

Recommendations from the ICM-VTE: Oncology

The ICM-VTE Oncology Delegates*

1 - VTE in Bone Metastasis

A. What is the overall risk for VTE in this patient population and what are the factors that increase VTE risk in this patient population?

B. What is the optimal VTE prophylaxis protocol in this patient population when also taking into consideration bleeding risk?

Response/Recommendation: Patients that undergo prophylactic fixation or pathological fracture fixation due to metastatic bone disease have a high risk of developing venous thromboembolism (VTE). Risk factors include patient characteristics such as age and comorbidities, as well as extent of surgery and duration of surgery. In the absence of contraindications, patients that undergo surgery or hospitalized patients should be administered thromboprophylaxis with or without mechanical prophylaxis. At this time, we do not have sufficient evidence to make specific recommendations for the type of thromboprophylaxis.

Strength of Recommendation: Limited.

Delegates vote: Agree 92.31% Disagree 0.0% Abstain 7.69% (Strong Consensus)

A. What is the overall risk for VTE in this patient population and what are the factors that increase VTE risk in this patient population?

Rationale: VTE, encompassing deep venous thrombosis (DVT) and pulmonary embolism (PE), is a major public health problem that affects 300,000 to 600,000 individuals in the United States each year and is accompanied by considerable morbidity and mortality. Some of that is related to bone tumors and bone metastasis¹.

Patients with long-bone or spinal metastases who undergo surgery have a high risk of developing VTE, with VTE diagnosed in 6% following long bone surgery¹ and with an overall incidence of VTE in spine surgery (16.9%)². The average age for patients with VTE in spine metastasis surgery was 57 years and 62% were male². Risk factors also include type of operation. One study noticed that it is highly unlikely for

patients with intramedullary nails to develop DVT compared to patients with knee prostheses (odds ratio [OR] = 0.11, relative risk [RR] = 1.16)³. Patients that underwent prophylactic fixation had a significantly higher rate of PE than the pathological fracture group (2.1% compared with 1.2%; $p = 0.008$), with an OR of approximately 2.0⁴.

Blood transfusions are known to increase the risk of VTE events in overall cancer patients. Khorana et al., found VTE rates of 7.2% (venous) and 5.2% (arterial) in cancer patients that received red blood cell transfusions. These rates were significantly higher than the comparative group that did not receive a transfusion. (3.8 and 3.1%)⁵. Therefore, a cautious approach to the use of blood transfusions during metastatic bone cancer surgery is recommended³.

Some studies have explored the association between operative time and postoperative VTE. Tominaga et al., found that 20 of 80 patients had VTE after spinal surgery. The median operative time for patients with VTE and without VTE was 212.5 minutes and 177.5 minutes, respectively. A large-scale retrospective study in spinal metastatic patients showed that longer operative time was independently associated with an increased risk of postoperative symptomatic VTE. The risk of VTE increased by 15% for every additional hour of surgery. Operative time of ≥ 4 hours was an independent predictor of VTE after spinal surgery⁶.

Patients who undergo surgical treatment for lower limb pathological fracture due to malignancy are at increased risk of DVT or death due to PE under current general thromboprophylaxis regimens. The risk is higher for the immediate postoperative period (10 days). The risk is increased by the presence of other metastases, arthroplasty reconstruction, and perioperative adjuvant therapy (radiotherapy, chemotherapy)³.

B. What is the optimal VTE prophylaxis protocol in this patient population when also taking into consideration bleeding risk?

Rationale: Previous studies have shown that the rate of VTE in patients receiving VTE prophylaxis was 9.1% in the

*A list of the ICM-VTE Oncology Delegates is included in a note at the end of the article.

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group that received early prophylaxis (days 1–3) and 35.7% in the delayed group (26.6% absolute risk reduction; $p=0.049$)². Patients who underwent prophylactic fixation of a metastatic femoral lesion had a significantly higher rate of PE than the pathological fracture group (2.1% compared with 1.2%; $p = 0.008$), with an OR of approximately 2.0⁴. There was no difference in VTE events between the type of anticoagulation used. (OR = 0.21, RR = 0.98)³.

There is limited literature on what the optimal prophylaxis for orthopedic oncology and metastasis surgery. The guideline for treatment for cancer patients in general stated by the American Society of Clinical Oncology (ASCO) is divided on patient categories, such as: hospitalized patients, outpatients, patients undergoing surgery, and patients with established VTE⁷. In hospitalized patients who have active malignancy and acute medical illness or reduced mobility, pharmacologic thromboprophylaxis should be offered in the absence of bleeding or other contraindications but should not be offered for the sole purpose of minor procedures or chemotherapy infusion⁷. Not all cancer outpatients require VTE prophylaxis, and the decision to use prophylaxis depends on the type of cancer being treated and the type of chemotherapeutic regimen⁷.

All patients with malignant disease undergoing major surgical intervention should be offered pharmacologic thromboprophylaxis unless contraindicated due to active bleeding, or high bleeding risk, or other contraindications. Thromboprophylaxis is initiated preoperatively. Mechanical prophylaxis should not be the only precautionary method used and should be combined with pharmacological thromboprophylaxis in high risk patients⁷.

Regarding the choice of VTE prophylaxis, different kinds of agents including low-molecular-weight heparin (LMWH), Vitamin K Antagonist (VKA), Direct Oral Anti Coagulants (DOAC) and also aspirin are appropriate. One study reported that aspirin significantly lowered the incidence of acute PE, but the risk of major bleeding is the same between two groups⁸.

A network meta-analysis reported that the OR for recurrent VTE in the group receiving VKA was 0.67 (95% confidence interval [CI], 0.40-1.15, $p = 0.147$), and 0.96 (95% CI, 0.52-1.75, $p = 0.886$) in the group LMWH⁹. Anticoagulants such as LMWH emerged with the highest cumulative ranking probability for the efficacy endpoint, while DOAC had the highest cumulative ranking probability for the safety endpoint¹⁰. Other studies reported that DOAC lowered the incidence of 6-month recurrent VTE when compared to LMWH (RR 0.56, 95% CI 0.40–0.79; $p < 0.001$, estimated heterogeneity [I^2] 59%)¹¹ and incidence of major bleeding was not significantly different between DOAC and LMWH treated patients (RR 1.56, 95% CI 0.95–2.47, $p = n.s.$)⁹. However, another meta-analysis showed that LMWH has significant reduction in recurrent VTE events (RR: 0.52; 95% CI: 0.36 to 0.74) whereas DOAC did not (RR: 0.66; 95% CI: 0.39 to 1.11)¹².

LMWH has shown efficacy and safety comparable with the use of DOAC in patients with cancer and VTE, with a non-significant trend toward a better efficacy with DOAC while

LMWH was associated with lower rates of bleeding over DOAC¹³. We conclude that larger studies regarding optimal VTE prophylaxis are required to make definitive conclusions as to the most efficacious and safe thromboprophylaxis in bone metastasis patients.

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2 - For Primary Bone Tumours/Sarcoma Patients

A. What is the overall risk for VTE in this patient population and what are the factors that increase VTE risk in this patient population? B. What is the optimal VTE prophylaxis protocol in this patient population when also taking into consideration bleeding risk?

Response/Recommendation: Patients undergoing sarcoma surgery have a high risk of venous thromboembolism (VTE) with multiple common risk factors relating to the patient population, surgery, and complications. Patients should have chemoprophylaxis with either low-molecular-weight heparin (LMWH) or aspirin (ASA) unless very high bleeding risk, combined with pneumatic compression.

Strength of Recommendation: Limited.

Delegates vote: Agree 92.31% Disagree 7.69% Abstain 0.0% (Strong Consensus)

Rationale: Major orthopaedic surgeries and oncological patients have increased risk for VTE, with the mean incidence of all VTE events in orthopaedic oncology patients being 10.7% (1.1% to 27.7%). Risk factors for increased events include endoprosthetic replacements, hip and pelvic resections, surgical procedures taking longer than 3 hours, and chemotherapy¹⁴, all of which are common with sarcoma surgeries. Higher preoperative white blood cell count (odds ratio [OR] 1.15, 95% confidence interval [CI] 1.01-1.29) and post-operative wound complications (OR 5.01, 95% CI 1.93-13.55) were found to be independent risk factors for VTE¹⁵. The risk of wound complications increased significantly in patients with primary bone sarcoma who received chemical prophylaxis (OR 2.21, 95% CI 1.00-4.87)¹⁵. Regarding pulmonary embolism (PE) specifically, primary malignant bone tumours, bone tumour resections and prosthetic reconstructions had significantly higher risk than soft tissue tumours or soft tissue tumour resections¹⁶.

There is varied evidence on whether chemoprophylaxis will decrease VTE rates. One study stated there was no identified significant difference with use of chemoprophylactic agent and incidence of VTE in patients undergoing mega-endoprosthetic reconstruction after cancer resection¹⁷. However, it was also found that in populations where there was consistent and careful prophylaxis until time of weight-bearing, there was a low occurrence of VTE events (1.1%)¹⁸. As stated above, chemoprophylaxis may increase wound complications, which in turn may increase chance of VTE events due to prolonged immobilization or additional surgeries. This would suggest that there should be allowance within this recommendation to modify the treatment depending on independent patient risk factors regarding prophylactic treatment.

There is limited literature on optimal prophylaxis. When looking at patients that had hip replacements for oncologic indications, there is a low rate of deep vein thrombosis (DVT) when pneumatic compression devices are supplemented with LMWH¹⁹. There was no significant difference regarding DVT rate when ASA versus LMWH was used to supplement the pneumatic compressions devices²⁰.

Given that there is multiple risk factors and a high overall risk within the population, and varied evidence suggesting either no improvement, to improvement with a combination of pneumatic and chemoprophylaxis, it would be recommended to give chemoprophylaxis unless specific patient factors such as

high bleeding risk suggest otherwise. The type of chemoprophylaxis can be surgeon's choice, with ASA and LMWH being viable possibilities. Routine prophylaxis until full weight-bearing has a chance of decreasing the possibility of VTE events in a high-risk population.

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3 - What orthopedic tumor-related surgeries require routine prophylaxis?

Response/Recommendation: Patients undergoing resection procedures for bone metastasis or procedures that involve prosthesis reconstruction are at higher risk of venous thromboembolism and require routine prophylaxis.

Strength of Recommendation: Limited.

Delegates vote: Agree 100.0% Disagree 0.0% Abstain 0.00% (Unanimous Strong Consensus)

Rationale: Most of the current literature that evaluated the risk of venous thromboembolism (VTE) after musculoskeletal oncology procedures were for primary and metastatic tumors involving the lower extremities²¹⁻³⁴. In studies that administered only mechanical prophylaxis or only had a low proportion of patients that received pharmacologic thromboprophylaxis, the VTE rates (2.7% – 23.4%) were higher when compared with studies that administered pharmacologic prophylaxis in most or all of the patients (1.1 – 6.3%)^{21-28,30-34}. However, clinical heterogeneity (e.g., tumor characteristics, including primary or metastatic tumor, benign or malignant tumor, soft tissue or bone tumor, tumor location, type of surgical procedure, agents for thromboprophylaxis, a protocol for VTE surveillance) across studies made it difficult to have a direct comparison of VTE rates between patients who received pharmacologic thromboprophylaxis with those that did not receive prophylaxis.

Several studies have identified certain tumor characteristics or procedure types as risk factors for VTE events. These include prosthesis reconstruction procedures^{32,35}, tumors located in the pelvis²⁵, hip or thigh³³, and bone metastasis^{21,29}. Three large retrospective case series administered pharmacologic thromboprophylaxis in most of the patients (75.7% – 100%) and validated relatively low VTE rates (1.1% – 4.6%) following prosthesis reconstruction after resection of primary malignant and metastatic lower limb tumors (mostly, around hip and knee joints), suggesting that pharmacologic thromboprophylaxis was effective for these complex procedures²³⁻²⁵.

Three large, retrospective case series reported VTE rates in patients who had been surgically treated for skeletal metastasis, including spinal²² and non-spinal metastasis^{36,37}. Most of the patients (79% – 86%) received pharmacologic thromboprophylaxis. The overall VTE rates were high (6 – 11.4%)³⁶⁻³⁸. Risk factors for VTE included the presence of pulmonary metastasis³⁷, intraoperative desaturation³⁷, and longer surgery duration³⁸. The results for intramedullary nailing as a risk factor VTE were inconclusive^{36,37}. Despite the need for thromboprophylaxis in patients with high VTE risks, individualized evaluation and weighing the potential risk of bleeding with the benefits of thromboprophylaxis is required. For patients who are not able to receive pharmacologic prevention due to a high risk for bleeding, a combination of inferior vena cava filter and mechanical compression device might be an effective alternative^{32,39}.

Currently, there is a lack of high-quality studies to conclude a specific population with regards to tumor characteristics or procedure type that requires prophylaxis. However, there is some evidence to support that patients undergoing resection procedures for bone metastasis or procedures that involve prosthesis reconstruction require prophylaxis because of a higher VTE risk.

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4 - How should VTE prophylaxis protocols be adjusted for surgical repairs of pathological fractures or orthopaedic surgery in a patient with a history of malignancy or concurrent malignancy?

Response/Recommendation: Patients undergoing surgical repairs of pathological fractures or those undergoing orthopaedic surgery with a history of malignancy or concurrent malignancy are at high risk for development of venous thromboembolism (VTE). While guidelines may provide some guidance in terms of choice of chemical agent and duration, the current evidence base is insufficient in determining optimal prophylaxis strategies, especially in light of factors that may further impact VTE risk in this high-risk population such as primary tumor site.

Strength of Recommendation: Limited.

Delegates vote: Agree 92.86% Disagree 7.14% Abstain 0.0% (Strong Consensus)

Rationale: Major orthopaedic surgery, history of or concurrent malignancy, and major injury including fractures all represent independent risk factors for VTE^{40,41}. For major elective orthopaedic surgery, VTE rates of >2%^{42,43} have been reported while this can be up to 15% or higher (depending on

various factors such as concomitant treatment, age, and type of malignancy) for patients with a malignancy⁴⁴ and 2-13% among patients with a pathological fracture⁴⁵⁻⁴⁸. It is unclear to what extent these independent risk factors represent a combined additive VTE risk in patients undergoing surgical repair of pathological fractures or other orthopaedic surgery with a history of malignancy or concurrent malignancy.

Given the co-existence of several individual risk factors, it is clear that this patient population should be considered at high risk of VTE⁴⁹. However, arguably the most commonly cited VTE prophylaxis guideline specific to orthopaedic surgery, published by the American College of Chest Physicians (ACCP)⁴³, does not provide clear guidance on prophylactic strategies for these patients. Moreover, while the American Academy of Orthopaedic Surgeons (AAOS) guideline includes studies that acknowledge cancer as a risk factor for VTE, it is solely focused on elective hip and knee arthroplasty surgery⁵⁰. Some risk-stratified guidance does exist in the ACCP guideline for VTE prophylaxis in non-orthopaedic surgical patients⁵¹ recommending pharmacologic prophylaxis with low-molecular-weight heparin (LMWH), (Grade 1B) or low-dose unfractionated heparin (Grade 1B) over no prophylaxis with the suggested addition of mechanical prophylaxis with elastic stockings or intermittent pneumatic compression (Grade 2C) for patients at high risk for VTE but not at high risk for major bleeding complications. For high-risk patients undergoing abdominal or pelvic surgery for cancer, extended-duration postoperative, pharmacologic prophylaxis (4 weeks) is recommended (Grade 1B).

The preference for LMWH, extended duration of prophylaxis (up to 35 days) and concomitant use of intermittent pneumatic compression is reflected in the ACCP guideline for VTE prophylaxis in orthopaedic surgical patients, for those with the highest VTE risk⁴³. This is also reflected in guidance from the United Kingdom's National Institute for Health and Care Excellence (NICE) with a recommended duration of one month and the addition of fondaparinux as an option for highest-risk orthopaedic surgeries⁵².

Overall, the most common long-bone pathologic fractures include femur, tibia and humerus fractures⁵³. The sparse literature focusing on VTE and prophylaxis in this specific patient population includes only a handful of observational studies^{45,46,54}, almost none including a comparison between chemical prophylaxis strategies. For example, Shallop et al., retrospectively reviewed VTE rates and prophylaxis among 287 patients with impending or pathologic long-bone fractures stabilized with intramedullary nailing⁵⁴. They found that LMWH (60.4% of cases) and warfarin (16.7% of cases) were the most commonly used chemical agents and protocols in all included centers directed chemical VTE prophylaxis for two weeks postoperatively. Importantly, the type of anticoagulant used was not associated with development of VTE, suggesting either a likely underpowered study (given the low number of VTE events) or the limited utility of the utilized chemical prophylaxis strategies to

impact VTE risk in this high-risk population⁵⁴. There was also no relationship between VTE prophylaxis and wound complications⁵⁴. One factor that did impact VTE risk was primary histology, with higher VTE risks seen in patients with a primary tumor of the lung⁵⁴.

Similarly, in a cohort of 85 lower limb pathologic fractures, Mioc et al., found LMWH to be the most commonly used prophylactic agent, and no association between type of agent and deep venous thrombosis (DVT) (pulmonary embolism [PE] was not considered), further suggesting that "a more aggressive prophylactic protocol should be used" in these patients⁴⁵.

In conclusion, while it is clear that patients with a (history of) malignancy undergoing orthopaedic surgery, or specifically, surgical repair of a pathological fracture, are at high risk for VTE, the current evidence base does not support a clear VTE prophylaxis strategy. Evidence-based guidance is lacking on the type of agent, duration of prophylaxis, and how to modify options based on additional risk factors such as site of primary tumor. There is some guidance from current guidelines, however, prospective comparative studies are needed to refine recommendations.

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Appendix

 Supporting material provided by the authors is posted with the online version of this article as a data supplement at [jbjs.org \(http://links.lww.com/JBJS/G809\)](http://links.lww.com/JBJS/G809).

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