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Venous Thromboembolism in Gynecologic Oncology Patients

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Cancer Care Alberta

Clinical Practice Guideline GYNE-010 – Version 1
www.ahs.ca/guru

Background

Venous thromboembolism (VTE) consisting of both deep vein thrombosis (DVT) and pulmonary embolism (PE) is one of the principal causes of morbidity and mortality in cancer patients[1]. The annual incidence of VTE in patients with cancer is 0.5% compared to 0.1% in the general population[2]. Cancer is associated with a higher rate of VTE events and bleeding. Patients with malignancy are four to seven times more likely to develop a VTE compared to other patients[3, 4]. Cancer treatment often includes surgery, which increases additional risk for thrombosis and bleeding.

The incidence of VTE is common in gynecologic cancer patients, with estimated rates in ovarian cancer ranging from 2%– 22% and in endometrial cancer, the rate increases up to 8.1% within 6 months of a new diagnosis[5, 6]. Studies showed that approximately 3% of newly diagnosed ovarian cancer patients develop a VTE before treatment and the risk increases to 12% in the neoadjuvant chemotherapy setting[7].This elevated baseline risk of VTE in gynecologic cancer patients puts pelvic surgery as a high-risk group.

There are many prophylactic and therapeutic strategies, along with pharmacologic agents available for the management of VTE in the gynecologic oncology patient population. The treatment options are based on risk factors, type and stage of cancer[8]. In this guideline the recommendations are divided into three different settings: preoperative, intraoperative and postoperative.

Guideline Questions

1. What are the prophylaxis recommendations for the prevention of VTE?
2. Should ambulatory patients with cancer receive anticoagulation for VTE prophylaxis?

Search Strategy

PubMed, MEDLINE and Cochrane database were searched for relevant studies, guidelines and consensus documents published up to February 2021. Results were limited to phase III clinical trials, comparative studies, controlled clinical trials, guidelines, meta-analyses, multicenter studies, practice guidelines, randomized controlled trials and systematic reviews involving human subjects (19+ years) and published in English. Online resources from oncology-based health organizations and guideline developers were also systematically searched, and relevant guidelines from the following organizations were considered in the development of our recommendations: American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and the National Comprehensive Cancer Network (NCCN).

The ECRI Guidelines Trust ® and Canadian Partnership Against Cancer Guidelines Database were also searched from 2010 to February 2021 for guidelines on treatment of VTE in gynecologic oncology patients.

Target Population

The following recommendations apply to female patients over 18 years of age who are receiving treatment for gynecologic malignancies.

Recommendations

Preoperative recommendations: These recommendations should begin before the induction of anesthesia.

- All patients undergoing major surgical intervention for malignant disease should be considered for thromboprophylaxis. (Level of Evidence: II Strength of Recommendation: B)[1, 9]
- Prophylaxis should be initiated pre-operatively and continued post-operatively while in hospital. (Level of Evidence: II Strength of Recommendation: C)[7, 9]
- All gynecologic cancer patients undergoing laparotomy or laparoscopy, lasting longer than 30 minutes should be offered pharmacologic thromboprophylaxis with low molecular weight heparin (LMWH). (Level of Evidence: I Strength of Recommendation: A)[9, 10]
- Pharmacologic thromboprophylaxis for patients undergoing major surgery for cancer should be started 2-12 h preoperatively. (Level of Evidence: I, Strength of Recommendation: A)[7, 9, 10]
- LMWH is recommended for thromboprophylaxis in patients with a gynecologic cancer. (Level of Evidence: I, Strength of Recommendation: A)[9]

Intraoperative recommendations: These recommendations should begin during surgery. The mechanical method can be added to the preoperative treatment recommendations, however should not be used as a sole treatment option.[11]

- Pneumatic compression stockings reduce the rate of VTE when compared to observation and is recommended for gynecologic oncology patients**.** (Level of Evidence: I, Strength of Recommendation: A)[7, 10]
- Patients should wear well-fitting compression stockings and have intermittent pneumatic compression. (Level of Evidence: III, Strength of Recommendation: C)[7, 10]
- In lower-risk surgical settings, the decision on appropriate duration of thromboprophylaxis should be made on a case-by-case basis. (Level of Evidence: III, Strength of Recommendation: C)[7, 10]

Postoperative recommendations: These recommendations should begin postoperatively or in the postoperative setting.

- Extended chemoprophylaxis (28 days post-op) should be prescribed to gynecologic cancer patients. (Level of Evidence: I, Strength of Recommendation: A)[7, 10-13]
- Extended prophylaxis with LMWH for up to 28 days postoperatively is recommended for higher-risk patients undergoing major open or laparoscopic abdominal or pelvic surgery

(restricted mobility, obesity or a history of VTE). (Level of Evidence: I, Strength of Recommendation: A) (Level of Evidence: I, Strength of Recommendation: A)[7, 9, 14]

- The risk of VTE is reduced when postoperative pneumatic compression stockings are combined with heparin in gynecologic patients. (Level of Evidence: II, Strength of Recommendation: B)[7, 9, 14]

Table 1: LMWH postoperative VTE dose for 28 days [13]

Anticoagulant	Standard Dosing	Dose adjustment	Renal Dosing
Unfractionated heparin (UFH)	5,000 to 7,500 units every 8 hours (expert opinion)	Consider 7500 IU (limited data)	No renal dose adjustment
Enoxaparin	40 mg subcutaneously once daily Start 12 hours preoperative	wt >100kg: 40-60mg subcutaneously twice daily	CrCl < 30ml/min: 20-30mg subcutaneously DAILY
Dalteparin	5000 units subcutaneously once daily	wt > 100kg: 7500 units subcutaneously daily	CrCl < 30ml/min: 2500-5000 units subcutaneously DAILY
Tinzaparin	4500 units subcutaneously once daily	wt >100kg: 75units/kg (ABW) subcutaneously daily	CrCl < 30ml/min: No dose adjustment
Fondaparinux	2.5 mg SC daily Start 6-8 hours post operatively or begin morning of surgery	Consider 5mg daily (Limited data)	Use caution CrCl 30-50ml/min Contraindicated CrCl<30ml/min

Prophylaxis in the ambulatory setting for cancer patients undergoing treatment: Direct oral anticoagulants (DOACs), factor Xa inhibitors and low molecular weight heparins (LMWHs) have been a recommended for VTE prophylaxis treatment in high-risk ambulatory cancer patients.[15] The risk of VTE is calculated by Khorana score for gynecological cancer patients. Site of tumour, hematological parameters and body mass index are the clinical parameters which are calculated by Khorana score to determine the risk factor for the cancer patients. The parameters are summarized in the appendix. The high-risk ambulatory patients should be offered thromboprophylaxis with apixaban, rivaroxaban, or LMWH provided there are no significant risk factors for bleeding or drug interactions. (Level of Evidence: I, Strength of Recommendation: A)[9, 14, 16]

Anticoagulation treatment with DOACs: It is recommended that anticoagulation, for an active VTE, beyond the initial 6 months should be offered to select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy. (Level of Evidence: I, Strength of Recommendation: A) [9, 14, 16]

Discussion

Gynecologic oncology patients are at a high-risk of VTE. There are various prophylactic treatment options available for the prevention of VTE in oncology patients.

Preoperative Approach for VTE Prevention

Preoperative treatment options are recommended for gynecologic oncology patients prior to surgery. Based on studies, approximately 3% of women with a new diagnosis of ovarian cancer develop a VTE before they start the cancer treatment [7]. The prospective study by Agnelli et al. showed that the incidence of postoperative VTE is 2-3 fold greater in the cancer patient undergoing surgery and varied widely amongst procedure performed and tumor type. The RISTOS project identified many factors such as; history of a previous VTE, age over 60 years, advanced cancer, anesthetic longer than 2 hours and prolonged bed rest as critical risk factors for VTE in the postoperative setting.[17] Several retrospective studies (in patients with gynecologic malignancy) have shown a decrease in rates of DVT and PE in post-operative setting when pharmacologic thromboprophylaxis is used.[18, 19]

Intraoperative Treatment Options

The intraoperative treatment options begin at the time of surgery. Mechanical options are generally combined with preoperative treatment options. Many studies showed that pneumatic compression devices decrease the rate of VTE as compared to no prophylaxis within the first 5 days post-operatively. [20, 21] The uses of graduated stockings have also shown to decrease rates of VTE when combined with other methods of prophylaxis.[22]

Postoperative Approach for VTE Prevention

These treatment options begin after surgery as the risk of VTE is increased during prolonged hospital stay.[7] The randomized control trial ENOXACAN II showed a significant decrease in VTE when patients received Enoxaparin prophylaxis for 28 days as compared to those who received it for 10 days.[23] Many studies support the reduction of VTE and DVT in patients with extended prophylaxis for 28 days.[24] [25]

Most of the guideline groups recommend extended thromboprophylaxis, for 28 days, in women undergoing gynecologic cancer surgery. A recent retrospective review by Pin et al. identified that extended prophylaxis is required for patients with endometrial cancer. The study showed the overall death rate in patients with VTE was 42% vs 9% in patients without VTE.[26] This supports a strong recommendation for use of postoperative VTE prophylaxis in endometrial cancer patients. The study also identified age, stage of disease, histology, and type of surgery as potential high-risk factors contributing to VTE in gynecological cancer patients.[26] Similarly, a meta-analysis by Xu et al. also identified surgery, obesity, older age, ascites, and higher ASA score, smoking history and previous history of VTE as risk factors for VTE in epithelial ovarian cancer patients. [27]

Prophylaxis in the Ambulatory Setting for Cancer Patients Undergoing Treatment

There are risks involved in cancer patients undergoing chemotherapy, with VTE being one of them. Prophylaxis with anticoagulation in ambulatory cancer patients has been studied. The AVERT trial showed a reduction in VTE 4.2% vs 10.2% (hazard ratio, 0.41; 95% confidence interval [CI], 0.26 to 0.65; P<0.001) in the apixaban treatment group compared to the placebo group. This trial included patients undergoing chemotherapy and had a modified Khorana score of 2 or higher. The Khorana score is a range from 0-6, and is used to identify cancer patients, at an increased risk of developing a VTE, that would benefit from thromboprophylaxis. Higher scores indicate a higher risk of VTE. This study concluded that the prophylactic use of apixaban lowers the rate of VTE in high-risk ambulatory cancer patients. [28] The CASSINI trial is another randomized double-blind trial, which evaluated the benefit and safety of prophylactic rivaroxaban in the prevention of VTE. [29] The CASSINI trial enrolled cancer patients on new systemic therapy with a Khorana score of 2 or higher and showed a 2.8% absolute reduction in VTE, with low bleeding rates in both groups of <2% . Both trials suggest that the rate of VTE can be reduced with the use of DOAC prophylaxis in high-risk cancer patients undergoing treatment. PROTECHT[30] and SAVE-ONCO[31] clinical trials also demonstrated reductions in the incidence of VTE with LMWH in ambulatory patients with cancer; however, the magnitude of VTE reduction was low. Based on low benefit risk profile for the LMWH trials, DOAC is recommended for VTE prophylaxis.

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Appendix A[9, 10]

Patient Characteristic	Risk Score
Site of Cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecological, bladder, or testicular)	1
Prechemotherapy platelet count ≥350 x 109/L	1
Prechemotherapy hemoglobin level < 100g/L or use of red cell growth factor	1
Prechemotherapy leukocyte count > 11 x 109/L	1
Body mass Index ≥ 35Kg/m2	1
Traditional risk categories	
High	≥3
Intermediate	1-2
Low	0
Currently proposed risk categories	
Intermediate to high	≥2
Low	<2

Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial Gynecological Tumour Team. Members include gynecologic oncologists, radiation oncologists, medical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gynecological Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2022.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of the guideline will be conducted in 2025. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

DOAC; Direct oral anticoagulants, DVT; deep vein thrombosis, LMWH; low molecular weight heparin, PE; pulmonary embolism, UFH; Unfractionated heparin, VTE; Venous thromboembolism

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Gynecological Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

Dr. Cynthia Wu has nothing to disclose

Dr. Gregg Nelson has nothing to disclose

Dr. Jay Easaw* has nothing to disclose

Dr. Sophia Pin * has nothing to disclose

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