underlying disease burden in cancer patients requiring IVC filter placement.

Regarding the outcome of death, some authors have found high mortality rates in cancer patients receiving IVC filters. Jarrett et al. studied 116 cancer patients receiving IVC filters and noted 30 day mortality rates of 31.2% overall and a 30 day mortality rate of almost 50% in patients with stage IV disease [22]. The poor mortality rates led the authors to suggest that cancer patients, particularly those with Stage IV disease, may derive little benefit associated with filter placement. In other reports however 30 day mortality rates were found to be lower. In their cohort, Athanasoulis et al. noted that cancer patients were noted to have a statistically significantly higher 30 day mortality rate (19.5 vs 14.3%, $p = 0.004$), rates that

Author Manuscript

Author Manuscript

Author Manuscript

were comparable to the rates that we found in our study (20.8 vs 14.6%). Wallace et al. found a 30 day mortality rate of 19% mortality rate and a 1 year mortality rate of 65%, similar to the 30 day mortality rate of 22% and the 1 year mortality rate of 64% in our study and by Athanasoulis. Wallace et al. also evaluated 30 day and 1 year survival by cancer type and found similar results for short term and longer term survival. At 30 days, survival proportions ranged from 66 to 87%, similar to the 61 to 93% survival probabilities in our study. Similarly at 1 year, they found survival proportions ranging from 28 to 47%, similar to the 17 to 48% we found in our study. Evaluating patients with metastatic disease, they also found similar 30 day and 1 year survival proportions (76%, 29%, respectively) compared with the survival proportions found in our study (73%, 27%, respectively). Finally, in the only randomized trial of inferior vena cava filters, patients who received IVC filters did not derive any short or long term mortality benefits [6]. The results suggest that although short and long term mortality rates may not be as grim as those cited by Jarrett, long term survival is limited in cancer patients receiving IVC filters and patients may not derive additional survival benefits from filter placement. Candidates for IVC filter placement should be carefully selected based on cancer type, stage and anticipated survival.

The limitations of our study include reliance on chart review for data collection and a high loss to follow up rate. In addition to revealing thrombotic complications, dedicated prospective surveillance has revealed numerous additional long term complications associated with IVC filters including filter perforation, penetration and hardware fracture [23]. Surveillance for venous thromboembolism events or filter complications was not uniform; rather surveillance was determined by patients' physicians on an individual basis. Nevertheless, loss to follow up was not statistically significantly different in cancer vs non-cancer patients (7.7 vs 12.1%, $p = 0.07$). In addition, uniform surveillance may detect more asymptomatic VTE events or filter complications, which are of debatable significance.

The reliance on retrospective chart review increased the probability of misclassification of exposures and outcomes. For the main exposure, cancer status, patients diagnosed with venous thromboembolism may have received follow up care at another institution and subsequently may have been diagnosed with malignancy at the other institution. However, loss to follow up rates were relatively low and for those who were not lost to follow up, it is likely that their cancer diagnosis would have been noted if they came back to our institution for any further management of venous thromboembolism or any other medical issues. Regarding VTE outcomes, patients with cancer may have received closer follow up for VTE outcomes than non-cancer patients. This possibility was also minimized by comparable follow up rates in both groups as well as the fact that both cancer and non-cancer patients had risk factors for VTE that led to IVC filter placement, suggesting an already heightened level of suspicion for VTE in all patients in the study.

In addition, we suspected that most of the covariates we collected would be intermediates in our study, that is consequences of cancer mediating its increased risk. Therefore, we only adjusted for demographic variables. The lack of a prospective study design prevented us from systematically collecting additional exposures such as prothrombotic mutations and smoking status, which could confound our study results. We attempted to collect information

regarding hypercoagulable states but given that this was a retrospective study, it is possible that surveillance biases may have influenced our study results.

Another limitation of our data is that our main study outcomes did not include VTE outcomes beyond 30 days. Beyond 30 days, loss to follow up was considerably higher, precluding us from making valid estimates of VTE rates beyond 30 days. However prospective studies of VTE have determined that the highest risk period for recurrence occurs in the immediate period after the initial event. In one population-based study, 25% of all recurrent thrombotic events that occurred within 1 year occurred within the first 30 days[24]. The 30 day endpoint is also consistent with the recommended window of retrievability of several commercially available optional filters.

The 30 day endpoint also limited the number of events we had available in our analysis. The reduced number of events may have limited our statistical power in being able to detect differences between cancer and non-cancer patients in terms of events such as PE and DVT/IVC thrombosis. Nevertheless, the number of PE events noted in our study (5.6% in cancer patients versus 2.0% in non-cancer patients) was comparable to numbers cited in other papers.

Finally our study compared cancer to non-cancer patients who have already received filters. Although 16% of PREPIC trial participants had cancer, a direct randomized comparison of filters versus no-filters would provide additional evidence to help clinicians determine if filters provide comparable benefits in terms of PE protection, complications, survival and cost. In the absence of randomized controlled trials, case control studies comparing cancer patients with filters to cancer patients without filters would help to answer some of these questions, particularly with additional information regarding anticoagulation status.

In conclusion, cancer patients have elevated risks of thrombotic complications compared with non-cancer patients after filter placement however these risks are not higher than expected based on historical controls. Although the risk of thrombotic complications may not be magnified for cancer patients as a result of filter placement, clinicians deciding whether or not to place filters must weigh potential protection against pulmonary embolism versus anticipated survival, particularly in patients with advanced stage cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding:

This work was supported by the National Heart Lung and Blood Institute at the National Institutes of Health (1F30HL094095-01 to AN).

References

1. Heit JA, Silverstein MD, Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism: A population-based case-control study. *Arch Intern Med.* 2000; 160:809–815. [PubMed: 10737280]
2. Blom JW, Doggen CJ, Osanto S, et al. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA.* 2005; 293:715–722. [PubMed: 15701913]
3. Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood.* 2002; 100:3484–3488. [PubMed: 12393647]
4. Palareti G, Legnani C, Lee A, et al. A comparison of the safety and efficacy of oral anticoagulation for the treatment of venous thromboembolic disease in patients with or without malignancy. *Thromb Haemost.* 2000; 84:805–810. [PubMed: 11127860]
5. Hutten BA, Prins MH, Gent M, et al. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: A retrospective analysis. *J Clin Oncol.* 2000; 18:3078–3083. [PubMed: 10963635]
6. Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. prevention du risque d'embolie pulmonaire par interruption cave study group. *N Engl J Med.* 1998; 338:409–415. [PubMed: 9459643]
7. Matsuo K, Carter CM, Ahn EH, et al. Inferior Vena Cava Filter Placement and Risk of Hematogenous Distant Metastasis in Ovarian Cancer. *Am J Clin Oncol.* May 24.2012
8. Barginear MF, Lesser M, Akerman ML, et al. Need for inferior vena cava filters in cancer patients: a surrogate marker for poor outcome. *Clin Appl Thromb Hemost.* May-Jun. 2009; 15(3):263–9. [PubMed: 18385149]
9. Wallace MJ, Jean JL, Gupta S, et al. Use of inferior vena caval filters and survival in patients with malignancy. *Cancer.* 2004; 101:1902–1907. [PubMed: 15386336]
10. Schwarz RE, Marrero AM, Conlon KC, et al. Inferior vena cava filters in cancer patients: Indications and outcome. *J Clin Oncol.* 1996; 14:652–657. [PubMed: 8636783]
11. Kim HS, Young MJ, Narayan AK, Hong K, Liddell RP, Streiff MB. A comparison of clinical outcomes with retrievable and permanent inferior vena cava filters. *J Vasc Interv Radiol.* Mar. 2008; 19(3):393–9. [PubMed: 18295699]
12. Haddad TC, Greeno EW. Chemotherapy-induced Thrombosis. *Thrombosis Research.* 2006; 118:555–568. [PubMed: 16388837]
13. Hernan MA, Hernandez-Diaz S, Werler MM, et al. Causal knowledge as a prerequisite for confounding evaluation: An application to birth defects epidemiology. *Am J Epidemiol.* 2002; 155:176–184. [PubMed: 11790682]
14. Achy-Brou AC, Frangakis CE, Griswold M. Estimating treatment effects of longitudinal designs using regression models on propensity scores. *Biometrics.* 2009
15. Becker SO, Ichino A. Estimation of average treatment effects based on propensity scores. *STATA Journal.* 2002; 2:358–377.
16. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. *Journal of the American Statistical Association.* 1984; 79:516–524.
17. Kaufman JA, Kinney TB, Streiff MB, et al. Guidelines for the use of retrievable and convertible vena cava filters: report from the Society of Interventional Radiology multidisciplinary consensus conference. *J Vasc Interv Radiol.* Mar. 2006; 17(3):449–59. [PubMed: 16567669]
18. Sesso HD, Paffenbarger RS, Lee IM. Comparison of national death index and world wide web death searches. *Am J Epidemiol.* 2000; 152:107–111. [PubMed: 10909946]
19. Millward SF, Grassi CJ, Kinney TB, et al. Reporting standards for inferior vena caval filter placement and patient follow-up: Supplement for temporary and Retrievable/Optional filters. *Journal of Vascular and Interventional Radiology.* 2005; 16:441. [PubMed: 15802441]
20. Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood.* 2008; 111:4902–4907. [PubMed: 18216292]

21. Athanasoulis CA, Kaufman JA, Halpern EF, et al. Inferior vena caval filters: Review of a 26-year single-center clinical experience. *Radiology*. 2000; 216:54–66. [PubMed: 10887228]
22. Jarrett BP, Dougherty MJ, Calligaro KD. Inferior vena cava filters in malignant disease. *J Vasc Surg*. Oct. 2002; 36(4):704–7. [PubMed: 12368729]
23. Wang SL, Lloyd AJ. Clinical review: inferior vena cava filters in the age of patient-centered outcomes. *Ann Med*. Nov. 2013; 45(7):474–81. [PubMed: 24099038]
24. Heit JA, Mohr DN, Silverstein MD, et al. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: A population-based cohort study. *Arch Intern Med*. 2000; 160:761–768. [PubMed: 10737275]

Figure 1.
Outcomes in Cancer Versus Non-Cancer Patients

Table 1

Demographic and clinical characteristics of the study population

	Included Patients (n = 672)			Excluded Due to Lack of Overlap in Propensity Score (n = 30)
	No Cancer (n = 426)	Cancer (n = 246)	p value	No Cancer (n = 30)
Demographics				
Age (SD)	57.4 (16.8)	61.9 (13.6)	0.004	21.0 (3.8)
Gender (% Female)	48.4	45.9	0.545	30.0
Ethnicity (%)				
White	55.9	73.2	0.000	13.3
African American	39.9	23.6		76.7
Other	4.2	3.3		10.0
% Censored Prior to 30 Days	6.1	3.7	0.173	20.0
Retrievable Filters (%)	64.1	52.9	0.004	80.0
Year of Procedure (%)				
2002	15.3	17.5	0.759	13.3
2003	15.3	15.0		0.0
2004	23.0	24.8		20.0
2005	21.4	17.5		33.3
2006	25.1	25.2		33.3
Indication for Filter				
Contraindication to AC	57.5	67.9	0.003	33.3
Prophylaxis	17.4	7.7		53.3
Complication of AC	12.2	10.6		0.0
Failure of AC	10.1	12.6		6.7
Thrombolysis	2.8	1.2		6.7
VTE at Presentation				
DVT	67.6	68.7	0.770	50.0
PE	27.2	41.9	0.000	26.7
IVC Thrombosis	1.9	4.1	0.091	3.3
Risk Factors				
Recent Surgery	20.7	28.1	0.029	0.0
Immobilization History (%)				
No Immobilization	58.5	81.7	0.000	73.3
Short Term Immobilization	37.1	17.9		13.3

	Included Patients (n = 672)			Excluded Due to Lack of Overlap in Propensity Score (n = 30)
	No Cancer (n = 426)	Cancer (n = 246)	p value	No Cancer (n = 30)
Long Term Immobilization	4.5	0.4		13.3
Recent Trauma	14.6	2.9	0.000	70.0
Hypercoagulable State	3.5	0.0	0.003	10.0
History of VTE	16.7	20.7	0.188	6.7
Estrogen Usage	0.7	0.4	0.629	0.0
History of CHF	8.2	2.9	0.006	0.0
Proteinuria	1.9	0.8	0.272	0.0
History of Resp Failure	6.1	0.8	0.001	0.0
History of Stroke	7.8	3.7	0.035	3.3
Obesity	6.1	2.4	0.032	0.0
Pregnancy-Related	1.2	0.0	0.088	3.3
Hemoglobin (g/dL)	10.2	11.2	0.000	10.5
Platelet ($\times 10^3$ / μ L)	232.4	263.9	0.001	242.5
White Count (per microliter)	10918.1	9975.7	0.076	10618.2

Table 2

Cancer Location and Type

Cancer Location and Type	Count	Percent	Percent Metastatic
Breast	6	2.44%	66.7%
CNS			
Glioblastoma	12	4.88%	16.7%
Other	11	4.47%	9.1%
GI			
Colorectal	26	10.57%	46.2%
Pancreatic	23	9.35%	47.8%
Esophageal	9	3.66%	44.4%
Other	27	10.98%	51.9%
GU			
Prostate	13	5.28%	30.8%
Bladder	7	2.85%	57.1%
Other	11	4.47%	54.5%
GYN			
Ovarian	12	4.88%	41.7%
Cervical	8	3.25%	12.5%
Other	9	3.67%	66.7%
Hematologic	17	6.91%	23.5%
Lung	29	11.79%	69.0%
OTHER			
Sarcoma	13	5.28%	61.5%
Other	7	2.85%	28.6%
Skin	6	2.44%	66.7%
Total	246	100.00%	

Table 3
Adjusted relative hazard (95% CI) of Outcomes in Cancer versus Non-Cancer Patients with IVC filters at 30 Days

Model	N	VTE (n = 68 events)	PE (n= 18 events)	DVT/IVC Thrombosis (n = 57 events)	VTE or Death (n = 171 events)	Death (n = 115 events)
Full Dataset (Hazard Ratios)						
Unadjusted	702	1.8 (1.1, 2.9)	2.3 (0.9, 5.6)	1.6 (0.9, 2.7)	1.6 (1.2, 2.1)	1.6 (1.1, 2.3)
Adjusted for Demographics	702	1.8 (1.1, 3.0)	2.2 (0.8, 5.9)	1.7 (1.0, 3.0)	1.6 (1.2, 2.2)	1.4 (1.0, 2.1)
Cropped Dataset Excluding Non-Overlapping Propensity Scores (Hazard Ratios)						
Unadjusted	672	2.0 (1.2, 3.3)	2.2 (0.9, 5.5)	1.8 (1.1, 3.2)	1.6 (1.2, 2.2)	1.5 (1.1, 2.2)
Adjusted for Demographics	672	1.9 (1.1, 3.2)	2.2 (0.8, 5.8)	1.7 (1.0, 3.0)	1.6 (1.1, 2.1)	1.5 (1.0, 2.1)
Multistate Model (Relative Risks)						
Propensity Score Weighted Models	585	2.0 (1.2, 3.3)	2.8 (1.0, 7.5)	1.7 (1.0, 3.1)	1.6 (1.2, 2.1)	1.4 (1.0, 2.1)

Table 4

Survival Probabilities in Cancer versus Non-Cancer Patients and Cancer Patients alone

Survival Probabilities	N	30 days	90 days	365 days	1825 days
Overall	702	0.83 (0.81, 0.86)	0.73 (0.69, 0.76)	0.59 (0.55, 0.62)	0.39 (0.35, 0.43)
Cancer?					
No	456	0.86 (0.83, 0.89)	0.79 (0.75, 0.83)	0.71 (0.67, 0.75)	0.52 (0.47, 0.57)
Yes	246	0.78 (0.72, 0.83)	0.60 (0.53, 0.66)	0.36 (0.30, 0.42)	0.15 (0.10, 0.21)
Cancer Location/Type					
CNS	23	0.78 (0.55, 0.90)	0.52 (0.31, 0.70)	0.26 (0.11, 0.45)	0.12 (0.02, 0.29)
Colorectal	28	0.89 (0.70, 0.96)	0.68 (0.47, 0.82)	0.39 (0.22, 0.57)	0.09 (0.01, 0.29)
Pancreatic	23	0.61 (0.38, 0.77)	0.43 (0.23, 0.62)	0.17 (0.05, 0.35)	0.17 (0.05, 0.35)
GU	33	0.82 (0.64, 0.91)	0.73 (0.54, 0.85)	0.48 (0.31, 0.64)	0.29 (0.14, 0.46)
GYN	29	0.93 (0.75, 0.98)	0.76 (0.56, 0.88)	0.45 (0.27, 0.62)	0.11 (0.02, 0.28)
Lung	29	0.66 (0.45, 0.80)	0.45 (0.27, 0.62)	0.24 (0.11, 0.41)	0.10 (0.02, 0.24)
Hematologic	18	0.78 (0.51, 0.91)	0.61 (0.35, 0.79)	0.39 (0.17, 0.60)	0.21 (0.06, 0.42)
All Others	65	0.77 (0.65, 0.85)	0.58 (0.46, 0.69)	0.40 (0.28, 0.52)	0.13 (0.05, 0.26)
Metastatic Disease?					
No	133	0.82 (0.74, 0.88)	0.66 (0.57, 0.74)	0.43 (0.34, 0.51)	0.20 (0.13, 0.28)
Yes	113	0.73 (0.64, 0.81)	0.52 (0.43, 0.61)	0.27 (0.20, 0.36)	0.10 (0.05, 0.18)
Brain Involvement					
No	204	0.78 (0.72, 0.83)	0.61 (0.54, 0.68)	0.38 (0.32, 0.45)	0.17 (0.12, 0.24)
Yes	42	0.76 (0.60, 0.86)	0.52 (0.36, 0.66)	0.24 (0.12, 0.37)	0.08 (0.02, 0.20)
Clot Risk of Cancer Type					
Low Risk	122	0.80 (0.72, 0.86)	0.62 (0.53, 0.70)	0.39 (0.31, 0.48)	0.15 (0.08, 0.24)
High Risk	92	0.77 (0.67, 0.85)	0.60 (0.49, 0.69)	0.35 (0.25, 0.44)	0.15 (0.08, 0.23)
Very High Risk	32	0.72 (0.53, 0.84)	0.50 (0.32, 0.66)	0.25 (0.12, 0.41)	0.18 (0.06, 0.33)

Table 5

Hazard Ratios (95% CI) for Outcomes in Cancer Patients with IVC filters

<u>Comparison (Model Adjusted for Demographics)</u>	<u>N</u>	<u>VTE (n = 33 events)</u>	<u>PE (n= 10 events)</u>	<u>DVT/IVC Thrombosis (n = 26 events)</u>	<u>VTE or Death (n = 78 events)</u>	<u>Death (n = 53 events)</u>
<u>Full Dataset</u>						
Very High Risk Compared to Low Risk	246	1.0 (0.3, 3.1)	4.6 (0.7, 31.0)	0.5 (0.1, 2.4)	1.1 (0.6, 2.2)	1.3 (0.8, 2.0)
High Risk Compared to Low Risk	246	0.9 (0.4, 1.9)	3.2 (0.7, 15.1)	0.7 (0.3, 1.7)	0.8 (0.5, 1.4)	1.1 (0.8, 1.5)
Metastatic vs Non-Metastatic	246	0.6 (0.3, 1.3)	0.9 (0.2, 3.5)	0.5 (0.2, 1.2)	1.1 (0.7, 1.8)	1.5 (1.1, 2.0)
Brain Involvement vs No Brain Involvement	246	1.0 (0.4, 2.6)	1.5 (0.3, 7.4)	1.0 (0.3, 3.0)	1.1 (0.6, 1.9)	1.4 (1.0, 2.0)

Footnote – Very High Risk cancers - pancreatic and gastric, High Risk cancers - lung, lymphoma, gynecological, and genitourinary cancers excluding prostate.