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**Appendix**

**1 -** **VTE in Bone Metastasis**

Rationale

1. ﻿Nomogram for Predicting the Postoperative Venous Thromboembolism in Spinal Metastasis Tumor: A Multicenter Retrospective Study
   1. ﻿There were 49 patients (11.9%) diagnosed with VTE within 90 days after spinal metastasis surgery
   2. ﻿Univariate logistic regression analysis showed that gender (P=0.628), age (P=0.903), primary tumor type (P=0.329, P=0.817), tumor location (P=0.296, P=0.937), number of spinal metastases (P=0.880), BMI (P=0.466, P=0.566), surgical procedure (P=0.672, P=0.223), preoperative radiotherapy (P=0.345), and preoperative chemotherapy (P=0.880) were not statistically significant
   3. ﻿preoperative Frankel score (OR=2.68, 95% CI 1.78- 4.04, P=0.001), blood transfusion (OR=3.11, 95% CI 1.61-6.02, P=0.041), Charlson comorbidity index (OR=2.01, 95% CI 1.27- 3.17, P=0.013; OR=2.29, 95% CI 1.25-4.20, P=0.017), and operative time (OR=1.36, 95% CI 1.14-1.63, P=0.001).
   4. ﻿As the operative time increases by 1 hour, the risk of postoperative VTE will increase by 36%
   5. ﻿Patients who have blood transfusion have three times the risk of suffering from VTE
   6. ﻿Charlson Comorbidity Index have been proven to be high-risk factors for postoperative VTE, including age (7), diabetes (32), cerebrovascular disease (33), solid tumors (22), and hemiplegia (6, 7). Therefore, we can completely believe that the Charlson Comorbidity Index can predict the arrival of VTE.
2. ﻿Symptomatic Venous Thromboembolism in Patients with Malignant Bone and Soft Tissue Tumors: A Prospective Multicenter Cohort Study
   1. ﻿Univariate analysis of risk factors for sVTE indicated that ischemic heart disease as a comorbidity (p = 0.018), maximum tumor diameter (p = 0.0061), bed rest after surgery (p = 0.050), and elevated preoperative platelet count (p = 0.0003) were significantly associated
   2. ﻿Multiple logistic regression analyses revealed that ischemic heart disease (odds ratio [OR] 8.28), maximum tumor diameter exceeding 8 cm (OR 4.35), and elevated preoperative platelet count (OR 7.92) were independent risk factors for sVTE
3. ﻿Adverse Events following Intramedullary Nailing in Metastatic Pathological versus Non-Pathological Femoral Shaft Fractures: A Retrospective Comparative Study
   1. No data about VTE
4. ﻿Optimal Treatment Approaches of Cancer- Induced Thrombosis (Expert Analysis, LOE V)
5. ﻿﻿Thromboembolic Disease in Patients with Metastatic Femoral Lesions: A Comparison Between Prophylactic Fixation and Fracture Fixation (Retrospective cohort)
   1. ﻿prophylactic fixation group had a significantly higher rate of PE than the pathological fracture group (2.1% compared with 1.2%; p = 0.008), with an odds ratio of approximately 2.0
   2. ﻿Univariate analysis indicated that the prophylactic fixation group ﻿had a significantly higher rate of DVT than those in the pathological fracture group (3.2% compared with 2.2%; p = 0.03)
6. ﻿Timing of Prophylactic Anticoagulation and Its Effect on Thromboembolic Events After Surgery for Metastatic Tumors of the Spine
   1. ﻿The average age for all patients was 57 years and 62% were male
   2. ﻿The rate of VTE was 9.1% in the early group (days 1–3) and 35.7% in the delayed group (26.6% absolute risk reduction; P=0.049)
   3. ﻿analysis showed that the delayed group did have a significantly higher risk of VTE compared with the early group (OR 6.43; 95% CI, 1.01–41.2; P=0.049).
7. ﻿The current status of prophylactic femoral intramedullary nailing for metastatic cancer (Expert Review)
8. ﻿Venous and Arterial Thromboembolism in Patients With Cancer (Expert Review)
9. ﻿Thromboembolism After Intramedullary Nailing for Metastatic Bone Lesions (Retrospective cohort)
   1. ﻿significantly increased risk of the development of VTE overall in patients with lung-cancer histology (OR = 7.49 [95% CI =1.56 to 36.07]; p = 0.012)
   2. ﻿The overall rate of wound complications was 3.3%. Although we did not find a relationship between the anticoagulant used and the development of wound complications
10. ﻿High Risk of Venous Thromboembolism After Surgery for Long Bone Metastases: A Retrospective Study of 682 Patients
    1. ﻿Symptomatic VTE was diagnosed in 6% (44 of 682) of patients; 22 had a PE and 22 had a DVT (Table 3). The median age of the 44 patients was 62 years
    2. ﻿**two factors were independently associated with, respectively, increased and decreased risk of symptomatic VTE development: longer duration of hospitalization (OR, 1.06; 95% CI, 1.02–1.11; p = 0.006) and higher preoperative hemoglobin levels** (OR, 0.75; 95% CI, 0.60–0.93; p = 0.011; Table 4)
    3. ﻿Patients who had a symptomatic VTE within 90 days had lower 1-year survival than did those without symptomatic VTE ﻿(27% [95% CI, 14%–40%] and 39% [95% CI, 35%–43%]; p = 0.041)
11. ﻿ ﻿Deep vein thrombosis following the treatment of lower limb pathologic bone fractures – a comparative study. (Retrospective cohort†)
    1. We noticed that it is highly unlikely for patients with intramedullary nails to develop DVT compared to patients with knee prostheses (OR = 0.11, RR = 1.16).
    2. ﻿Adjuvant therapy in relation with DVT events proved significant (OR = 12.62, RR = 10.08).
    3. There was no statistical significance found ﻿when correlating DVT events with the type of anticoagulation (OR = 0.21, RR = 0.98)
    4. and the amount of blood transfusion units required (OR = 0.14, RR = 0.77).
12. ﻿What Impact Does Venous Thromboembolism and Bleeding Have on Cancer Patients’ Quality of Life?
    1. Overall risk VTE incidence rate from eight studies combining data from high-risk samples was 68.0 per 1,000 person-years (95% CI, 48.0 to 96.4; heterogeneity I2 = 93.4%), with average follow-up durations ranging from 1 mo to 26 mo.
    2. Cancers of the pancreas (59 per 1,000 person-years) and brain (48 per 1,000 person-years) were associated with the greatest and second greatest risk of VTE among average-risk patients
    3. the risk of VTE among all cancer patients receiving high-risk treatment increased slightly to 72.7 per 1,000 person-years (95% CI, 44.2 to 119.5)
    4. There were insufficient numbers of studies comprising patients receiving anticoagulants to perform an equivalent analysis for other cancer types.
13. ﻿Screening for Occult Cancer in Unprovoked Venous Thromboembolism
    1. occult cancers (26%; 95% CI, 9 to 51) were missed by the strategy of limited screening plus CT (P=1.0)
    2. occult cancers (29%; 95% CI, 8 to 58) were missed by the limited screening strategy
    3. missed occult cancer over the 1-year follow- up period indicated no significant between- group difference (log-rank chi-square test with 1 degree of freedom, 0.03; P = 0.87)
    4. Patients with unprovoked venous thrombo- embolism and a negative screening result for occult cancer with the limited screening strategy had an incidence of cancer diagnosis of 0.93% (95% CI, 0.36 to 2.36) over the following year
14. ﻿Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update
    1. ﻿Clinical Question 1. Should hospitalized patients with cancer receive anticoagulation for VTE prophylaxis?
       1. Recommendation 1.1. Hospitalized patients who have active malignancy and acute medical illness or reduced mobility should be offered pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).
       2. Recommendation 1.2. Hospitalized patients who have active malignancy without additional risk factors may be offered pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications (Type: evidence based; Evidence quality: low; Strength of recommendation: moderate).
       3. Recommendation 1.3. Routine pharmacologic thromboprophylaxis should not be offered to patients admitted for the sole purpose of minor procedures or chemotherapy infusion, nor to patients undergoing stem-cell/ bone marrow transplantation (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).
    2. Clinical Question 2. Should ambulatory patients with cancer receive anticoagulation for VTE prophylaxis during systemic chemotherapy?
       1. Recommendation 2.1. Routine pharmacologic thromboprophylaxis should not be offered to all outpatients with cancer (Type: evidence based; Evidence quality: intermediate to high; Strength of recommendation: strong).
       2. Recommendation 2.2. High-risk outpatients with cancer (Khorana score of 2 or higher prior to starting a new systemic chemotherapy regimen) may be offered thromboprophylaxis with apixaban, rivaroxaban, or low- molecular-weight heparin (LMWH) provided there are no significant risk factors for bleeding and no drug interactions. Consideration of such therapy should be accompanied by a discussion with the patient about the relative benefits and harms, drug cost, and duration of prophylaxis in this setting (Type: evidence based; Evidence quality: intermediate to high for apixaban and rivaroxaban, intermediate for LMWH; Strength of recommendation: moderate).
       3. Recommendation 2.3. Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should be offered pharmacologic thromboprophylaxis with either aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).
    3. Clinical Question 3. Should patients with cancer undergoing surgery receive perioperative VTE prophylaxis?
       1. Recommendation 3.1. All patients with malignant disease undergoing major surgical intervention should be offered pharmacologic thromboprophylaxis with either unfractionated heparin (UFH) or LMWH unless contraindicated because of active bleeding, or high bleeding risk, or other contraindications (Type: evidence based; Evidence quality: high; Strength of recommendation: strong). ﻿
       2. Recommendation 3.2. Prophylaxis should be commenced preoperatively (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).
       3. Recommendation 3.3. Mechanical methods may be added to pharmacologic thromboprophylaxis but should not be used as monotherapy for VTE prevention unless pharmacologic methods are contraindicated because ﻿of active bleeding or high bleeding risk (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).
       4. Recommendation 3.4. A combined regimen of pharmacologic and mechanical prophylaxis may improve efficacy, especially in the highest-risk patients (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).
       5. Recommendation 3.5. Pharmacologic thromboprophylaxis for patients undergoing major surgery for cancer should be continued for at least 7 to 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 surgery for cancer who have high-risk features, such as restricted mobility, obesity, history of VTE, or with additional risk factors. In lower-risk surgical settings, the decision on appropriate duration of thromboprophylaxis should be made on a case-by-case basis (Type: evidence based; Evidence quality: high; Strength of recommendation: moderate to strong).
    4. ﻿Clinical Question 4. What is the best method for treatment of patients with cancer with established VTE to prevent recurrence?
       1. Recommendation 4.1. Initial anticoagulation may involve LMWH, UFH, fondaparinux, or rivaroxaban. For patients initiating treatment with parenteral anticoagulation, LMWH is preferred over UFH for the initial 5 to 10 days of anticoagulation for the patient with cancer with newly diagnosed VTE who does not have severe renal impairment (defined as creatinine clearance less than 30 mL/min) (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).
       2. Recommendation 4.2. For long-term anticoagulation, LMWH, edoxaban, or rivaroxaban for at least 6 months are preferred because of improved efficacy over vitamin K antagonists (VKAs). VKAs are inferior but may be used if LMWH or direct oral anticoagulants (DOACs) are not accessible. There is an increase in major bleeding risk with DOACs, particularly observed in GI and potentially genitourinary malignancies. Caution with DOACs is also warranted in other settings with high risk for mucosal bleeding. Drug-drug interaction should be checked prior to using a DOAC (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).
       3. Recommendation 4.3. Anticoagulation with LMWH, DOACs, or VKAs beyond the initial 6 months should be offered to select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy. Anticoagulation beyond 6 months needs to be assessed on an intermittent basis to ensure a continued favorable risk-benefit profile (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak to moderate). Recommendation
       4. 4.4. Based on expert opinion in the absence of randomized trial data, uncertain short-term benefit, and mounting evidence of long-term harm from filters, the insertion of a vena cava filter should not be offered to patients with established or chronic thrombosis (VTE diagnosis more than 4 weeks ago), nor to patients with temporary contraindications to anticoagulant therapy (eg, surgery). There also is no role for filter insertion for primary prevention or prophylaxis of pulmonary embolism (PE) or deep vein thrombosis due to its long-term harm concerns. It may be offered to patients with absolute contraindications to anticoagulant therapy in the acute treatment setting (VTE diagnosis within the past 4 weeks) if the thrombus burden was considered life-threatening. Further research is needed (Type: informal consensus; Evidence quality: low to intermediate; Strength of recommendation: moderate).
       5. Recommendation 4.5. The insertion of a vena cava filter may be offered as an adjunct to anticoagulation in patients with progression of thrombosis (recurrent VTE or extension of existing thrombus) despite optimal anticoagulant therapy. This is based on the panel’s expert opinion given the absence of a survival im- provement, a limited short-term benefit, but mounting evidence of the long-term increased risk for VTE (Type: informal consensus; Evidence quality: low to intermediate; Strength of recommendation: weak).
       6. Recommendation 4.6. For patients with primary or metastatic CNS malignancies and established VTE, anti- coagulation as described for other patients with cancer should be offered, although uncertainties remain about choice of agents and selection of patients most likely to benefit (Type: informal consensus; Quality of evidence: low; Strength of recommendation: moderate). ﻿Recommendation
       7. 4.7. Incidental PE and deep vein thrombosis should be treated in the same manner as symptomatic VTE, given their similar clinical outcomes compared with patients with cancer with symptomatic events (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate). ﻿Recommendation
       8. 4.8. Treatment of isolated subsegmental PE or splanchnic or visceral vein thrombi diagnosed incidentally should be offered on a case-by-case basis, considering potential benefits and risks of anti- coagulation (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate)
    5. ﻿ClinicalQuestion 5. Should patients with cancer receive anticoagulants in the absence of established VTE to improve survival?
       1. Recommendation 5. Anticoagulant use is not recommended to improve survival in patients with cancer without VTE (Type: evidence based; Evidence quality: high; Strength of recommendation: strong)
    6. ﻿Clinical Question 6. What is known about risk prediction and awareness of VTE among patients with cancer?
       1. Recommendation 6.1. There is substantial variation in risk of VTE between individual patients with cancer and cancer settings. Patients with cancer should be assessed for VTE risk initially and periodically thereafter, particularly when starting systemic antineoplastic therapy or at the time of hospitalization. Individual risk factors, including biomarkers or cancer site, do not reliably identify patients with cancer at high risk of VTE. In the ambulatory setting among patients with solid tumors treated with systemic therapy, risk assessment can be conducted based on a validated risk assessment tool (Khorana score; Table 1) (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 6.2. Oncologists and members of the oncology team should educate patients regarding VTE, particularly in settings that increase risk, such as major surgery, hospitalization, and while receiving systemic antineoplastic therapy (Type: informal consensus; Evidence quality: insufficient; Strength)

**2 - For Primary Bone Tumours/Sarcoma Patients**

**Search Terms**

((((((orthopedic procedure[MeSH Terms]) OR (orthopedic procedures[MeSH Terms])) OR (orthopedic procedure)) OR (orthopedic procedures)) OR (orthopaedic procedures)) OR (orthopaedic procedure)) AND ("Venous Thromboembolism"[Mesh] OR "Venous Thrombosis"[Mesh] OR "pulmonary embolism" OR "deep vein thrombosis") AND (((Prevention and Control[MeSH Subheading]) OR (prevention[Title/Abstract])) OR (prevent\*[Title/Abstract]) OR (prophylaxis[tw])) AND (((("Neoplasms"[Mesh] AND musculoskeletal) OR "Soft Tissue Neoplasms"[Mesh]) OR ("Bone Neoplasms"[Mesh]) OR ("Muscle neoplasm"[Mesh]) OR (bone metastasis) OR (soft-tissue sarcoma)) NOT "Skull Neoplasms"[Mesh])

*Total Results:*

31 Results Found, 18 excluded, 1 added, total of 14 papers reviewed

*Inclusion*

* Bone tumours
* Soft tissue sarcomas
* Years 1990 to present

*Exclusion*

* Skull tumours
* Other soft tissue tumours

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

**Search Terms**

(Orthopedic) AND (Musculoskeletal tumor OR Tumor OR Sarcoma OR Oncology OR Neoplasms OR Metastasis) AND (("Venous Thromboembolism"[Mesh]) OR ("Venous Thrombosis"[Mesh]) OR ("Pulmonary Embolism"[Mesh]) OR (pulmonary embolism OR pulmonary embolus OR pulmonary thromboembolism) OR (Venous Thrombosis OR Venous Thromboses OR Venous Thromboembolism) OR (Deep Venous Thrombosis OR Deep Venous Thromboses OR Deep Vein Thrombosis OR Deep Vein Thromboses) OR (PE OR VTE OR DVT OR Blood Clot OR Blood Clots)) AND ((VTE Prophylaxis OR Thromboprophylaxis) OR ("Anticoagulants"[Mesh] OR Anticoagulants OR Anticoagulant OR anticoagulation OR anti-coagulation OR Antithrombins OR Factor Xa Inhibitor OR Factor Xa Inhibitors) OR (Thrombin Inhibitor OR Thrombin Inhibitors) OR ("Heparin"[Mesh] OR Heparin OR Dalteparin OR Enoxaparin OR Nadroparin OR Tinzaparin) OR ("Warfarin"[Mesh] OR Warfarin OR Coumadine OR Coumadin) OR ("Aspirin"[Mesh] OR Aspirin))

*Total Results:*

173 Results Found.*Inclusion*

* Patients with surgically treated primary benign, malignant, or metastatic musculoskeletal tumors
* Stated primary or secondary study objective: incidence of venous thromboembolism, deep vein thrombosis or pulmonary embolism
* Original article
* English article

*Exclusion*

* Case reports, systematic or narrative reviews, letters to the editor, commentary or in vitro studies
* Not in English

**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?**

**Search Terms**

("Venous Thromboembolism"[Mesh] OR "Venous Thrombosis"[Mesh] OR "pulmonary embolism"[tw] OR "deep vein thrombosis"[tw]) AND (("Fractures, Bone"[Mesh] AND (("Neoplasm Metastasis"[Mesh]) OR metastasis[tw])) OR (pathological fracture [tw]))

*Total Results:*

36 Results Found, after applying inclusion/exclusion criteria 1 result, an additional reference was added after scanning references of the included study.

*Inclusion*

* Cohort including patients undergoing orthopaedic surgery with history of malignancy or concurrent malignancy, or, more specifically, surgical repair of a pathological fracture
* At least one chemoprophylactic agent described
* Venous thromboembolism rates reported (either pulmonary embolism, deep venous thrombosis or both)
* English articles

*Exclusion*

* Not in English