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2008 SOR guidelines for the treatment of venous thromboembolism in patients with cancer: Report from the working group☆

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☆ SOR: Standards, Options: Recommendations.

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Abstract

Venous thromboembolism (VTE) is a major therapeutic issue in cancer patients. Advances in this field and heterogeneities in clinical practices prompted us to establish guidelines in the management of VTE in cancer patients according to the SOR (Standards, Options and Recommendations) methodology. A literature review of the studies published on this topic between 1999 and 2007 was performed. The guidelines were developed from the analysis of 38 out of 418 publications selected. They were peer-reviewed by 65 independent experts. The treatment of VTE in patients with cancer, including those with intracranial malignancies, should be based on low-molecular-weight heparins administered at therapeutic doses for at least 3 months. In the event of recurrent VTE, pulmonary embolism with hemodynamic failure or contra-indication to anticoagulant treatment, the indications and usages of vena cava filters and thrombolytic drugs should be the same as in non-cancer patients.

Keywords: Cancer; Clinical practice guidelines; Low-molecular-weight heparins; Thrombolytics; Unfractionated heparin; Vena cava filters; Venous thromboembolism; Vitamin K antagonists

1. Introduction

Cancer is a major risk factor for the occurrence of venous thromboembolism (VTE) [1,2]. Although VTE, defined as deep-vein thrombosis (DVT) or pulmonary embolism (PE), is a preventable disease, it is reported in 15 to 20% of patients with cancer [3]. Its incidence is 4–6-fold higher in patients with cancer than in those without this disease [2]. The risk of VTE is influenced by the characteristics of the underlying neoplasm (histological type, stage and site of cancer) [4]: for example, the risk is especially high in patients with mucinous adenocarcinoma of the digestive tract, pancreatic cancer, lung cancer, ovarian cancer, acute promyelocytic leukemia, or myeloproliferative disorders [3,5,6]. Furthermore, the likelihood of VTE recurrence increases in patients with active cancer or receiving antineoplastic treatments [2,7,8]. Importantly, VTE is responsible for the death of one out of seven hospitalized cancer patients [3]. It is also an independent risk factor for death in cancer patients [9].

In patients treated for VTE, cancer increases both the risk of treatment failure and the risk of a severe hemorrhagic event. Therefore, the treatment of VTE in these patients represents a major therapeutic issue in routine practice. The therapeutic principles applied in France up to 2007 were derived mainly from the North American recommendations [10] and from the official recommendations published by the Italian Association of Medical Oncology [11]. In view of recent major therapeutic advances, the wide heterogeneity in clinical practices, as well as the lack of national recommendations in cancer patients with VTE, a multidisciplinary working group was set up to develop national guidelines for this setting according to the well-standardized procedure of the SOR (Standards, Options and Recommendations) methodology. The SOR program encompasses the progressive development of clinical practice guidelines for the standardization of 'good clinical practice' throughout the various disciplines involved in cancer care [12]. Initiated in 1993, it uses a methodology based on a literature review and a critical appraisal performed by a multidisciplinary working group of experts [13]. It has been led by the French National Cancer Institute since May 2008. The details of this program and the complete presentation of the current guidelines are available on the SOR website [14].

2. Methods

2.1. Literature review and analysis

A literature review of all the studies published between January 1999 and January 2007 was performed using the MEDLINE database and the following subject headings: cancer, venous thromboembolism, and anticoagulant drugs. A prospective follow-up of the literature on this subject was continued up to January 2008. National guidelines and several sites of Evidence-Based Medicine were also consulted. The literature search was limited to publications in English or in French.

Meta-analyses, systematic reviews, randomized clinical trials, or non-randomized prospective or retrospective studies in the absence of randomized clinical trials, were included in the analysis. Editorials, letters to the editor, case reports, publications without an abstract, press releases and animal studies were excluded.

The studies taken into account concerned the therapeutic management of confirmed VTE in patients with cancer (excluding catheter-associated thrombosis). In the absence of specific studies on patients with cancer, we also analyzed

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studies performed in the general population of VTE patients that also included a subgroup analysis of patients with cancer. Studies in patients with catheter-related thrombosis, tumor-associated thrombosis, or a history of cancer in remission for more than 5 years were not analyzed. Studies on the prevention of VTE were also excluded.

The main study outcomes were rates of VTE recurrence, major bleeding, thrombocytopenia, and death. Major bleeding was defined as fatal bleeding, bleeding into a critical organ, or clinically overt bleeding associated with a decrease in hemoglobin level of more than 2 g/dL or leading to the transfusion of two or more units of blood [15].

2.2. Critical appraisal and data extraction

The quality of the studies was evaluated by means of a validated reading grid assessing their methods and clinical relevance [16]. Two reviewers (DKC, LB) extracted the data in a double-blind manner. Any discrepancies between reviewers were resolved by consensus.

2.3. Consensus development

Following the selection and critical appraisal of the articles, a first version of the guidelines was established, based on the conclusions and corresponding levels of evidence derived from analysis of the selected studies. The level of evidence depended not only on the type and quality of the studies reviewed, but also on the consistency of the data (Table 1). In the absence of any clear scientific evidence, judgment was based on the professional experience and consensus of the expert group ('expert agreement'). In these guidelines, the recommendations were classified as Standards or Options (Table 2). The document was then peer-reviewed in November 2007 by 65 independent experts encompassing all the medical and surgical specialties involved in the management of patients with cancer (including oncologists (33%), anesthesiologists and surgeons (9%), and hematologists (5%)), according to the AGREE grid [13], and their comments were integrated in the final version in February 2008.

Table 1
Definitions of level of evidence.

Level	Definition
Level A	Based on one or several high-quality meta-analyses or on several high quality randomized clinical trials with consistent results
Level B	Based on good quality evidence from randomized trials (B1) or prospective or retrospective studies (B2), with consistent results when considered together
Level C	Based on studies that are weak, with inconsistent results when considered together
Level D	Absence of any scientific data or only a series of cases available

Table 2
Classification of recommendations.

Recommendations	Definition
Standards	Procedures or treatments considered to be the "gold standard" by unanimous decision of the experts
Options	Procedures or treatments acknowledged to be appropriate by the experts One of the options may be preferred by the experts

3. Results

3.1. Results of the search

Overall, 38 out of 418 references concerning the treatment of VTE (excluding catheter-associated thrombosis) in patients with cancer were identified and used for establishing these guidelines [17–54]. We also identified one consensus guideline not specific to cancer patients [10], and four consensus guidelines specific to cancer patients [11,55–57].

3.2. Short-term unfractionated heparin (UFH) followed by vitamin K antagonists (VKA)

No randomized study specifically studied the benefit-risk ratio of short-term UFH followed by VKA in the treatment of VTE in patients with cancer. We identified three retrospective cohort studies on this topic [17–19], together including about 100 patients with cancer (Table 3). In these studies, the rates of recurrent VTE and major bleeding were high, varying on average from 25% to 30% and 15% to 30%, respectively (*Level of evidence: C*). In one of these studies, there was a high rate of VKA overdose (67%), underlining the need for close laboratory monitoring in patients treated with these drugs [18].

We also analyzed the data obtained in the control group of a randomized study comparing short-term UFH + VKA with long-term low-molecular-weight heparins (LMWH) [20]. The respective rates of VTE recurrence and major bleeding at 3 months in patients treated with short-term UFH + VKA were 10% and 7% (*Level of evidence: B2*). In this study, the rate of bleeding was positively related to the bleeding risk defined at randomization, 2.1% in low-risk patients and 11.5% in high-risk patients.

3.3. Short-term LMWH followed by VKA

No randomized study or meta-analysis specifically studied the benefit-risk ratio of short-term LMWH followed by VKA in the treatment of VTE in patients with cancer.

We identified eight meta-analyses [21–28] comparing short-term LMWH *versus* short-term UFH in the initial treatment of VTE, both drugs being continued with VKA (Table 4). The percentage of patients with cancer (when specified) varied between 5% and 22%. In the general population

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Table 3
Curative treatment of venous thromboembolism: short-term UFH followed by VKA.

Reference	Type of study (study date)	Type of patients	No. of patients	Treatment	Follow-up	VTE recurrence	Safety	Death
Calligaro et al. [17]	Retrospective cohort (1987–1989)	Stage III/IV cancer and proximal DVT and/or PE	23	UFH (continuous iv infusion) for ≥5 days followed by VKA for 3 months	10 (1–42) months	30%	Major bleeding: 30% (1 fatal) Thrombocytopenia: 13%	10% during hospitalization
Chan and Woodruff [18]	Retrospective cohort (1986–1989)	Cancer and DVT	31	UFH alone ($n=6$) UFH followed by VKA ($n=23$) VKA alone ($n=2$)	Not specified	13% (2 pts with UFH and 4 with VKA)	Major bleeding: 35% Minor bleeding: 21%	42% at 3 months
Debourdeau et al. [19]	Multicenter retrospective cohort (1991–1993)	Active cancer or cancer in remission with adjuvant therapy and DVT or PE treated with anticoagulant for at least 3 months	71	UFH (continuous iv infusion or sc, 3×/day) followed by VKA Thrombolysis before UFH in 11 pts, followed by vena cava filter placement in 5 pts	185 ± 25 days	24% (7 pts with UFH, 8 with VKA and 2 during transition from UFH to VKA)	Major bleeding: 12% (9 pts with UFH and 1 with VKA)	33% at the end of follow-up
Hull et al. [20]	Multicenter randomized, open-label clinical trial (LITE) (1994–2003)	Cancer and proximal DVT	100 (corresponding to the control group of the LITE study)	UFH (continuous iv infusion) followed by VKA initiated between days 1 and 6	12 months	10% at 3 months 16% at 12 months	Total bleeding: 24% Major bleeding: 7% at 3 months	19% at 3 months 47% at 12 months

DVT: deep-vein thrombosis; iv: intravenous; PE: pulmonary embolism; pts: patients; sc: subcutaneous; UFH: unfractionated heparin; VKA: vitamin K antagonists.

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Table 4
Curative treatment of venous thromboembolism: short-term LMWH *versus* short-term UFH (meta-analyses).

Reference	Number of studies analyzed (period of study selection)	Patients (% of cancer patients)	VTE recurrence (LMWH *versus* UFH)	Major bleeding (LMWH *versus* UFH)	Death (LMWH *versus* UFH)
Lensing et al. [21]	10 studies (1984–1994)	1512 (12%)	RR [95% CI] = 53% [18–73], $p < 0.01$	RR [95% CI] = 68% [31–85], $p < 0.05$	RR [95% CI] = 64% [24–83], $p < 0.01$
Siragusa et al. [22]	13 studies (1980–1994)	1723 (9%)	RR [95% CI] = 0.39 [0.30–0.80], $p = 0.006$	RR [95% CI] = 0.42 [0.20–0.90], $p = 0.01$	RR [95% CI] = 0.51 [0.20–0.90], $p = 0.01$. In the subgroup of cancer pts: RR [95% CI] = 0.33 [0.20–0.90], $p = 0.01$
Hettiarachchi et al. [23]	13 studies (not specified)	4019 (6–23% depending on the studies) Of note, the majority of studies excluded pts with PE	OR [95% CI] = 0.77 [0.56–1.04], p = NS[a]	OR [95% CI] = 0.60 [0.38–0.95], $p < 0.05$[a]	OR [95% CI] = 0.72 [0.55–0.96], $p < 0.05$[a]
Gould et al. [24]	11 studies (1985–1997)	3674 (5–22% depending on the studies)	RR [95% CI] = 0.85 [0.63–1.14], p = NS	RR [95% CI] = 0.57 [0.33–0.99], $p < 0.05$	OR [95% CI] = 0.71 [0.53–0.94], $p < 0.05$. In the subgroup of cancer pts: OR [95% CI] = 0.57 [0.31–1.03], p = NS
Dolovichet al. [25]	13 studies (1975–1996)	4447 (cancer pts not specified)	RR [95% CI] = 0.85 [0.65–1.12], p = NS	RR [95% CI] = 0.63 [0.37–1.05], p = NS	RR [95% CI] = 0.76 [0.59–0.98], $p = 0.03$
Rocha et al. [26]	21 studies (1985–1999)	4472 (cancer pts not specified)	OR [95% CI] = 0.78 [0.59–1.04], p = NS	OR [95% CI] = 0.65 [0.46–0.98], $p = 0.047$	OR [95% CI] = 0.68 [0.50–0.91], $p = 0.012$
Quinlan et al. [27]	12 studies (1966–2003)	1951 (pts with non-massive PE/cancer pts not specified)	OR [95% CI] = 0.68 [0.42–1.09], p = NS	OR [95% CI] = 0.67 [0.15–1.88], p = NS	–
Mismetti et al. [28]	3 studies (1980–2004)	1503 (pts with DVT ± PE; enoxaparin *versus* UFH)	RR [95% CI] = 0.81 [0.52–1.26], p = NS[b]	–	–

DVT: deep-vein thrombosis; LMWH: low-molecular-weight heparins; NS: not significant; sc: subcutaneous; OR: odds reduction; RR: risk reduction or relative risk; UFH: unfractionated heparin; VKA: vitamin K antagonists; VTE: venous thromboembolism.

[a] The proportion of cancer pts had no influence on the estimated treatment effects of LMWH.
[b] The results were not modified by the presence of symptomatic PE.

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Table 5
Curative treatment of venous thromboembolism: short-term LMWH followed by VKA.

Reference	Type of study (~~study date~~)	Patients (number and characteristics)	Treatment	Follow-up	VTE recurrence	Major bleeding	Additional information
Bona et al. [29]	Prospective cohort (1991–1996)	312 pts with VTE ± cancer (104 with cancer: 82% with solid tumors and 18% with hematologic malignancies)	VKA (INR: 2–3)	Not specified	With cancer: 1.5%/month Without cancer: 0.3%/month ($p = 0.02$)	With cancer: 0.4%/month Without cancer: 0.2%/month (p = NS)	INR between 2 and 3: With cancer: 47.5%. Without cancer: 56% $p = 0.01$
Palareti et al. [30]	Prospective cohort (1993–1994)	828 pts with VTE ± cancer (95 with cancer: 80% with solid tumors and 15% with hematologic malignancies)	VKA	From inclusion up to August 31, 1996	With cancer: 6.8% Without cancer: 2.7% ($p = 0.059$)	With cancer: 5.4% Without cancer: 0.9% ($p = 0.002$)	Minor bleeding: With cancer: 16.2%. Without cancer: 3.6% $p < 0.001$
Prandoni et al. [31]	Prospective cohort (1986–1997)	842 pts with VTE ± cancer (181 with cancer: 59% with stage III/IV cancer)	UFH, LMWH or thrombolytics followed by VKA (INR: 2–3) for at least 3 months	3–12 months	With cancer: 16.5% Without cancer: 4.9% ($p < 0.05$)	With cancer: 9.4% Without cancer: 3.4% ($p < 0.05$)	Recurrence of VTE and major bleeding positively related to cancer stage
Vucic et al. [32]	Prospective cohort (2000–2001)	31 pts with DVT + cancer (58% with solid tumors and 42% with hematologic malignancies)	Heparin (iv or sc) followed by VKA (initiated between days 5 and 10) for at least 6 months	6 months	PE: 2 pts (1 fatal)	3 pts (11%)	Death at 6 months: 5 pts (1 fatal PE)
CANTHANOX Meyer et al. [33]	Multicenter randomized, open-label clinical trial (1995–1999)	75 pts with DVT or PE + cancer (control group, 52% with metastatic cancer and 9% with hematologic malignancies)	Enoxaparin (1.5 mg/kg 1×/day, sc) followed by VKA (INR: 2–3) for 3 months	3 months	6%	16% [95% CI: 8.6–26.3]	Fatal bleeding: 8% [95% CI: 3.0–16.6]
CLOT Lee et al. [34]	Multicenter randomized, open-label clinical trial (1999–2001)	338 pts with DVT or PE + cancer (control group, 75% with metastatic cancer and 9% with hematologic malignancies)	Dalteparin (200 IU/kg 1×/day, sc) for 5–7 days followed by VKA	6 months	16.9%	4%	Any bleeding: 19%
ONCENOX Deitcher et al. [35]	Multicenter randomized, open-label clinical trial (2001–2002)	34 pts with DVT or PE + cancer (control group, 53% with metastatic cancer)	Enoxaparin (1 mg/kg 2×/day, sc) for at least 5 days followed by VKA (initiated on day 2) for 6 months	6 months	6.7%	2.9%	Any bleeding: 53%

CI: confidence interval; DVT: deep-vein thrombosis; INR: international normalized ratio; iv: intravenous; LMWH: low-molecular-weight heparins; NS: not significant; sc: subcutaneous; UFH: unfractionated heparin; VKA: vitamin K antagonists; VTE: venous thromboembolism.

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Table 6
Curative treatment of venous thromboembolism: long-term LMWH *versus* short-term heparin followed by VKA.

Reference	Type of study ~~(study date)~~	Patients (number and characteristics)	Treatment	Follow-up	VTE recurrence	Major bleeding	Additional information
CANTHANOX Meyer et al. [33]	Multicenter randomized, open-label clinical trial (1995–1999)	146 with DVT or PE + cancer (53% with metastatic cancer and 11% with hematologic malignancies)	A: Enoxaparin (sc, 1.5 mg/kg 1×/day) followed by VKA (INR: 2–3) for 3 months B: Enoxaparin (sc, 1.5 mg/kg 1×/day) for 3 months	3 months	A: 6%. B: 3% (p = NS)	A: 16% [95% CI: 8.6–26.3]. B: 7% [95% CI: 2.3–15.7] (p = NS)	Fatal bleeding: A: 8% [95% CI: 3.0–16.6]. B: 0% [95% CI: 0–5.1] (p = 0.03) Death at 6 months: A: 22.7% [95% CI: 13.8–33.8]. B: 11.3% [95% CI: 5.0–21.0] (p = NS)
CLOT Lee et al. [34]	Multicenter randomized, open-label clinical trial (1999–2001)	676 with DVT or PE + cancer (67% with metastatic cancer and 10% with hematologic malignancies)	A: Dalteparin (sc, 200 IU/kg 1×/day) for 5–7 days followed by VKA B: Dalteparin (sc, 200 IU/kg 1×/day for 1 month followed by 150 IU/kg 1×/day for 5 months)	6 months	A: 16.9%. B: 8% HR [95% CI] = 0.48 [0.30–0.77] (p = 0.002)	Low bleeding risk: A: 4%. B: 6% (p = NS) High bleeding risk: A: 19%. B: 14% (p = NS)	Death at 6 months: A: 41%. B: 39% (p = NS)
ONCENOX Deitcher et al. [35]	Multicenter randomized, open-label clinical trial (2001–2002)	102 with DVT or PE + cancer (58% with metastatic cancer)	A: Enoxaparin (sc) 1 mg/kg 2×/day for at least 5 days followed by VKA for 6 months B: Enoxaparin (sc) 1 mg/kg 2×/day for 5 days followed by 1 mg/kg 1×/day for 175 days C: Enoxaparin (sc) 1 mg/kg 2×/day for 5 days followed by 1.5 mg/kg 1×/day for 175 days	6 months	A: 6.7%. B: 3.4%. C: 3.1% A *versus* B + C: p = NS	A: 2.9%. B: 6.5%. C: 4.0% A *versus* B + C: p = NS	Serious adverse events: A: 50%. B: 51.6%. C: 63.9% A *versus* B + C: p = NS
LITE Hull et al. [20]	Multicenter randomized, open-label clinical trial (1994–2003)	200 with proximal DVT + cancer (42% with metastatic cancer and 12% with hematologic malignancies)	A: UFH (continuous iv infusion) followed by VKA initiated between Days 1 and 6 B: Tinzaparin (sc, 175 IU/kg 1×/day)	12 months	A: 16%. B: 7% RR = 0.44 (p = 0.044) Absolute difference [95% CI] = −9% [−21.7;−0.7]	Low bleeding risk: A: 2.1%. B: 0% (p = 0.001) High bleeding risk: A: 11.5%. B: 14.5% (p = NS) Any bleeding: A: 24%. B: 27% (p = NS) Absolute difference [95% CI] = 3.0% [−9.1;15.1]	Death at 3 months: A: 19%. B: 20% (p = NS) Absolute difference [95% CI] = 1.0% [−10.2;11.9] Death at 12 months: A: 47%. B: 47% (p = NS) Absolute difference [95% CI] = −0.0% [−14.6;13.2]

CI: confidence interval; DVT: deep-vein thrombosis; HR: hazard ratio; INR: international normalized ratio; iv: intravenous; NS: not significant; PE: pulmonary embolism; RR: risk ratio; sc: subcutaneous; UFH: unfractionated heparin; VKA: vitamin K antagonists; VTE: venous thromboembolism.

of patients with VTE, regardless of the presence or absence of cancer, LMWH were more effective than (in two meta-analyses) or at least as effective as (in six meta-analyses) UFH. In terms of bleeding risk, LMWH were significantly safer than UFH in five meta-analyses. Similar results were reported in the subgroup of patients with cancer, studied in one meta-analysis [23]. A beneficial effect of LMWH *versus* UFH was also observed with regard to the risk of death. This observation was confirmed in a meta-analysis specifically performed in patients with cancer: in 629 cancer patients, the death rate was reduced from 22% with UFH to 15% with LMWH (odds ratio [95% confidence interval] = 0.61 [0.40–0.93]) [58]. Overall, these results favor the use of short-term LMWH relative to short-term UFH in the initial treatment of acute VTE (*Level of evidence: A*). Since these meta-analyses did not show any striking differences in the subgroup of patients with cancer (although it is possible that the benefit of LMWH may be less substantial in these patients), the experts considered that this conclusion may be applied to that population.

We also identified four prospective cohort studies [29–32] on the initial treatment of VTE in patients with cancer (Table 5). Due to differences in study design, the rates of recurrent VTE and major bleeding vary substantially between these studies. However, overall, the results consistently show that, compared with patients without cancer, patients with cancer exhibit a higher risk of recurrent VTE (2–16.9%) and major bleeding (2.7–16%) (*Level of evidence: B2*). The data concerning the impact of cancer stage on the risk of major bleeding are equivocal [30,31]. In contrast, VTE recurrence appears to be positively related to cancer stage [31].

Three randomized studies [33–35] were specifically performed in patients with cancer and used short-term LMWH followed by VKA as one of the treatments compared (Table 5). In these studies, including a total of 447 patients, the rate of recurrent VTE was 6–16.9% and that of major bleeding was 2.9–16% (*Level of evidence: B2*).

Furthermore the experts considered that, in practice, UFH, any LMWH, as well as fondaparinux or danaparoid, approved for the short-term treatment of VTE in the general population of patients with or without cancer, may be used in patients with cancer. With VKA, the target INR (international normalized ratio) should be between 2.0 and 3.0. Nevertheless, owing to drug interactions and frequent variations in the plasma level of inflammatory proteins, INR stability is difficult to achieve and bleeding events are frequent in cancer patients.

3.4. Long-term LMWH versus short-term heparin followed by VKA

We identified four randomized studies [20,33–35] comparing the benefit-risk ratio of long-term LMWH with that of short-term heparin followed by VKA in patients with cancer (Table 6). In three of these studies, the heparin used in the control group was a LMWH, whereas it was UFH in the fourth study. Two trials showed a significant benefit of long-term LMWH in terms of VTE recurrence [20,34]. In all the selected trials, the safety, in terms of bleeding risk, in patients receiving long-term LMWH was at least as good as in those treated with short-term heparin followed by VKA. Of note, in the prematurely stopped CANTHANOX study, enoxaparin was more effective than VKA in terms of time to an event of the primary outcome (composite of major bleeding or recurrent VTE within 3 months) ($p = 0.04$ by the log rank test) [33].

Two meta-analyses were performed on studies comparing long-term LMWH with short-term heparin followed by VKA in the general population of patients with VTE, regardless of the presence or absence of cancer [36,37]. In the first meta-analysis [36], comprising eleven studies, 1115 out of 2907 patients had cancer. In these patients, long-term LMWH significantly reduced recurrent VTE with a relative risk [95% confidence interval] of 0.53 [0.36–0.77] ($p = 0.001$). This result was further confirmed when the LITE study was included [20]. However, no difference in terms of bleeding risk was shown. In the second meta-analysis on seven studies totaling 1379 patients, only one study included cancer patients [37]. In the overall population, the rates of clinical events were comparable in the long-term LMWH group and VKA group, 4.5% *versus* 6.5% for VTE, 0.9% *versus* 2% for major bleeding and 5.9% *versus* 5.3% for death, respectively.

Finally, two small non-randomized studies evaluated the long-term tolerability of LMWH in 28 and 40 inpatients with advanced cancer who were receiving palliative care [38,39]. Long-term LMWH were found to improve the quality of their life and to be more acceptable than VKA. The CLOT study showed that this result was not limited to palliative care patients [59].

In conclusion, these results consistently showed that in cancer patients with VTE, compared with short-term LMWH followed by VKA, long-term LMWH (3–6 months) significantly reduced the risk of VTE recurrence by approximately 50% without increasing the bleeding risk; this treatment had no effect on mortality (*Level of evidence: A*).

In practice, among the various LMWH, only enoxaparin (150 IU/kg once daily), dalteparin (200 IU/kg once daily for 1 month followed by 150 IU/kg once daily) and tinzaparin (175 IU/kg once daily) have been shown to be beneficial, and therefore may be used, in this setting. The optimal duration of treatment remains uncertain. The CLOT trial showed the value of a 3–6-month treatment [34]. In the absence of data and guidelines concerning pursuance of this treatment beyond 6 months, we recommend continuation of the anticoagulant treatment as long as the cancer is active or is treated with chemotherapy or hormonal therapy. The choice between LMWH and VKA depends on their benefit-risk ratio (influenced by drug interactions, chemotherapy, invasive procedures, and general health status) and acceptability.

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Table 7
Curative treatment of venous thromboembolism: vena cava filters.

Reference	Type of study (~~study date~~)	Patients (number and characteristics)	Treatment	Follow-up	Thrombotic events	Adverse events	Death/Survival
Cohen et al. [41]	Retrospective cohort (1 center) (1986–1989)	29 with DVT and/or PE + cancer (18 with vena cava filter and 11 with anticoagulant drugs)	Vena cava filter (Greenfield) or UFH (continuous iv infusion) for 7 to 10 days followed by VKA	7 months (mean)	VTE: 0% *versus* 9% with UFH + VKA	Bleeding: 0% *versus* 27% with UFH + VKA	Death related to treatment: 0% *versus* 18% with UFH + VKA (p = NS)
Cohen et al. [42]	Retrospective cohort (1 center) (1985–1990)	41 pts with DVT and/or PE and cancer (56% with metastatic cancer)	Vena cava filter (no data on anticoagulant treatment)	6.4 months (mean)	PE: 2.4% (n = 1, fatal PE)	Filter-related complications: 4.8%	–
Hubbard et al. [43]	Retrospective cohort (1 center) (1984–1989)	31 pts with VTE (PE: 32%; inferior vena cava thrombosis: 26%) and advanced cancer	UFH iv, then placement of vena cava filter without any other associated anticogulant drug	31.8 pts-year	PE: 0%. Filter thrombosis: 19%	Bleeding: 0%. Lower-extremity edema: 26%. Need for anticoagulant: 0%. Filter withdrawal: 0%	–
Schwarz et al. [44]	Retrospective cohort (1 center) (1980–1992)	182 with VTE (DVT: 53%; PE: 25%; DVT + PE: 21%) and cancer (83% with stage III–IV cancer; 93% with anticoagulation contra-indicated)	UFH iv (60%), then placement of vena cava filter (no data on associated anticoagulant treatment)	Not specified	PE: 2% (n = 4, 2 being fatal). DVT: 6%	Complications related to filter placement: 3%	Hospital death: 10%. Survival at 1 year: 40%
Greenfield et al. [45]	Retrospective cohort (1 center) (1988–1994)	166 with VTE and cancer (36% with metastatic cancer; 22% with lymph node metastasis; 62% with anticoagulation contra-indicated)	Vena cava filter associated with anticoagulant treatment (37%)	Not specified	PE: 1.8%. DVT: no data	Filter-related complications: 9.6% (n = 16, 13 receiving anticoagulant drugs)	Mean survival: 10 months. Fatal PE: 4.7%
Ihnati et al. [46]	Retrospective cohort (1 center) (1991–1996)	60 with VTE (DVT: 88.6%; PE: 4.8%; DVT + PE: 6.6%) and cancer (65% with anticoagulation contra-indicated)	Vena cava filter (2 pts with low-dose VKA)	13.1 months (mean)	VTE: 17% (8 DVT and 2 PE)	Puncture site hematoma: 2 pts	Survival at 1 year: 35% (38% in pts with anticoagulant alone)
Jarrett et al. [47]	Retrospective cohort (1 center) (1993–2000)	116 with VTE and cancer (45% with anticoagulation contra-indicated)	Vena cava filter (no data on anticoagulant treatment)	12.2 months (mean)	PE: 2.6%. DVT: 1.7%	Localized hematoma: 4.3%	Survival: at 30 days: 68.8%. at 3 months: 57.4%. at 1 year 26.8% (13.7% in stage IV cancer *versus* 77.9% in stage I-II-III cancer, $p < 0.001$)
Wallace et al. [48]	Retrospective cohort (1 center) (2000–2003)	308 with VTE and cancer (87% with solid tumors and 13% with hematologic malignancies)	Vena cava filter	Not specified	PE: 1.3%. Vena cava thrombosis: 4.5%	Retroperitoneal hemorrhage: 2 pts. Filter complications: 2 pts	Survival at 1 year: Solid tumor: 35%. Hematologic malignancy: 48% Fatal PE: n = 4 PE contributing to death: n = 10
Zerati et al. [49]	Retrospective cohort (1 center) (1998–2004)	50 with VTE and cancer (80% with anticoagulation contra-indicated)	Vena cava filter with anticoagulation as soon as possible	5 years	PE: 2%. Vena cava thrombosis: 4%. Filter thrombosis: 2%	Filter migration: 0%	Survival: 60% No VTE-related death Median survival: 496 days
Schunn ~~et al.~~ [50]	Retrospective cohort (1 center) (1998–2003)	55 with VTE (DVT: 76%; PE: 11%; DVT + PE: 13%) and stage III–IV cancer	Vena cava filter (40% with anticoagulant treatment)	248 ± 49 days (mean) 136 days (median)	VTE: 18.2% (*versus* 18.7% in 16 pts treated with anticoagulant alone)	Post-insertion complications: 12.7%	Survival at 1 year: 19% (*versus* 12.5% in 16 pts treated with anticoagulant alone, p = NS)

DVT: deep-vein thrombosis; iv: intravenous; NS: not significant; PE: pulmonary embolism; UFH: unfractionated heparin; VKA: vitamin K antagonists; VTE: venous thromboembolism.

3.5. Thrombolytics

Only one retrospective multicenter cohort study on the use of thrombolytic drugs in patients with VTE and cancer was identified (comprising patients from five randomized studies) [40]. This study included 57 cancer patients with PE, who were treated with tissue plasminogen activator or urokinase followed by intravenous UFH. Pulmonary angiography and scan revealed a reduction in clot burden of 77% and 72%, respectively. There was a 6% rate of recurrent VTE within 14 days after treatment administration. Major hemorrhages within 72 h after treatment administration were reported in 12% of patients. Although these data are insufficient to conclude the value of thrombolytic drugs in patients with VTE and cancer, they suggest that the use of thrombolytic drugs is possible in these patients, with a 6% rate of VTE recurrence and a 12% rate of major hemorrhage (*Level of evidence: C*). Furthermore, this study indicates that the presence of cancer *per se* does not represent a contra-indication to thrombolytic therapy for the treatment of PE.

3.6. Vena cava filters

In international guidelines, the routine use of vena cava filters in addition to anticoagulant drugs is not recommended in the general population of patients with VTE, regardless of the presence or absence of cancer [10]. The placement of vena cava filters is recommended in patients with a contra-indication for anticoagulant treatment, or in patients with recurrent VTE despite adequate anticoagulation [10]. There are no specific recommendations for patients with cancer. However, the high risk of recurrent VTE and hemorrhage in this group of patients (more than 5% for both events in CLOT, LITE, ONCENOX and CANTHANOX, [20,33–35]) warrants analysis of the benefit of these devices in cancer patients with VTE.

Very few data have been published on the use of vena cava filters in cancer patients with VTE. In the sole published randomized clinical trial that studied the benefit of vena cava filters in patients with VTE, no data were reported on the subgroup of cancer patients (representing about 10% of the 400 patients randomized) [60]. We identified ten retrospective cohort studies, including eight non-comparative studies and two studies comparing the efficacy of vena cava filters *versus* heparin followed by VKA [41–50] (Table 7). The size of the study populations varied between 29 and 308 patients. The main reason for vena cava filter placement was contra-indication to anticoagulant treatment. The results of these studies are somewhat heterogeneous, notably due to the large differences between these studies concerning the type

Table 8
Curative treatment of venous thromboembolism in patients with intracranial malignancies.

Reference	Type of study (study date)	Patients (number and characteristics)	Treatment	Follow-up	Thrombotic events	Adverse events
Schmidt et al. [51]	Prospective (1998–2001)	11 with DVT + malignant glioma	Tinzaparin (sc, 175 IU/kg/day for 10 days followed by 100 IU/kg/day for 3 months) Compression stockings for 10 days and recommended for 3 months	Not specified	0%	No bleeding or heparin-induced thrombocytopenia
Altschuler et al. [52]	Retrospective 1986 (not specified)	23 with VTE (DVT: 65%; DVT + PE: 35%) + malignant glioma	UFH (continuous iv infusion) followed by VKA for 3 months	Not specified	PE: 1 patient	Bleeding: 17.4% (4 pts with gastro-intestinal bleeding) Treatment discontinuation: 8 pts (4 for gastro-intestinal bleeding)
Levin et al. [53]	Retrospective, multicenter (1977–1991)	49 with DVT or PE + intracranial primary or metastatic tumor	Vena cava filter ($n = 42$) Heparin + VKA ($n = 5$) No treatment ($n = 1$) Vena cava ligation ($n = 1$)	Not specified	Vena cava filter: EP: 11.9%. DVT: 21.4%	Vena cava filter: Post-insertion complications: 7.1% Vena cava thrombosis or filter thrombosis: 26.2% Heparin + VKA: no severe bleeding event
Schiff and DeAngelis [54]	Retrospective (1980–1992)	51 with DVT or PE + brain metastases	Heparin + VKA ($n = 42$) Vena cava filter ($n = 10$)	Not specified	Heparin + VKA: 12% (none fatal) Vena cava filter: 40%	Severe intracranial bleeding;. Heparin + VKA: 7% (3 pts). Vena cava filter: 0%

DVT: deep-vein thrombosis; iv: intravenous; PE: pulmonary embolism; UFH: unfractionated heparin; VKA: vitamin K antagonists; VTE: venous thromboembolism.

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of recurrent VTE analyzed and the associated use of an anticoagulant treatment (when specified). Nevertheless, despite various methodological limitations, the results obtained in the eight non-comparative studies appear to be consistent, supporting, if indicated, the use of vena cava filters in patients with cancer (*Level of evidence: C*). However, whether their placement requires the concomitant administration of an anticoagulant drug, at prophylactic or therapeutic doses, remains unknown. Owing to the high risk of filter thrombosis, it seems reasonable, in the absence of any contra-indication, to administer therapeutic doses of anticoagulant drugs in patients with a vena cava filter. Nevertheless, the placement of vena cava filters remains an invasive procedure, potentially associated with iatrogenic complications (nephrotoxicity, infection, and filter thrombosis, perforation or migration); furthermore, their efficacy has not yet been convincingly demonstrated. Their use should therefore be questioned in patients with advanced cancer, even in those with VTE recurrence despite optimal anticoagulant treatment or a contra-indication to anticoagulant therapy [47,50]. Temporary or retrievable (or optional) vena cava filters may prove to be particularly valuable in this population, but this remains to be studied.

3.7. Patients with intracranial malignancies

Patients with primitive or metastatic intracranial malignancies exhibit a high risk of both VTE and bleeding. For example, the rate of symptomatic DVT in patients with malignant glioma, the most frequent primitive brain tumor, is 20–30% [61–65]. Moreover, the risk of bleeding is the main cause of the reluctance of physicians to use anticoagulants in this setting [66]. We therefore specifically analyzed the treatment of VTE in patients with intracranial malignancies.

We identified one non-randomized prospective [51] and three retrospective [52–54] studies (Table 8). Overall, the number of patients included in these studies was low (between 11 and 51 patients) and the characteristics of these patients were heterogeneous. An anticoagulant treatment (long-term LMWH or UFH + VKA) was administered to a total of 91 patients in the four studies. Depending on the study, the rates of recurrent VTE and major bleeding varied between 0% and 12%, and 0% and 17.4%, respectively. Severe cerebral bleeding was reported in three patients (7%), two of these having received supratherapeutic anticoagulation according to laboratory criteria [54]. In two studies assessing the value of vena cava filters in a total of 52 patients, the rate of VTE recurrence was high, about 40% [53,54].

In conclusion, the use of anticoagulant drugs in the treatment of VTE in patients with intracranial malignancies is associated with a VTE recurrence rate of 0 to 12% and a rate of intracranial hemorrhage between 0% and 7% (*Level of evidence: C*). Overall, these data suggest that, in most cases, anticoagulants may be administered for the treatment of VTE in patients with intracranial malignancies.

4. Recommendations

Based on a literature review and the well-argued judgment of experts, the 2008 SOR guidelines for the treatment of VTE in patients with cancer are as follows:

4.1. Standards

1. The treatment of VTE in patients with cancer should be based on the use of LMWH administered at therapeutic doses for at least 3 months.
2. With regard to the initial treatment (up to 10 days), there are no specific requirements for patients with cancer; all drugs approved for this indication (including LMWH, UFH, fondaparinux, and danaparoid) may be used.
3. Beyond the first 10 days, the treatment of VTE in patients with cancer should be based on the use of LMWH administered at therapeutic doses, optimally for 6 months, and otherwise, for at least 3 months. This treatment has been validated with the following drugs and dosage regimens: dalteparin 200 IU/kg once daily for 1 month, then 150 IU/kg once daily; enoxaparin 150 IU/kg once daily; and tinzaparin 175 IU/kg once daily.

   In the event of severe renal impairment, the treatment should be based on the use of UFH, rapidly followed (possibly as early as the first day) by VKA for at least 3 months.
4. In the event of severe PE (hemodynamic failure), the indications and usages of thrombolytic drugs are the same as in non-cancer patients.
5. In the event of absolute contra-indication to anticoagulant treatment, or VTE recurrence despite optimal anticoagulant treatment, vena cava filters should be considered. If the placement is indicated on the grounds of VTE recurrence, the anticoagulant treatment should be continued. If the placement is prompted by a contra-indication to anticoagulation, the anticoagulant treatment should be resumed once the contra-indication no longer applies.
6. In the event of VTE in patients with intracranial malignancies, the indications and usages of VTE treatment are the same as those in cancer patients with non-intracranial tumors.

4.2. Options

1. In the event of refusal or impossibility of LMWH administration for 3 months, short-term use of LWMH followed by VKA for at least 3 months may be proposed.
2. It is recommended to administer LMWH for between 3 and 6 months; LMWH should be used according to the same therapeutic dosage regimen as that used in the first 3 months.
3. In the event of a first VTE episode secondary to a transient risk factor, if the cancer is not active or is not treated, the anticoagulant treatment may be discontinued after 6 months.

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4. Beyond the first 6 months, the anticoagulant treatment should be continued as long as the cancer is active or treated (chemotherapy or hormonal therapy). The choice between LMWH and VKA depends on their benefit-risk ratio (influenced by drug interactions, chemotherapy, invasive procedures, and general health status) and acceptability.
5. If a vena cava filter is considered, the use of a retrievable (or optional) filter may be discussed.

5. Perspective

Since the establishment of these guidelines, an updated version of the American College of Chest Physicians (ACCP) clinical practice guidelines on the treatment of VTE (8th ed.) [67], as well as two Cochrane reviews and meta-analyses on the treatment of VTE in patients with cancer [68,69], have been published. Overall, the conclusions of these studies are concordant with the recommendations proposed by our working group. In order to facilitate the implementation of the various guidelines available for the treatment of VTE in cancer patients to the everyday practice, the homogenization of all the various documents currently proposed by several European and International consensus working groups [11,55–57,67] would certainly be very valuable.

Conflict of interest

The authors declare no conflict of interest.

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