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Anticoagulation for the prevention of VTE in cancer surgery

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Abbreviations used in this review
ASCO = American Society of Clinical Oncology
CAT = cancer-associated thrombosis
CI = confidence interval
CRP = C-reactive protein
DVT = deep vein thrombosis
ITAC = International Initiative on Thrombosis and Cancer
NCCN = National Comprehensive Cancer Network
OR = odds ratio
PE = pulmonary embolism
RCT = randomised controlled trial
RR = relative risk
SC = subcutaneous
VEGF = vascular endothelial growth factor
VTE = venous thromboembolism

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This review focuses on the prevention of venous thromboembolism (VTE) in patients undergoing surgery for cancer and reports on the current recommendations for VTE prophylaxis in cancer surgery from a number of international guidelines. Cancer patients are at significantly higher risk of developing VTE than individuals without cancer, and this risk is exacerbated in those undergoing surgery.[1-3] Recent advances in surgical techniques, new VTE detection methods and particularly the introduction of pharmacological and mechanical VTE prophylaxis have demonstrated significant improvements in the risk of VTE for this patient group.[4] However, advances allowing for more extensive procedures in older and sicker patients, and peri-operative chemotherapy/radiotherapy continue to contribute to the risk of VTE.[5] Given the clear evidence of the benefit of thromboprophylaxis in cancer patients undergoing surgery, the use of prophylactic anticoagulants in this group should be strongly supported, particularly noting the need for extended prophylaxis in high-risk patients undergoing major abdominal surgery. It is essential that surgeons recognise risk factors for the development of VTE in individual cancer patients and take appropriate measures to decrease the risk of its occurrence, morbidity and mortality. This review is sponsored by an educational grant from Sanofi.

Introduction

Compared with the general population, patients with cancer have a 4- to 7-fold higher risk of developing VTE, comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), experience a 3-fold higher risk of VTE recurrence despite anticoagulation, and have a 2- to 3-fold higher risk of major bleeding while receiving such therapy.[2,3] The highest 1-year incidence of VTE is reported in patients with cancers of the brain, lung, uterus, bladder, pancreas, kidney, and stomach. In these tumour types, cancer-associated thrombosis (CAT) risk increases 4- to 13-fold when metastases are present as opposed to localised disease.[1] Cancer patients are more likely to develop upper-limb DVT, bilateral thrombi or iliocaval thrombi than patients without cancer, and are more likely to develop atypical thromboses such as Budd-Chiari syndrome, extrahepatic portal vein obstruction, and mesenteric vein thrombosis.[1] It is estimated that up to 20% of cancer patients will develop VTE, with the risk being the highest in the initial period following diagnosis.[6] The risk of VTE in malignancy is further provoked by surgery, with cancer surgery associated with a 2-fold higher risk of post-operative DVT and over a 3-fold higher risk of fatal PE when compared with similar surgeries in non-cancer patients.[1,5]

The mechanisms of CAT, of which VTE is the commonest form, are multi-factorial and not fully understood, but it is recognised that patients with malignancy commonly exhibit a hypercoagulable or prothrombotic state that contributes to the increased risk of CAT, with abnormalities in each component of Virchow's triad (stasis of blood flow, endothelial injury, hypercoagulability).[1,6] The procoagulant state in cancer arises from an interaction between tumour cells and the haemostatic system and the varying incidence of VTE seen among different cancer types is thought to be partly due to different levels of plasma tumour procoagulants.[7] Moreover, tumours themselves may increasingly compress veins leading to venous stasis thus encouraging thrombosis.[6]

Cancer treatment itself contributes to the risk of CAT, with cytotoxic chemotherapy exhibiting a multifactorial influence to the risk of thrombosis via vascular injury through apoptosis and von Willebrand factor elevations, 5-fluorouracil driving thrombin formation in combination with depleted protein C activity, and VEGF inhibitors, immunomodulatory agents and small molecule inhibitors `priming' the endothelium to be more susceptible to injury.[8] Furthermore, indwelling devices such as tunneled/non-tunneled catheters, implanted ports and peripherally inserted central catheters through which cancer therapies are delivered are also associated with an increased risk of CAT, as are blood vessel damage and stasis following surgery.[1]

The burden of CAT

Individuals who develop VTE at cancer diagnosis or within the first year, exhibit a significantly worse prognosis than cancer patients without VTE.[6] CAT is associated with reduced quality of life, interruptions and delays in cancer treatments, and an estimated 6-fold decrease in survival compared to cancer without thrombosis.[9,10] In fact, VTE is the second leading cause of death in patients with cancer, second only to the progression of cancer itself.[6,11-13]

On average, post-operative patients with VTE stay in hospital 1 week longer than those without VTE, resulting in significantly higher healthcare costs.[14] Following recovery from CAT, patients may experience long-term morbidities including pulmonary hypertension and post-thrombotic syndrome manifesting as limb swelling, pain, oedema, venous ectasia, fibrosis, and skin induration (estimated to occur in 23-60% of patients within 2 years of an asymptomatic DVT episode).[11,15] Furthermore, a diagnosis of VTE impacts on future surgery, pregnancy, oestrogen use, life insurance and sometimes long-haul travel.[11]

Risk factors for CAT

It is of critical importance to recognise risk factors for the development of VTE in order to decrease its associated morbidity and mortality.[14] Patient-specific risk factors for VTE, bleeding risks and the type of surgical procedure must all be taken into account when balancing the risks and benefits of specific methods of thromboprophylaxis in cancer surgery.[15,16] Most hospitalised patients will have at least one risk factor for VTE and up to 40% will have ≥3 risk factors. Individuals undergoing colorectal surgery are considered to be at high risk of VTE.[17]

The risk of CAT is variable and influenced by a range of factors that can be grouped into four main categories:[18,19]

Tumour related – e.g., type, grade and stage of cancer, time since diagnosis

Treatment related – e.g., anti-cancer therapy, surgery, prolonged hospitalisation, central venous catheter use

Patient related – e.g., patient age, gender, ethnicity, history of VTE, genetics, comorbidities, extremes of bodyweight, varicose veins

Biomarkers – e.g., platelet and clotting activation related (D-dimer levels etc), clotting factor related (FVIII, CRP etc), blood related (levels of platelets, haemoglobin, leucocytes)

A number of studies have reported on risk factors for VTE following surgery in cancer patients, with variable findings. Multivariable logistic regression analysis of data from the US Nationwide Inpatient Sample between Jan 1999 and Dec 2009 involving 2,508,916 patients with cancer undergoing colectomy, cystectomy, esophagectomy, gastrectomy, hysterectomy, lung resection, pancreatectomy, or prostatectomy identified the following as risk factors for VTE following major cancer surgery: older age (OR 1.03; $p<0.001$), female sex (OR 1.25; $p<0.001$), black race (vs white; OR 1.56; $p<0.001$) and Charlson comorbidity Index score ≥3 (OR 1.85; $p<0.001$).[19] A recent meta-analysis by Li et al., involving approximately 1.5 million patients with cancer undergoing oncologic surgery and followed for 7-90 days, identified age, radiation, transfusion, and operative time as possible risk factors for post-operative VTE (**Table 1**).[7]

Table 1. Pooled ORs for association of commonly studied risk factors for VTE events in patients undergoing oncologic surgery[7]

Potential risk factors	No. of studies	Total no. of participants	Pooled OR/ SMD	95% CI	P value	I^2
Male	17	85,997	0.99	0.69–1.42	0.964	85.6
Age	14	104,390	0.46	0.40–0.53	<0.001	93.8
Advanced cancer	13	28,500	1.11	0.75–1.64	0.612	67.0
Chemotherapy	17	234,278	1.12	0.96–1.30	0.143	0
Radiation	10	172,762	1.29	1.03–1.62	0.030	34.6
Smoker	19	335,163	0.80	0.70–0.92	0.001	17.2
Transfusion	8	111,108	1.96	1.48–2.59	<0.001	57.0
Operative time	7	148,399	1.12	1.07–1.16	<0.001	100

Post-surgical VTE risk and mortality varies by cancer type

Understanding the risk of developing VTE following different surgeries in cancer patients is a key component in decision-making regarding the choice, intensity and duration of thromboprophylaxis.[20] It is well recognised that the risk of VTE associated with surgery varies considerably with the location of malignancy.[1]

The aforementioned meta-analysis by Li et al., revealed an overall post-operative VTE incidence of 2.3%, with the highest risk in those with lung cancer (8.1%), and bone and soft tissue cancer (10.6%), and the lowest risk in those with breast cancer (0.3%).[7] **Figure 1** shows the pooled estimates of VTE incidence for 14 cancer types. The overall incidence of VTE-related mortality was 0.3%. Among 13 studies evaluating the impact of VTE on all-cause mortality, those with versus without VTE exhibited significantly increased odds of fatal events (OR 11.15; 95% CI 4.07-30.56) (**Figure 2**).

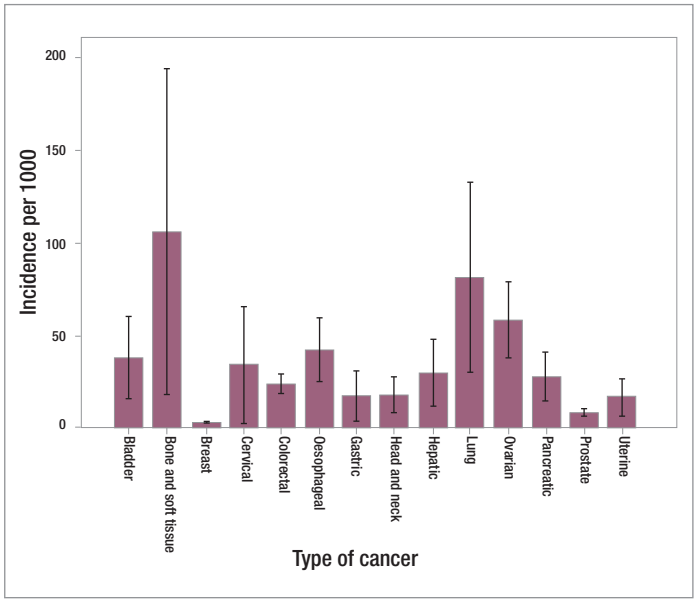

Figure 1. Pooled estimates of VTE incidence after oncologic surgery for 14 cancer types.[7]

Findings from The @RISTOS Project, a clinical outcome-based prospective study on VTE after general, gynaecologic or urologic cancer surgery in a total of 2373 patients (mean age 63.6 years; 1.7% with a history of VTE) at 31 Italian surgery departments with a high rate of cancer operations, revealed post-surgical VTE incidence rates of 2.83%, 2.0% and 0.87%, respectively.[5] In-hospital antithrombotic prophylaxis was given to 81.7% of patients in the study, but only 30.7% received post-discharge prophylaxis, with as few as 23.3% receiving such treatment for >21 days.

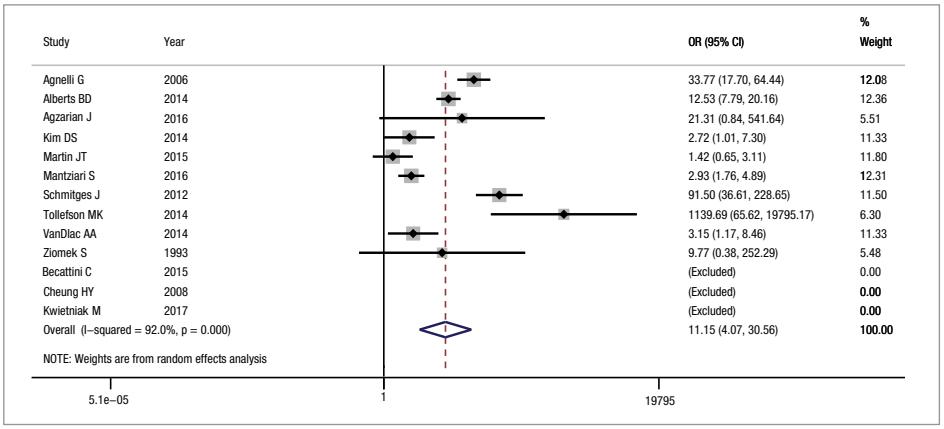

Figure 2. Summary forest plot of all-cause mortality for VTE versus no VTE across 13 studies.[7]

Table 2. Incidence of VTE within 91 days of surgery among patients with malignancy[20]

Surgical procedure	Number of surgeries	Average length of stay (days)	91-day incidence of thromboembolism			
			N	% Total	95% CI	% After discharge
Neurosurgery						
Neurosurgery involving excision, destruction or biopsy of brain tissue	5139	6.0	184	3.6	3.2-4.0	2.9
Excision, destruction, or exploration and decompression of spinal cord	1545	6.3	31	2.	1.4-2.6	1.0
Head and neck surgery						
Biopsy of lymphatic structure, or excision of regional lymph node	8170	3.5	114	1.4	1.2-1.6	0.8
Radical neck dissection	3045	5.1	21	0.7	0.4-0.9	0.1
Thyroid or parathyroid surgery	6027	2.5	9	0.2	0.1-0.2	0.1
Cardiac, thoracic or breast surgery						
Bronchoscopy of the lung with or without biopsy	7559	6.5	155	2.1	1.8-2.3	1.2
Open lung biopsy	1067	5.7	20	1.9	1.2-2.6	1.3
Heart catheterisation	2535	3.5	45	1.8	1.3-2.2	0.6
Pneumonectomy, complete, lobe or segment	12989	8.3	209	1.6	1.4-1.8	0.7
Coronary artery bypass grafting: 1, 2, 3 or 4 vessels or mammary artery	2243	8.2	34	1.5	1.1-1.9	0.8
Percutaneous transluminal coronary angioplasty of ≥1 vessel +/- thrombolytic agent	2660	3.3	18	0.7	0.4-0.9	0.3
Insertion of a permanent pacemaker	1033	2.5	6	0.6	0.2-1.0	0.3
Unilateral or bilateral extended simple mastectomy	34206	2.3	138	0.4	0.4-0.5	0.4
Peritoneal biopsy	1034	6.6	29	2.8	2.0-3.7	1.7
Gastrointestinal surgery						
Permanent colostomy	1249	9.7	33	2.6	1.9-3.4	1.7
Exploratory laparotomy	2600	7.1	63	2.4	1.9-2.9	1.2
Partial or total pancreatic resection	1283	16.3	30	2.3	1.6-3.0	1.1
Bilroth I or partial gastrectomy with jejunal anastomosis or transposition	3986	12.1	91	2.3	1.9-2.7	1.0
Excision of small bowel	2302	10.7	49	2.1	1.6-2.6	1.2
Peritoneal adhesiolysis	1832	8.5	34	1.9	1.3-2.4	0.9
Open Cholecystectomy	2250	6.7	40	1.8	1.3-2.2	1.2
Right, transverse, left sigmoidectomy or total colectomy	28949	8.4	491	1.7	1.6-1.8	0.9
Splenectomy	1137	6.9	18	1.6	1.0-2.2	0.5
Resection of the rectum: abdominal-perineal resection; pull through; laparoscopic	7797	9.0	119	1.5	1.3-1.8	0.9
cholecystectomy	2274	2.5	20	0.9	0.6-1.2	0.5
Urologic surgery						
Radical cystectomy	2512	12.0	92	3.7	3.1-4.5	2.0
Percutaneous nephrostomy with or without fragmentation of stone	1163	6.9	42	3.6	2.7-4.5	1.4
Unilateral or bilateral nephrectomy	7306	6.6	143	2.0	1.7-2.2	0.2
Radical prostatectomy	28034	5.2	429	1.5	1.4-1.7	1.1
Transurethral prostatectomy	14055	2.7	69	0.5	0.4-0.6	0.4
Endoscopic destruction of a bladder lesion	9308	2.2	39	0.4	0.3-0.5	0.3
Gynaecological surgery						
Remove both ovaries with/without removal of tubes	1986	6.8	45	2.3	1.7-2.8	1.1
Total abdominal hysterectomy	17020	4.9	199	1.2	1.0-1.3	0.7
Orthopaedic surgery						
Total hip arthroplasty or revision	2611	6.1	81	3.1	2.5-3.7	1.7
Internal fixation-femur without reduction, or with closed reduction	1238	6.1	37	3.0	2.2-3.8	1.6
Partial hip arthroplasty	2320	6.9	64	2.8	2.2-3.3	1.7
Total knee arthroplasty or revision	2334	5.6	55	2.4	1.8-2.9	1.0
Open reduction with internal fixation of the femur	3198	6.7	75	2.4	1.9-2.8	1.5
Excision of intervertebral disc	1300	4.6	12	0.9	0.5-1.4	0.4
Other surgery						
Excisional debridement of wound	1338	8.4	25	1.9	1.2-2.5	0.8
Radical excision of skin lesion	1826	4.9	20	1.1	0.7-1.5	0.8

Analysis of data from the California Patient Discharge Data Set on 258,720 patients with malignancy revealed post-surgical VTE incidence rates ranging from 0.2% following surgery for thyroid cancer to 3.7% following radical cystectomy (**Table 2**).[20] A limitation of this study was the absence of information on use or non-use of thromboprophylaxis, but the percentage of patients given effective thromboprophylaxis was estimated to be >45%.

Retrospective analyses of data from the US Nationwide Inpatient Sample involving patients with cancer undergoing major surgery revealed an overall post-surgical in-hospital VTE rate of 1.3% with a 5.3-fold increase in risk of mortality in those developing VTE compared to those who did not ($p < 0.001$).[19] Prostatectomy (3.9%) and hysterectomy (5.2%) were associated with the lowest risk of mortality following VTE.

Assessing the risk of VTE in cancer patients

The most widely used model for identifying high-risk patients who could benefit from thromboprophylaxis is the Khorana risk scoring model (**Table 3**), developed for ambulatory patients receiving chemotherapy.[21] The model takes into account cancer site, the use of erythropoiesis stimulating agents, platelet count, leucocyte count and BMI, and stratifies patients into low, intermediate, and high risk of VTE.[21,22] Patients with a Khorana score of ≥2 are considered at intermediate to high risk of VTE.[13,22]

Table 3. Khorana predictive model for chemotherapy-associated VTE[21]

Patient characteristic	Risk score
Cancer site	
• Very high risk (stomach, pancreas)	2
• High risk (lung, gynaecological, bladder, testicular, lymphoma)	1
Prechemotherapy platelet count ≥350×10⁹/L	1
Haemoglobin level <100 g/L, or red-cell growth factor use	1
Prechemotherapy leucocyte count ≥11×10⁹/L	1
BMI ≥35 kg/m²	1

HAEMATOLOGIST EXPERT COMMENT

While the Khorana score is relevant in decisions regarding prophylaxis in patients receiving chemotherapy, this is not reported as a tool for decision-making peri-operatively. Rather, peri-operative prophylaxis should be the standard for all patients in whom the bleeding risk is acceptable, with extension of prophylaxis particularly for those with cancer-related major abdominal procedures, particularly with other traditionally recognised VTE risk factors such as prior VTE, obesity, reduced mobility, older age or advanced-stage disease.

Assessing the risk of major bleeding complications

Post-operative bleeding is a significant potential complication associated with the use of antithrombotics and increases the risk of reoperation, transfusion-related complications, surgical-site infection and death.[23] While there are no validated models to predict risk factors for post-operative bleeding, several factors have been identified and are separated into patient-specific (general risk factors) and those that are related to surgery (**Table 4**).[23]

HAEMATOLOGIST EXPERT COMMENT

This risk of bleeding is definitely a juggling act which is not as well defined as the need to initiate pharmacological prophylaxis. In the American Society of Haematology 2019 guidelines, which address surgery in general rather than cancer surgery specifically, major neurosurgery and urological procedures such as radical prostatectomy are recognised as situations where the bleeding risk may require use of mechanical prophylaxis alone rather than a pharmacological or combined approach. The risk factors summarised in **Table 4** are commonly exclusions for the inclusion of a patient in clinical trials of prophylaxis and a judgement balancing the pros and cons is required.

Table 4. Risk factors for major post-operative bleeding[23]

General risk factors
Active bleeding
Previous major bleeding - Gastrointestinal bleed: 7 days - Intracranial bleed: 12 months - Recent intraocular surgery: 2 weeks - Other: 3 months
Previous bleeding from similar procedure
Untreated bleeding disorder
Severe renal or hepatic failure
Thrombocytopenia (<50,000/<100,000 and declining)
Acute stroke
Uncontrolled hypertension (>180/120 mm Hg)
Lumbar puncture, epidural, or spinal anaesthesia within previous 4 hours or next 12 hours
Use of anticoagulants, antiplatelets, NSAIDs or thrombolytic drugs
Epistaxis and menstrual bleeding are NOT contraindications to pharmacological thromboprophylaxis
Procedures in which complications may have especially severe consequences
Craniotomy
Spinal surgery
Spinal trauma
Reconstructive procedures involving free flap

Procedure-specific risk factors
Abdominal surgery - Male sex - Pre-operative haemoglobin level <13 g/dL - Malignancy - Complex surgery (≥2 procedures, difficult dissection, more than 1 anastomosis)
Pancreaticoduodenectomy - Sepsis - Pancreatic leak - Sentinel bleed
Hepatic resection - Number of segments - Concomitant extrahepatic organ resection - Primary liver malignancy - Lower pre-operative haemoglobin level platelet counts (Pre-operative anaemia/ thrombocytopenia)
Cardiac surgery - Older age - BMI >25 kg/m² - Concomitant antiplatelet therapy - Nonelective surgery - Longer bypass time - Placement ≥5 grafts - Operation other than CABG
Thoracic surgery - Pneumonectomy - Extended resection - Primary or metastatic malignancy
Orthopaedic surgery - Difficult to control surgical bleeding - Extensive surgical dissection - Revision surgery
Trauma surgery - Severe head injuries - Conservatively managed liver or spleen injuries - Spinal column fracture with epidural haematoma - Pelvic fractures

BMI = body mass index; CABG = coronary artery bypass grafting; NSAID = nonsteroidal anti-inflammatory drug

Peri-operative thromboprophylaxis for patients with cancer

Antithrombotics approved for use in NZ for the prevention of VTE in cancer patients:

- LMWH (enoxaparin)
- Unfractionated heparin

A systematic review and meta-analysis undertaken by Guo and colleagues involving 39 studies investigating the efficacy and safety of thromboprophylaxis in cancer patients undergoing surgery revealed a significantly reduced incidence of DVT in patients receiving thromboprophylaxis versus those not receiving such therapy (0.5% vs 1.2%; RR 0.51; 95% CI 0.27-0.94, p = 0.03), but a significantly increased risk of bleeding events (RR 2.51; 95% CI 1.79-3.51, p < 0.0001).[24] In this study, low-molecular-weight heparin (LMWH) reduced the incidence of DVT compared with unfractionated heparin (RR 0.81; 95% CI 0.66-1.00, p = 0.05).

A number of studies have compared the efficacy and safety of unfractionated heparin with that of LMWH in cancer patients undergoing surgery and have demonstrated similar efficacy but greater manageability with LMWH.[4] One of the studies, a double-blind, randomised multicentre trial in patients undergoing abdominal or elective pelvic oncological surgery, found similar safety and efficacy in reducing the risk of DVT between the LMWH enoxaparin 40 mg once daily beginning 2 hours before surgery and unfractionated low-dose heparin 3 times daily, both given for 8-10 days.[25] At 3-months' follow-up, 18.2% of LMWH recipients and 14.7% of enoxaparin recipients had developed DVT; major bleeding event rates were 4.1% and 2.9%, respectively.

A recent systematic review and meta-analysis of 33 trials including 11 trials of patients (n = 2037) undergoing surgery for cancer, revealed that thromboprophylaxis was associated with a significantly reduced risk of VTE (RR 0.51; 95% CI 0.32-0.81) and DVT (RR 0.53; 95% CI 0.33-0.87), with no significant increase in the risk of major bleeding compared with pooled results of patients not receiving thromboprophylaxis (RR 2.35; 95% CI 0.74-7.52, p = 0.1482).[26]

A 2018 Cochrane systematic review and meta-analysis involving 20 RCTs compared the relative efficacy and safety of anticoagulants for peri-operative thromboprophylaxis in 9771 individuals with cancer.[27] The analysis found no difference between LMWH and unfractionated heparin nor LMWH and fondaparinux* in their effects on mortality, thromboembolic outcomes, nor major or minor bleeding. Compared with unfractionated heparin, LMWH exhibited a significantly lower incidence of wound haematoma (RR 0.70; 95% CI 0.54-0.92).

These findings provide a strong case for thromboprophylaxis with LMWH, unfractionated heparin or fondaparinux* in patients undergoing oncological surgery, with preference given to LMWH due to its greater manageability (once-daily administration) and the lower risk of heparin-induced thrombocytopenia.[4] These agents should be used in association with graduated compression stockings.[4]

*fondaparinux approval lapsed in NZ

HAEMATOLOGIST EXPERT COMMENT

The use of pre-operative prophylaxis (first dose 2-12 hours pre-op) is standard in oncology surgery guidelines back to at least 2012 and is presumably based on the trial design for the initial trials demonstrating efficacy where pre-operative dosing was used. I could only find one study that specifically addressed the question of pre-operative versus post-operative commencement of prophylaxis. This single centre study at a large US Cancer Centre compared around 2000 patients of whom 55% received pre-operative prophylaxis at nurse assessment pre-operatively (intervention group) with nearly 5000 who started post-operatively.[28] At this institution, the post-intervention group as a whole (of whom just over half received pre-operative dosing) had lower bleeding rates and VTE rates. The groups were gathered over a period of just 12 months in total, so it seems unlikely other management changes explained the difference, but the study is single-centre and unrandomised. Particular issues to consider with implementing such a policy are the use of neuraxial anaesthesia and defining any particularly high bleeding risk procedures to exclude.

Duration of thromboprophylaxis

Findings from the California Patient Discharge Data Set revealed that a considerable number of VTE events were diagnosed after discharge from hospital, including 79% of post-neurosurgery VTE cases.[20] The findings are supported by a number of prospective studies, including the @RISTOS Project, showing that 40% of VTE events occurred after 21 days post-surgery.[5]

Extended use of LMWH out to 4 weeks after surgery has been shown to significantly reduce the risk of VTE in patients undergoing major surgery.[29-33] In the multicentre ENOXACAN II study, the efficacy of 1 week versus 4 weeks of enoxaparin 40 mg/day post-operatively was compared in patients undergoing open, elective, curative surgery for a malignant tumour of the gastrointestinal tract (other than the esophagus), genitourinary tract, or female reproductive organs.[29] Patients all received open-label treatment with 40 mg of enoxaparin once daily, with the first dose given 10 to 14 hours pre-operatively, for 6 to 10 days, followed by either 40 mg of SC enoxaparin (n = 165) or placebo (n = 167) once daily for 19 to 21 days, over a total treatment period of 25 to 31 days during the double-blind period. At the end of the double-blind treatment period, VTE had occurred in 12% of placebo recipients versus 4.8% of enoxaparin recipients (p = 0.02); at 3-months' follow-up the rates were 13.8% versus 5.5%, p = 0.01.

A meta-analysis of three RCTs of extended thromboprophylaxis (3-4 weeks after surgery) with LMWH in major abdominal surgery (70.6% of patients had neoplastic disease) revealed a significant reduction in the incidence of VTE with such therapy compared to in-hospital prophylaxis (5.93% vs 13.6%; RR 0.46; 95% CI 0.28-0.7); DVT 5.93% versus 12.9% (RR 0.46; 95% CI 0.29-0.74), proximal DVT 1% versus 4.72% (RR 0.24; 95% CI 0.09-0.67).[30] The analysis also demonstrated the relative safety of extended thromboprophylaxis with regard to bleeding risk, with no significant difference in major or minor bleeding between the two groups; 3.85% versus 3.48% (RR 1.12; CI 95% 0.61-2.06).

The meta-analysis by Guo and colleagues involving 39 studies revealed that standard extended thromboprophylaxis after cancer surgery significantly decreased the incidence of DVT as compared with conventional thromboprophylaxis (RR 0.57, 95% CI 0.39-0.83, p = 0.003).[24] These findings were supported by a study investigating VTE in patients undergoing colorectal surgery for suspected or confirmed malignancy, and in a Cochrane review of RCTs investigating extended-duration thromboprophylaxis (typically LMWH) for 4 weeks after open abdominal or pelvic surgery (VTE incidence 14.3% vs 6.1%; OR 0.41; 95% CI 0.26-0.63).[31,32] The benefit of extended thromboprophylaxis has also been demonstrated in patients undergoing laparoscopic resection for colorectal cancer in an RCT investigating either 7 days or 28 days of heparin therapy, with VTE rates of 9.7% and 0.9%, respectively (relative risk reduction 91%; 95% CI 0.3-0.99).[33]

HAEMATOLOGIST EXPERT COMMENT

For me, the benefits of extended prophylaxis are clear and it is reasonable to follow the guidelines summarised in the section below. There is some variation over which major surgery procedures to include extended prophylaxis with, and other VTE risk factors variably included as criteria. In general, if a patient is able to comply and they have advanced disease, or have had a major operation and are older, or have been in bed for more than 4 days, or have gastrointestinal malignancy, or are obese, have prior VTE or a relevant family history, this is appropriate given the data summarised here. Most patients can manage a daily injection of prophylactic enoxaparin, and the special authority for community funding includes high-risk surgery. Note a standard minimum course is 7 to 10 days, not just hospital stay, which may be less than that, and extended prophylaxis means continue up to 4 weeks.

Guideline recommendations for thromboprophylaxis in cancer surgery

A number of major societies and organisations have published guidelines and guidance for thromboprophylaxis in patients undergoing surgery for cancer. These include the American Society of Clinical Oncology (ASCO), the International Initiative on Thrombosis and Cancer (ITAC), and the National Comprehensive Cancer Network (NCCN).[13,22,34] **Table 5** provides a summary of the guidelines.

All three guidelines recommend thromboprophylaxis be started pre-operatively, with the ITAC guidelines specifying a time period for starting of 2-12 hours pre-operatively.[13,22,34]

ASCO and ITAC recommend that thromboprophylaxis be continued for ≥7-10 days and all three guidelines recommend thromboprophylaxis for up to 4 weeks in those at high risk undergoing abdominal and/or pelvic surgery.[13,22,34] ASCO defines high-risk patients as those with restricted mobility, previous VTE, obesity or additional risk factors, while NCCN defines high-risk patients as those with an anaesthesia time >2 hours, previous VTE, gastrointestinal malignancies, advanced-stage disease, bed rest of ≥4 days, or age >60 years.[22] The ITAC uses risk assessment tools, such as the Khorana Risk Scoring Model to determine risk.[13]

Table 5. Summary of the ASCO, ITAC and NCCN guidelines on VTE prophylaxis in surgical patients with cancer[13,22,34]

Guideline	Recommendation
ASCO 2020	All patients undergoing major surgery should be offered pharmacological prophylaxis with UFH or LMWH unless contraindicated Prophylaxis should be commenced pre-operatively Mechanical prophylaxis should not be used as monotherapy unless pharmacologic prophylaxis is contraindicated Combined pharmacologic/mechanical prophylaxis may improve efficacy, especially in highest-risk patients Pharmacologic prophylaxis should be continued for at least 7–10 days. Extended prophylaxis with LMWH for up to 4 weeks post-operatively is recommended for patients undergoing major open or laparoscopic abdominal or pelvic cancer surgery with high-risk features (restricted mobility, obesity, history of VTE, or additional risk factors). In lower-risk surgical settings, the decision on appropriate duration of thromboprophylaxis should be made on a case-by-case basis
ITAC 2019	LMWH (if CrCl ≥30 mL/min) once daily or low-dose UFH three times a day is recommended. Pharmacologic prophylaxis should be started 2–12 hours pre-operatively and continued for at least 7–10 days. No data to suggest one LMWH superior to another. Insufficient evidence to support fondaparinux[#] as an alternative to LMWH Use of highest prophylactic dose of LMWH is recommended Extended prophylaxis (4 weeks) with LMWH to prevent post-operative VTE after major laparotomy and laparoscopic surgery is indicated in patients with a high VTE risk and low bleeding risk. The price of LMWH may influence choice Mechanical thromboprophylaxis is not recommended as monotherapy, except when pharmacologic prophylaxis is contraindicated IVC filters are not recommended for routine prophylaxis
NCCN 2020	Prophylactic dose LMWH, UFH, or fondaparinux[#] with or without PCD is recommended Consider pre-operative dosing with UFH or LMWH for high-risk surgery patients with or without PCD If anticoagulant prophylaxis is contraindicated, mechanical prophylaxis is recommended Out-of-hospital VTE prophylaxis is recommended for up to 4 weeks post-surgery for high-risk patients with abdominal or pelvic cancer

[#]Approval lapsed in NZ
CrCl, creatinine clearance; IVC, inferior vena cava; LMWH, low-molecular-weight heparin; PCD, pneumatic compression device; UFH, unfractionated heparin; VTE, venous thromboembolism

A SURGEON'S PERSPECTIVE

It is fair to say that the application of peri-operative thromboprophylaxis by surgeons is incomplete and highly variable, despite clear evidence supporting its role in reducing thrombosis-related complications and death. Incomplete application is particularly notable in the immediate pre-operative setting, where consensus guidelines of major organisations in surgical oncology including the NCCN, ASCO, and the ITAC advocate that both mechanical and chemical thromboprophylaxis begin 2-12 hours before "knife-to-skin," in addition to continuing for at least 7-10 days post-operatively, and extending up to 4 weeks for those at high risk. Importantly, factors defining high-risk individuals are very common among the operative cancer patient population, including anaesthesia time greater than 2 hours and age greater than 60, as well as other frequently encountered features including obesity and advanced-stage disease. The lack of uniform adoption seems particularly stark given that VTE has been reported to represent the second leading cause of death in cancer patients, second only to cancer progression itself.

On the other hand, it is fair to consider that surgeons can cite credible rationale for incomplete adherence to peri-operative thromboprophylaxis guidelines. As quoted in this review, while prophylaxis clearly reduces the relative risk of DVT by half, it also doubles the relative risk of bleeding events relative to patients not receiving such therapy. While the overall incidence of clinically significant bleeding is low, surgeons are not immune to practicing anecdotally and based on their own worst bleeding experience. When bleeding happens, cancer surgeons usually take direct responsibility through actions of their knife, while any thrombotic complications can be considered at least partially resulting from the underlying cancer itself. Also relevant, but even harder for data to quantify, are surgical concerns about how heightened intra- and peri-operative bleeding might affect technical ability to achieve oncological goals like adequacy of resection while minimising collateral damage and maximising operative efficiency. Each of these points are not justifications for ignoring existing guidelines, but are relevant to understanding the surgeon's point of view when considering how strictly they are applied.

In my own practice I now routinely advocate pre-operative chemoprophylaxis prior to any major cancer surgery that I perform in head and neck, melanoma, and sarcoma tumour streams. In a similar vein, based on evolving data relevant to my role as a plastic surgeon, I advocate continuation of therapeutic anticoagulation for pre-existing indications such as atrial fibrillation with any cutaneous surgery and skin-based flap reconstruction procedure. These have been easier to incorporate into routine practice as general acceptance and experience is gained. Ultimately, it is important for each of us to constantly question best practice with critical consideration of the best evidence and experience available to us, while keeping the individual patient at the center of their own management plan.

HAEMATOLOGIST EXPERT'S CONCLUDING REMARKS

Overall, the use of peri-operative prophylaxis in cancer surgery has an excellent evidence base. The limited data available show a high rate of symptomatic VTE event rates with mechanical methods alone. Low molecular weight heparin is generally favoured over unfractionated heparin as the dosing is most often daily versus more frequent, and in NZ unfractionated heparin needs to be drawn up in comparison to pre-packaged vials. There is also a higher rate of heparin-induced thrombocytopenia potentially with unfractionated heparin, although this remains rare in this population.

DOACs such as rivaroxaban have not been trialled to my knowledge in the abdominal surgery prophylaxis group and we do see gastrointestinal bleeds sometimes if these are restarted early, so the injected products are still favoured at this time. It is a harder risk-benefit equation in the early days after higher bleeding risk procedures and this is accounted for in most recent guidelines. However, for the majority of general surgical/abdominal procedures or gynaecological cancer, major surgery prophylaxis can be started either in the early post-operative phase or potentially before surgery.

TAKE-HOME MESSAGES

- Cancer patients have a higher risk of VTE and this is elevated further by surgery
- CAT is associated with significant morbidity and mortality
- Risk factors for post-operative VTE in cancer surgery include previous VTE, older age, female sex, obesity, duration of surgery, restricted mobility, radiation and transfusion
- Post-surgical VTE risk and mortality varies by cancer type
- A large proportion of VTE events occur >3 weeks post cancer surgery
- Peri-operative thromboprophylaxis significantly reduces the risk of post-surgical VTE
- Extended prophylaxis for 3-4 weeks post cancer surgery further reduces the risk of VTE without significantly increasing the risk of major or minor bleeding
- International guidelines recommend starting thromboprophylaxis with LMWH or unfractionated heparin 2-12 hours prior to cancer surgery and continuing thromboprophylaxis for ≥7-10 days, or up to 4 weeks (with preference given to LMWH) in those at high risk undergoing abdominal and/or pelvic surgery
- Risk factors for VTE should be taken into account when balancing the risks and benefits of specific methods of thromboprophylaxis.

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