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I, Rachna Raman, hereby submit this original work as part of the requirements for the degree of Master of Science in Epidemiology (Environmental Health).

It is entitled:

Inferior vena cava filters in the management of cancer-associated venous thromboembolism: A systematic review

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Inferior vena cava filters in the management of cancer-associated venous
thromboembolism: A systematic review

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by

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Abstract

To systematically review outcomes after Inferior vena cava (IVC) filtration in cancer associated venous thromboembolism (VTE). A comprehensive review of English language literature was performed using MEDLINE, COCHRANE library, Embase and CINAHL; on outcomes (i.e.: Pulmonary embolism, recurrent DVT, post phlebitic syndrome and survival), following IVC filtration in cancer associated VTE. Fourteen studies with 2154 cancer patients receiving IVC filters post VTE were included. All of these were observational studies. The mean duration of follow up was 0.7-38 months, mean patient age 56.8-68 years. Of these, 47%-87% had stage 3 or 4 cancers. Of the 47-93% of filters inserted secondary to contraindications to anticoagulation (AC), 10-33% were placed for *relative* contraindications. Recurrent PE was seen in 0-6%, fatal PE in 0-4.5%, recurrent DVT in 0-18.2%, Post phlebitic syndrome (PPS) in 0-2.7%, and IVC thrombosis (ICVT) in 3% of cancer patients. Median survival post filter insertion was 2-10 months. Evidence for or against IVC filter insertion in cancer associated VTE is in the form of observational studies only. Preliminary data show similar safety and efficacy of filters in cancer and non-cancer populations. The combination of filters and anticoagulation is no more effective than either modality alone. Retrievable filters are an attractive option for prevention of VTE in the presence of temporary risk factors or temporary contraindications to anticoagulation in patients who have a reasonable life expectancy but there is no evidence to support their preferential use in patients with advanced malignancy.

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Introduction

Venous thromboembolism (VTE) occurs in 4-20% of patients with cancer¹. This rate is about 4.1 fold greater than in patients without cancer and chemotherapy increases the risk to 6.5-fold greater^{2, 3}. Clinically significant pulmonary embolism (PE) will develop in 50% of patients with deep venous thrombosis (DVT) of the proximal veins if left untreated^{4, 5}, with mortality rates as high as 17%-34%^{6, 7}. Given the high frequency of VTE in cancer patients and their increased propensity to develop bleeding and thrombotic complications during therapy^{7,8}, oncologists are likely to be faced with difficult therapeutic decisions in their patients with VTE⁸⁻¹¹.

Since the introduction of the stainless steel Greenfield filter in 1973, inferior vena cava (IVC) filters are being placed increasingly in the prevention and treatment of VTE¹². As indications for their use have expanded, IVC filter use in cancer patients has reached considerable proportions¹³ (52.8% of IVC filters were placed in cancer patients in one large single center study)¹⁴. However IVC filters are not free of complications and their efficacy and safety has yet to be studied prospectively in patients with cancer. Several studies have questioned their utility in patients with advanced cancer¹⁵⁻²⁰. Literature on their effect on clinical outcomes (recurrent VTE, survival, complications) in cancer is scant and often not published in journals typically read by oncologists.

The purpose of this article is to systematically review the published literature on the use of IVC filters in the presence of malignancy and identify 1) the evidence available in this patient population 2) the impact of IVC filters on clinical outcomes (early and long term complications, survival and recurrent VTE) 3) the existing controversies regarding the use of IVC filters in cancer and potential answers to them.

Methods:

Literature search and data analysis:

A comprehensive search of English literature was performed using the Medline database, Cochrane library, CINAHL and EMBASE. The search terms used were “IVC filters AND cancer”, “VTE AND cancer”, “Outcomes with IVC filters AND cancer”, “survival AND IVC filters in cancer”, “IVC filters versus anticoagulation”, “complications of IVC filters” and “anticoagulation AND cancer”. Abstracts were reviewed (RR) and studies that met all the following criteria were **included**: 1) At least 20% of the patient population had an underlying malignancy, 2) Reported one or more clinical outcomes of interest (VTE, survival, and other clinically relevant complications) associated with IVC filtration in cancer patients 3) Outcomes were clearly defined and reported. We **excluded**: 1) Case reports only 2) Studies assessing the above outcomes in a population with a specific tumor site or histological type only ^{17, 18, 20}, 3) Studies in which filters were inserted via an open as opposed to a percutaneous approach. The reference lists of the selected articles were reviewed carefully to identify additional studies that met the above-mentioned criteria. Information from each article on study design, patient characteristics, cancer type and stage, indications for filter placement, VTE post-filter placement and complication rates were entered into a database for analysis. Event rates were calculated by dividing the number of patients suffering from an event by the total number of patients in the particular treatment group. A formal combined meta-analysis was not performed because of the heterogeneity of the study populations and methodology.

Outcomes and definitions

To satisfy study criteria as a new event, a deep vein thrombosis (DVT) must be objectively documented to represent an extension of the index DVT or demonstrate involvement of a new vascular territory post-filter insertion on imaging. Insertion site thrombosis (IST) was defined as any thrombosis occurring at the site of initial filter insertion. To qualify as an outcome event, a pulmonary embolism (PE) must be objectively confirmed with or without DVT post-IVC filtration. Any PE leading directly or indirectly to death was regarded as fatal. Postphlebotic syndrome (PPS) was defined as worsening or persistent local edema with or without pain, changes in skin pigmentation, or venous ulcers post-DVT and IVC filtration.

Major bleeding was defined according to the International Society of Thrombosis and Haemostasis criteria as bleeding that results in death, and/or symptomatic critical organ involvement or blood loss exceeding 2 g/dl or transfusion of 2 or more units of blood²¹. Minor bleeding refers to any clinically evident bleeding that did not fulfill the criteria for major bleeding. “Fatal bleeding” refers to any bleeding contributing directly or indirectly to death.

The index VTE was diagnosed by means of venous duplex ultrasound, CT venogram, contrast venogram, CT pulmonary angiogram or ventilation perfusion scan (V/Q scan), depending on the clinical presentation and the standard of practice at the time of study. Follow up information was mostly based on chart reviews. In all but one study²², only symptomatic patients underwent follow up diagnostic imaging to confirm DVT or PE. Consequently, the true incidence of recurrent VTE may have been underestimated by most studies.

Table 1: Studies of vena cava filters for treatment of VTE in cancer patients.

Study	Number of Subjects (N)	Median/Mean age (in years)	Stage 4 disease (%)	Follow up duration (months)	Type of study
Barginear et al. ²³	144	62	NR	NR	Retrospective cohort
Schleich et al. ²²	26	68	NR	38	Prospective case series
Athanasoulis et al. ¹⁴	926	62.2	NR	36	Retrospective cohort
Wallace et al. ³²	308	60	50%	12	Retrospective cohort
Lossef et al. ²⁷	34	61	47%	5.2	Retrospective case series
Schunn et al. ³⁰	55	58	50%	8	Retrospective case control
Ihnat et al. ²⁶	60	60	50%	13.1	Retrospective cohort
Walsh et al. ¹⁹	18	56.8	88%	20.6	Retrospective case series
Magnant et al. ²⁸	48	67	87%	11	Retrospective cohort
Schwarz et al. ³¹	182	59	63%	NR	Retrospective cohort
Greenfield et al. ²⁵	166	57.8	72%	NR	Retrospective cohort
Jarrett et al. ¹⁶	116	66.7	78%	12.2	Retrospective cohort
Caligaro et al. ²⁴	20	60	50%	10	Retrospective case series
Rosen et al. ²⁹	61	66	51%	0.7	Retrospective case series

N= Patients with cancer who received IVC filters; NR= Not reported

Results:

Study characteristics:

Fourteen studies published from 1995-2008 looked at one or more of the outcomes of interest in 2154 patients with all stages of cancer who had received IVC filters from 1973 to 2000^{14, 16, 19, 22-32}. All the studies identified were retrospective cohort studies or case series, except 1 prospective study that enrolled 100 patients, 26% of whom had cancer²². The number of cancer patients with VTE receiving filters ranged from 26²² to 926¹⁴. Five studies compared outcomes with AC and IVC filters.^{23, 24, 26, 30, 33, 34}. The mean age of subjects ranged from 56.8 to 68 years with the mean duration of follow up after filter deployment varying from 3 weeks to 38 months (Table 1). The proportion of patients with stage 4 disease varied from 47% to 87%. The location of the primary tumor was reported for 944 of 2154 patients (Figure 1).

The filter types studied included the Greenfield filter (Boston Scientific Corporation, Natick MA), the TrapEase filter (Cordis Corporation, Miami Lakes, FL), the Vena Tech-LP filter (B. Braun Medical Inc., Bethlehem, PA), the LGM Vena Tech (B. Braun Medical Inc., Bethlehem, PA), the Simon Nitinol (C.R. Bard, Inc. Tempe AZ), the Bird's nest filter (Cook Inc. Bloomington IN) and the Günther tulip filter (Cook Inc. Bloomington IN). The Greenfield filter was studied in the greatest number of subjects. The Mobin-Uddin filter, which was removed from the United States market in 1977, was inserted in a total of 29 subjects in a single study¹⁴. The exact proportion of each type of filter and their influence on outcomes could not be precisely determined as this information was not available for most patients.

Fig. 1 Distribution of various tumor types in 944 cancer patients treated with an IVC filter. Asterisk "Others" includes skin cancers such as melanoma, connective tissue tumors, CNS tumors (6–38%) and head and neck cancers

Outcomes after IVC filter placement: does the presence of an underlying malignancy alter the statistics?

The primary purpose of inserting IVC filters is the prevention of PE, particularly clinically significant and fatal PE.

The ideal filter would be able to achieve this goal without causing significant acute or long-term complications. Complications resulting from IVC filter insertion can be broadly divided into those occurring at the time of filter insertion, those resulting from device failure, and those occurring during long term follow up³⁵.

Of the fourteen studies included in our review, 12 reported rates of acute and long-term complications following filter placement (Table 2). Two of these studies, however, did not report outcomes separately for the cancer and non-cancer populations^{14, 28}. Hence, when calculating pooled event rates, results from these two studies have not been included.

Over a follow-up period of 5.3 months to 20.6 months, PE occurred in 3.5% (37/1043) of patients. Fatal PE occurred in 2.5% (27/1043) of patients. DVT was diagnosed in 6.8% (46/674) of cases while postphlebotic syndrome was noted in 0.9% (9/982) of patients (fig 2). Only one case of Phlegmasia cerulea dolens was noted. IVCT was noted in 3% of cases (56/1897). Other filter-related complications noted were 13 ISTs, 5 filter migrations, 4 asymptomatic IVC perforations, 3 misplaced filters, 12 insertion site hematomas, 2 insertion site infections, 1 contrast reaction and 1 episode of superficial venous thrombophlebitis. Fatal complications included 2 retroperitoneal hemorrhages, 2 ventricular arrhythmias, 1 case of venous gangrene and 1 acute IVCT leading to renal and respiratory failure. Therefore, the total fatal complication rate of IVC filter placement was 0.5% (6/1043).

In his IVC filters metaanalysis in a mixed patient population³⁶, Streiff noted that PE occurred in 2.6-3.8% of cases and was fatal in about 1.9% post-filter insertion. DVT was identified in 6%-32% of cases after filter placement while PPS was noted in 12.9% to 41% of cases, depending on the duration and intensity of surveillance. IVCT was noted in 3.6%-11.2% of cases while IST was noted in 23%-36% of filter insertions.

Other acute (within 24 hours) and chronic complications included misplacement, local hematoma, pneumothorax, cerebrovascular accident, IVC perforation, guide wire entrapment, infection, air embolism, arrhythmias, migration, tilting, strut fracture, venous gangrene and phlegmasia cerulea dolens.^{14, 37} These events were infrequent and rarely fatal (migration to the heart, fracture and retroperitoneal hemorrhage, ventricular arrhythmias, IVCT and renal failure). The review included studies that had a mean follow up duration of 5.8-18 months

Table 2: Major Clinical Events after IVC filter placement in cancer patients

Study	Number of subjects (N)	Mean follow up (months)	DVT (%)	PE(%)	Fatal PE(%)	IVCT (%)	PPS(%)
Wallace et al.	308	12	NR	18/308 (5.8)	14/308 (4.5)	14/308 (4.5)	7/308 (2.3)
Lossef et al.	34	5.3	1/34 (2.9)	0	0	1/34 (2.9)	0
Schunn et al.	55	8	10/55 (18.2)	3/55 (5.5)	0	1/55 (1.8)	0
Ihnat et al.	60	13.1	6/60 (10)	2/60 (3.3)	0	1/60 (1.7)	1/60 (1.7)
Walsh et al.	41	20.6	0	0	0	0	0
Schwarz et al.	182	NR	11/182 (6)	4/182 (2.2)	2/182 (1.1)	0	0
Greenfield et al.	166	NR	13/166 (8)	3/166 (1.8)	3/166 (1.8)	1/166 (0.6)	1/166 (0.6)
Jarrett et al.	116	12.2	2/116 (1.7)	3/116 (2.6)	0	0	0
Caligaro et al.	20	10	3/20 (15)	0	0	0	0
Rosen et al.	61	0.7	NR	4/61 (6)	4/61 (6)	NR	NR
Athanasoulis et al.	926	36	46/1731 (2.7)*	97/1731 (5.6)*	65/1731 (3.8)*	40/915 (4.4)	48/1731 (2.7)*
Magnant et al.	47	11	0*	2/84 (2.4)*	2/84 (2.4)*	1/84 (1.2)*	0*

N: Number of patients with cancer receiving IVC filters, IVCT: Inferior vena cava thrombosis, PPS: Post-phlebotic syndrome NR: Not reported, * rates not specific to cancer patients

The event rates observed in our review, fall within the range noted previously after IVC filters placement, except for markedly lower rates of DVT and post-phlebotic syndromes.

This information should be interpreted in the context that most of these studies were small case series and that they only reported symptomatic events. In addition, the diagnosis of post-phlebitic syndrome was subject to inter-observer bias as validated scales to define PPS were not used in any of these studies. PPS is known to occur in about 50% of cases after an index DVT.³⁸ When studies are conducted over longer periods of time (> 6 years) rates may be as high as 58.8%³⁹. In our review, the mean period of follow up was short (5.3 months to 20.6 months), therefore, this may also account for the low observed rates of PPS.

Based upon the limited available information, it can be contended that IVC filters may be at least as efficacious in patients with cancer in preventing PE as those without cancer. The rate of acute and chronic fatal complications is low. Given their overall poor survival, it appears that placement of IVC filter in patients with advanced cancer may not add significantly to the incidence of long-term complications of recurrent DVT and PPS following an initial episode of VTE. Therefore, if indications for filter placement are present, clinicians should not avoid IVC filter use solely on the basis that their patient has an underlying cancer.

Fig. 2 Post-IVC filtration events in cancer patients. *DVT* deep venous thrombosis, *PE* pulmonary embolism, *IVCT* IVC thrombosis, *PPS* post-phlebitic syndrome

Survival after IVC filter insertion in cancer patients

Occurrence of VTE in cancer portends a poor prognosis. Several retrospective studies have noted that VTE may mark the progression of cancer and is more likely to occur concurrently with either recurrence of or metastasis from the primary disease^{25, 40, 41}. Cancer patients who suffer VTE have been noted to have worsened overall survival than those without thrombosis⁴²⁻⁴⁴. LMWH treatment has been associated with improved survival in cancer patients in some studies an effect that maybe due to the anti-angiogenic properties of heparin⁴⁵⁻⁴⁸. However, there are no prospective trials that have evaluated survival benefit from IVC filtration in patients with cancer and VTE.

Of the 14 studies included in the review, 9 reported median survivals in patients with cancer following placement of IVC filters^{14, 16, 19, 22, 23, 25-27, 30}. The median survival post-IVC filtration ranged from 2-10 months for all stages of cancer, from 3-6.6 months for stages 3 and 4 together and from 2 -6 months for stage 4 cancers. While the extent of cancer was found to be a significant predictor of mortality in all studies; type of primary tumor, gender, and the type of the initial episode of VTE (DVT/PE) were not predictive. Rosen et al²⁹, however did report poor overall survival in cancer patients with a supra-inguinal thrombus at the time of diagnosis²⁹. Age and the presence of bleeding as an indication for filter placement were found to be significant predictors of 1-year mortality by Wallace et al.³² Though ambulatory status was a significant predictor of better survival in stage 4 cancer in one study³⁰, others did not find a similar association between performance status and survival at one year²³. In hospital mortality rates following filter placement ranged from 10%-33%^{19, 24, 28, 29, 31} with the mean length of hospitalization ranging from 1-193 days^{27, 31}. The cause of death leading to mortality before discharge was the underlying malignancy and multisystem organ failure in 59 patients, fatal PE in 6, sepsis in 3 and procedure related complications in 2 (fatal ventricular arrhythmia and acute IVCT).

Patients requiring IVC filtration in these studies appear to have poor overall survival, likely because most of the patients had metastatic disease at the time of filter placement. The best median survival noted in this population was 6 months. It appears that most of the in-hospital mortality in these patients was directly related to their underlying malignancy. In patients with such advanced disease, insertion of an IVC filter does not improve significantly the life expectancy.

Anticoagulation versus IVC filter in cancer

Outcomes in cancer patients receiving anticoagulation have been compared to those receiving IVC filtration in five of the 14 studies listed (Table 3). Four studies examined thrombohemorrhagic outcomes as well as survival^{24, 26, 30, 34} while one focused on survival alone²³ (Table 3). No significant differences were noted between the two modalities with respect to age, gender or tumor type. Most patients in the AC group received initial treatment with LMWH or UFH followed by LMWH or warfarin for an average duration of 3 months. A heparin bolus was administered at the initiation of AC in 2 studies only^{24, 34}. Patients were anticoagulated to a PTT and PT of 1.5-2 times normal in all the studies. Over a follow up of 8 months to 13 months, 4.3%-20% of patients on AC developed DVT and 1-10% developed PE of which 1 was fatal. During a similar follow up duration, DVT was noted in 10%-18.2% of patients in the IVC filter group and 0-5.5% of them suffered PE of which none were fatal. While no bleeding events were seen in the IVC filter group, the rate of all bleeding complications in the AC group ranged from 6.25-35%. Major bleeding occurred in 16 patients (16/ 192, 8%). Bleeding was fatal in 3 patients (3/192, 1.5%). IVC filters were ultimately placed in 23%-35% of patients who underwent initial treatment with AC alone. The median survival in the filter only group ranged from 3 to 6 months while that in the AC group was 3.5 to 13 months.

These studies did not find a statistically significant difference in the median survival, 30-day mortality and 1-year mortality in the treatment groups, after accounting for cancer stage. Only an abstract was available for the one study²³ that noted a significant difference in the survival between the two groups and it did not account for the stages of malignancy. The wide range of median survival can be accounted for mainly by the proportion of patients with stage 3 and 4 of malignancies in various studies.

This is reflected in the lower overall median survival reported by Inhat et al²⁶. and Shunn et al³⁰ who had 70% - 100% patients with stage 3 and 4 cancers in both treatment groups.

Table 3: Clinical outcomes and survival in cancer patients treated with Anticoagulation versus IVC filters

Study	N	N- AC only	N- IVC filter only	Surviva l- AC only (mos.)	Surviva l- IVC filter only (mos)	P value	DVT/P E-AC only (%)	DVT/P E-IVC filter (%)	Bleedin g- AC only (%)	Bleedin g-IVC filter (%)
Barginear et al.	206	58	73	13	2	<0.0002	NR	NR	NR	NR
Inhat et al.	166	138*	60	7	6	NS	4.3/1	10/3.3	13	0
Schunn et al	71	16	55**	3.5	3	NS	6.25/6.25	18.2/5.5	6.25	0
Cohen et al ³⁴	29	11	18	NR	NR	NR	NR/9	NR/0	27	0
Calligaro et al.	30	20** *	20	NR	NR	NR	20/10	15/0	35	0

N: number of cancer patients, AC: Anticoagulation; IVC: Inferior vena cava filter, NR: Not reported, NS: Not significant. * 28 of these needed an IVC filter. **Of 55 patients receiving IVC filters only 16 were matched to the control. ***10 later got IVC filters

Similarly, no significant differences were noted in the rates of VTE associated with the 2 different modalities. However, the mean duration of anticoagulation indicates that patients treated in these studies receive inadequate course of anticoagulation by conventional standards which dictate that cancer patients receive long-term anticoagulation for as long as their malignancy is present and under therapy^{1, 49, 50}. In regards to bleeding complications, Calligaro et al.²⁴ and Cohen et al.³⁴ found bleeding to be significantly higher in patients treated with AC. Previous studies of AC in malignancy have reported a 12%-50% rate of all bleeding⁵¹⁻⁵³. A large proportion of these hemorrhagic complications occurred in the presence of supratherapeutic INRs. An attempt was made to strictly monitor INR in the studies mentioned in Table 3, with only 4 bleeding episodes accounted for by a high INR.

The particularly high rate of bleeding observed by Calligaro et al.²⁴ and Cohen et al.³⁴ could in part be explained by the use of heparin bolus as a part of initial treatment in these two studies. If we omit cases of major bleeding noted in these 2 studies, the overall rate of major bleeding with AC would be 3% (6/192). Of note, it is unlikely that these complications had any effect on overall survival given that none of the thromboembolic complications and only 0-5% of bleeding events proved fatal in these studies. The influence of anticoagulant or primary tumor type on overall survival could not be assessed because of the small proportion of subjects in each of these groups.

Combining anticoagulation and IVC filtration in patients with cancer

Since cancer patients are at higher risk for recurrent thromboembolism than patients without cancer¹¹, they are more likely than patients without cancer to be treated with IVC filters and AC. Therefore, it would be useful to determine the utility of combined modality anti-thrombotic therapy with filters and AC in cancer patients. In the landmark PREPIC study by Decousus et al.⁵⁴ addition of IVC filters to at least 3 months of anticoagulation was associated with a significant reduction of symptomatic and asymptomatic PE at 12 days (hazard ratio 0.22; 95% Confidence Interval (CI) 0.05 to 0.90) and symptomatic PE at 8 years (HR 0.37; 95%CI 0.17 to 0.79) although DVT was more common in the filter group (HR 1.52; 95%CI 1.02 to 2.27) and there was no impact on mortality (HR 0.97; 95%CI 0.74 to 1.28). In this trial, 32% of the patients who received filters had cancer and were randomly assigned to getting a combination of AC and filters or AC only. Hence data specific to this subgroup was not provided^{54, 55}. It would be of interest to know whether combining the two modalities added any benefit in cancer patients with VTE.

Few if any observational studies have looked into combining IVC filters and AC in cancer patients with VTE. In a retrospective case-control study Billet et al.⁵⁶ compared outcomes in 251 patients who received IVC filters in addition to AC (AC-filter) to 1377 patients on anticoagulation only (AC only). More than 50% of their study population received therapeutic anticoagulation (INR of at least 2) in both the groups for at least one year. Cancer was present in 30.7% and 26.7% of the subjects in the AC-filter and the AC only groups, respectively. Indications for filter placement in addition to therapeutic anticoagulation were massive PE, or recurrent VTE on adequate AC, or poor prognosis. No difference in the rates of recurrent PE at 90 days (HR 1.02, P = 0.95) and 5 years (HR 0.96, P = 0.88) was found in the 2 groups. They noted a non significant trend towards an increase in DVTs in the AC-filter group for the total cohort (41.4% AC-filter vs. 36.2% AC-Only. P = 0.12). Interestingly overall mortality was higher in the filter group, but the difference was no longer evident when adjusted for cancer, age and albumin levels (< 3.5g/dl). Indeed, when adjusted for albumin they saw no difference in the rate of recurrent VTE even in cancer patients assigned to the two groups. They concluded that IVC filters do not offer additional benefit to any population of patients who can tolerate AC.

In their case control study on patients with advanced cancer and VTE, Shunn et al³⁰ did not find any significant difference in the rates of recurrent VTE between 22 patients who received AC with IVC filtration and 33 patients who received IVC filters only. Additionally, Greenfield et al.²⁵ noted that of the 37% of cancer patients in their series who received AC with IVC filters, 15% developed bleeding or thrombocytopenia warranting discontinuation of AC. Unfortunately, no other series report outcomes with combined treatment modalities in patients with cancer and ethically designed RCTs to address this clinical question are unlikely to be done, mainly because the most common indication for IVC filter placement in a cancer population is the presence of contraindications to AC.

Indications for placement of IVC filters in cancer patients

Some authors have suggested that presence of cancer alone was an indication for primary filter placement for treatment and prevention of VTE^{24, 33, 34, 53}. This recommendation was based on the high rates of bleeding complications observed in cancer patients in these studies. However, these studies were all conducted in the era before widespread use of the INR in anticoagulation monitoring and therefore were likely due to suboptimal AC monitoring. More recent observational studies and randomized controlled trials of VTE therapy have demonstrated that anticoagulation can be safely prescribed in the vast majority of cancer patients^{11, 57}. Consequently, the NCCN and ASCO guidelines both recommend anticoagulation, preferably with a low molecular weight heparin, as the treatment of choice for VTE in cancer. Insertion of an IVC filter in cancer patients is only recommended for patients with contraindications to anticoagulation or failure of adequate long term AC^{1, 50}.

Even after 3 decades of being in use, guidelines for IVC filtration are still evolving and 46%-65% filters are now being inserted for broader or relative indications¹². On review of indications that were used to place vena cava filters in the 2250 patients with malignancy we found that 47%-93% of patients received filters secondary to presence of contraindications to anticoagulation. In 10%-35% of patients these were relative contraindications or situations where filters were inserted prophylactically (table 4). In another 6%-38% of instances, filters were placed due the presence of central nervous system (CNS) malignancies (primary and/or metastatic). The histological type of CNS malignancies was not described in most studies. Complications from anticoagulation accounted for 9.6%-55% of filter placements in various series of which the major contributor was hemorrhage.

Heparin induced thrombocytopenia (HIT) was cited as an indication for filter placement in 4-15% of cases in 3 series. Failure of anticoagulation due to recurrent DVT /PE served as an indication for filter placement in 4%-25% of cases. (Figure 3)

Contraindications to AC account for the majority of filter placements in these studies. However, a considerable proportion of filters in cancer are placed for “broader indications” and relative contraindications to anticoagulation. A particularly high number of these are placed in patients with CNS malignancies (both primary and metastatic), which per our review are better characterized as a relative contraindication to AC (except in cases of highly vascular metastasis from melanoma, renal cell cancer or choriocarcinoma). In the absence of definite clinical evidence for benefit of IVC filtration when used for such relative indications, and on any survival benefit of their use in advanced malignancy; oncologists must keep a high threshold for their use in patients with advanced malignancy and VTE who do not have absolute indications for filter placement.

Table 4: Indications for IVC filter placement identified in this review

1. Contraindications to anticoagulation

Absolute

- Active bleeding
- High risk for bleeding (e.g., recent CNS hemorrhage or trauma, recent large stroke, high bleeding risk CNS tumors-melanoma, renal cell cancer, thyroid cancers, choriocarcinoma)—

Relative

- Cerebral tumors and metastasis other than the above
- Perioperative management of VTE
- Pericardial tumors
- Significant thrombocytopenia (< 50,000/ μ L) not amenable to transfusional support

2. Complications on anticoagulation

- Overt gastrointestinal bleeding or life threatening bleeding on AC like:
Retroperitoneal hemorrhage, massive hemoptysis, hemothorax, intracranial bleed, pericardial tamponade

3. Failure of adequate anticoagulation:

- Recurrent VTE despite adequate anticoagulation

4. Inability to undergo anticoagulation.

- Poor compliance, risk of falls.

5. Relative indications for filter placement (Broader indications)

- Pre or post pulmonary embolectomy
- Extensive free-floating ilio-femoral thrombi
- Prevention of PE in patients with chronic obstructive pulmonary disease and DVT
- Prevention of PE in patients with minimal cardiopulmonary reserve and DVT
- Substantial PE burden
- Peptic ulcer disease

IVC filters in the presence of CNS tumors

Though we did not perform a systematic review of literature on outcomes with IVC filtration in CNS tumors, a review on IVC filtration in malignancy would not be complete without addressing this area of controversy. Considerable amount of literature has been devoted to studying outcomes with IVC filtration in this patient population as VTE has a particularly high incidence in the presence of brain tumors (up to 60%)^{58, 59}. Moreover, CNS malignancies have long been regarded as an absolute contraindication to AC based on the concern for the life threatening complication of Intracranial hemorrhage (ICH) which can lead to mortality rates as high as 45%^{60, 61}.

Particularly notorious in this regard is the presence of CNS lymphoma^{58, 59, 62}. Management is further complicated by their poor functional status, requirement for neurosurgical interventions, and an inherent tendency of some of these tumors to undergo spontaneous hemorrhage.

Despite the concerns for increased risk of bleeding with AC several retrospective studies have failed to find an increase in the rate of clinically significant ICH in patients who have received therapeutic anticoagulation^{10, 18, 20}. On the other hand, markedly high rates of recurrent VTE (up to 62%) have been reported after placement of IVC filters in these subjects¹⁰. Nevertheless, no prospective trials have been done in this field and no existing studies have assessed these outcomes in case of CNS metastasis from melanomas, renal cell cancer, germ cell tumors or thyroid cancer^{20, 63, 64}; all these being primaries that are highly likely to bleed. Until further clinical evidence, the ASCO guidelines recommend that in the absence of radiographic evidence of ICH or other absolute contraindications to AC all patients with primary brain tumors and VTE should be considered as candidates for AC. AC should be avoided in the presence of intracranial tumors that are highly liable to bleed (Melanomas, renal cell cancer, germ cell tumors and thyroid cancers^{63, 65, 66}). In these cases placement of an IVC filter may be appropriate depending on the overall prognosis of the patient. Neither modality of treatment has been shown to have a survival benefit in these patients.

Fig. 3 Indications for IVC filter insertion in cancer patients.
AC anticoagulation

Retrievable filters: Do they solve the dilemma?

Retrievable filters (RFs) are a new generation of IVC filters that have been available in the US since 1990 and can either be left in place as permanent filters or removed after they are no longer deemed necessary. Based on the results of the PREPIC trial⁵⁴ and the concern for long term complications associated with permanent filters, Retrievable filters seem to be an attractive alternative for patients with temporary contraindications to AC. Moreover, unlike Temporary filters they are not connected to the skin via a tethering catheter and do not pose a risk of infections.

The Amplatz filter was the first RF on market but was withdrawn secondary to high rates of caval occlusions^{67, 68}. The first generation RFs: Günther Tulip (GTF) (Cook Inc. Bloomington IN), Recovery Nitinol filter (RNF) (C.R. Bard, Inc. Tempe AZ) and the OptEase filter (OEF) (had been in use over a decade, though the second generation of RFs; (the ALN and the C-lect filters) are becoming increasingly popular now. These filters are made of a single body of metal instead of multiple struts molded together to reduce the incidence of migration⁶⁹. Like the permanent filters they are inserted percutaneously via the internal jugular or femoral approach. After a certain period in situ, their edges get embedded into the IVC walls and thereafter they can be left as permanent filters. Various studies report attempted retrieval of 48%⁷⁰ to 100%⁷¹ of RFs, with successful removal of 78%⁷²-100%⁷¹ of them. Prior to retrieval, patients undergo cavography to identify any significant tilts or thrombi that could contraindicate removal and are placed on AC⁷⁰. In the absence of contraindications (as listed in table 5), retrieval is usually a safe procedure. Patients who have an ongoing risk for VTE need to be placed on AC post removal⁷⁰.

Table 5: Relative contraindications to removal of Retrievable filters

Filter tilt > 15 degrees with respect to the caval axis
Ongoing risk of VTE in the presence of contraindications to anticoagulation
Large trapped thrombi (occupying > 40% of the filter diameter)
Limited life expectancy
Poor cardiopulmonary reserve

Several questions still remain unanswered. There is no consensus on the average implantation time (time in situ), after which RFs can be removed safely. Though several observational studies have noted safe removal after implantation times ranging from 9⁷³-475⁷⁴ days, most manufacturers recommend a maximum implantation time of 10-14 days⁷⁵.

Besides, there are no set guidelines regarding the retrieval of filters with trapped emboli which may be present in 3%-50% of RFs at the time of retrieval. Moreover long term prospective studies on complications associated with RFs left as permanent filters are lacking. Similarly, there are no RCTs comparing outcomes on RFs with those on permanent filters and current data suggesting no statistically significant difference in their efficacies are based on observational studies⁷⁶. A comprehensive set of guidelines for the use of optional filters was set forth by Dvovich et al. in 2006⁷⁷.

Some advocate advanced malignancy as an indication for use of RFs. However, in our review we did not find any strong evidence to support or refute this notion. Per our review, in cancer patients, just like in the noncancerous population, retrievable filters seem to be an attractive option for temporary indications, as elucidated by Keeling et al.⁷⁸ (table 6). Careful patient selection is imperative in such cases as even though the filter is placed for a short period of time one must remember that retrieval requires a brief period of anticoagulation. Besides, in patients with a limited life expectancy from their underlying malignancy, filter removal is a futile procedure.

Table 6: Indications for placement of retrievable filters

Temporary contraindications to anticoagulation in the presence of temporary risk for VTE
Recent or near term surgery with DVT
Spinal/Brain surgery with prolonged period of immobility
Prophylaxis for high risk trauma patients
Thrombolysis for ilio-caval thrombus
Venous reconstructions
Pregnancy
Prophylaxis in high risk major orthopedic surgery
Prophylaxis for major surgery with significant risk of VTE: bariatric surgery, hypercoagulable states, remote h/o DVT/PE

Conclusions

Management of cancer associated VTE is a complex clinical situation that oncologists face frequently. Over the last two decades a significant proportion of this population underwent IVC filter insertions following VTE due mostly to presence of contraindications to AC. Evidence in this regard exists in the form of nonrandomized observational studies with patients having a wide range of primary tumors in different stages at the time of index VTE, unknown comorbidities affecting outcomes of interest in most series, short durations of follow up and varying intensity of surveillance. Preliminary data from these suggest the following:

1. AC remains the mainstay of primary and secondary prophylaxis for VTE in patients with cancer, unless absolutely contraindicated.
2. Presence of a CNS tumor is not an absolute contraindication to anticoagulation other than for metastasis from Melanomas, renal cell cancer, germ cell tumors and thyroid cancers.
3. In patients with absolute contraindications to anticoagulation, IVC filters should be considered for secondary prophylaxis of PE and in selected high risk cases, for primary prophylaxis of PE.

4. The presence of an underlying malignancy does not alter the efficacy of IVC filters in secondary prevention of PE, with no additional complications other than those known for filters in mixed patient populations.
5. Cancer patients who end up getting IVC filters for secondary prophylaxis of PE have a short life expectancy (2-10 months) likely reflecting the advanced nature of their disease at the time of index VTE. This in turn goes with the previous reports of VTE being a poor prognostic factor in the presence of cancers.
6. In ambulatory patients with advanced malignancy at the time of index VTE, long term complications with IVC filtration like, DVT and PPS are less likely because of their short life expectancies.
7. A combination of AC and IVC filters is no more efficacious than either modality alone.

Prospective studies are needed to further address the adequate management of cancer associated VTE.

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