Venous thromboembolism syndrome in gynecological cancer

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Venous thromboembolism (VTE) could be presented as an initial clinical feature in some cancer patients or a complication followed by various cancer treatments, which all indicates a poor outcome. This review focuses on elucidating the relationship of VTE and the main gynecological cancers including ovarian, endometrial, and cervical cancers. First, the general VTE information about gynecological cancer are introduced; second, the risk factors of VTE developing in gynecological cancer were discussed; third, we do a retrospective analysis on a novel treatment targeting coagulation cascade; and last, we analyze VTE as a remarkable complication followed by recombinant human erythropoietin and anti–vascular endothelial growth factor treatment in gynecological cancer patients. In summary, the interaction between the coagulation system and cancer progression is a novel promising area to be explored in the study of VTE in patients with gynecological cancer.

KEYWORDS: antiangiogenic, gynecology, VEGF, venous thromboembolism.

The history of a known association between coagulation and cancer dates back to 1865, when Armand Trousseau observed that patients who presented idiopathic venous thromboembolism (VTE) frequently had underlying occult gastric and pancreatic cancers(1). The two types of VTE associated with cancer are idiopathic, or primary VTE, in which the patients have occult cancer but present with VTE symptoms first, and secondary VTE, in which the patients with a diagnosed cancer develop VTE later, during their treatment or disease progression. These abnormalities can be found during autopsy in more than 50% of cancer patients(2). Both types of VTE indicate a poor outcome in cancer patients. This interaction of VTE and cancer has only recently become more apparent.

In the past several decades, a series of retrospective studies have shown an increasing incidence of cancer in patients with idiopathic VTE (average incidence, 6.5–16.5%) compared with that in patients without idiopathic VTE or those with secondary VTE (1.8–7.1%).(3–8) Notably, two other large retrospective analyses demonstrated that the incidence of cancer increased during the first year following the diagnosis of VTE, and the effect persisted for up to 10 years(9,10). After the data from two large population-based studies were pooled and the thrombotic status of 3069 patients was determined, the first-year incidence of various types of cancer was calculated(9–11). Prostate cancer was the most frequent (13.5%), followed by cancer of the lung (10.5%), colon (8.6%), pancreas (7.3%), gastrointestinal tract (5.9%), ovaries (5.6%), and uterus (2%)(11).

In one most recent prospective studies, 3220 patients aged 18–70 years who were first diagnosed with deep venous thrombosis (DVT) or pulmonary embolism (PE) were matched with 2131 control participants(12). The overall risk of VTE was increased sevenfold in the patients who had malignancies compared with persons without malignancies. Patients with hematologic malignancies had the highest risk of developing VTE.
VTE and gynecological cancer

The three major gynecological cancers (ovarian, endometrial, and cervical) have all been shown to be associated with VTE\(^1\),\(^2\),\(^7\)\(^,\)\(^8\), but there has never been a reported large retrospective study so far. We only get the data from the study on VTE and multiple types of cancer. One retrospective study indicated a significant relationship between idiopathic VTE and the later development of a malignancy\(^9\). Of 145 patients with idiopathic VTE who had no evidence of a coexisting cancer, 11 (7.6%) were subsequently diagnosed with cancer. One of these 11 patients was diagnosed with ovarian cancer within 12 months. The incidence of cancer in the patients with recurrent idiopathic venous thrombosis was higher than that in the patients with secondary (thrombosis associated with a well-recognized risk factor other than cancer) venous thrombosis \(P = 0.008\); OR, 9.8) or in the patients with idiopathic venous thrombosis that did not recur \(P = 0.024\); OR, 4.3)\(^8\).

Generally, studies have confirmed that cancer patients who were diagnosed with VTE have a worse prognosis than malignant patients without VTE\(^1\)\(^9\),\(^2\)\(^0\). Morgan et al.\(^1\)\(^8\) investigated 95 patients who had ovarian, endometrial, and cervical cancers with concurrent VTE, but only 74 patients have adequate data to follow up. VTE was diagnosed within 3 months of surgery in 28 patients (28/74, 38%), within 3 months of radiation in 32 patients (32/74, 43%), and within 3 months of chemotherapy in 25 patients (25/74, 34%). Forty-three patients (43/95, 45%) were diagnosed with VTE at the time of their cancer presentation. The other patients (52/95, 55%) were diagnosed with VTE at the time of recurrence or progression of disease. The median survival of all patients from the time of VTE diagnosis was 7.8 months, with only about 20% of patients surviving 5 years\(^1\)\(^8\). Univariate analysis showed that survival was significantly worse for patients with cervical cancer and for those treated with radiotherapy within 3 months of the diagnosis of VTE. Multivariate analysis showed a twofold increased risk of death due to VTE\(^1\)\(^8\). The survival of patients with DVT from the time of cancer diagnosis was significantly worse than that of a matched control group without DVT\(^1\)\(^8\).

Another large retrospective analysis included 451 patients with gynecological cancer, 177 patients with corresponding preoperative benign tumors, and 112 healthy women as controls. This study analyzed the clinical parameters associated with blood clotting preoperatively, which include red blood cell aggregation, plasma viscosity (pv), and the levels of the hematocrit, hemoglobin, leukocytes, platelets, and fibrinogen\(^1\)\(^7\). pv was a significant risk factor for overall survival (OS) in patients with ovarian cancer \(P = 0.02\) and for subsequent thrombosis in patients with ovarian \(P = 0.02\) and cervical cancers \(P = 0.007\). Notably, the aggregation of red blood cells was significantly higher in the cancer patients than in the controls. These results were consistent with those in the previous studies of ovarian cancer\(^2\)\(^1\). In patients with gynecological cancer, the combination of an increased red blood cell aggregation and high pv impair blood flow and put patients at risk for a prothrombotic status, which can induce hypoxia in the microcirculation. The low concentration of oxygen in the tumors of patients with cervical cancer can make tumor cells resistant to radiotherapy and is a poor prognostic factor for OS\(^2\)\(^2\). Hypoxia in the microenvironment favors thrombosis and then promotes tumor cell proliferation and metastasis\(^2\)\(^3\),\(^2\)\(^4\).

Current studies focus mostly on the prevention of secondary VTE in patients with gynecological cancer, that is, those who develop DVT or PE during their cancer treatment or disease progression. DVT and PE are major complications that result in significant morbidity and mortality after surgery for gynecological malignancies. DVT has been observed postoperatively in approximately 38% of patients with gynecological cancer\(^2\)\(^5\). PE, which accounts for 3% of all deaths following surgery for gynecological cancer\(^2\)\(^6\), is the leading cause of postoperative death in high-risk patients with ovarian, cervical, and endometrial cancers\(^2\)\(^7\).

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Prophylaxis against DVT should therefore be used in an effort to decrease the incidence of PE. In addition, the incidence of recurrent DVT and postthrombotic syndrome may be as high as 28% in patients with ongoing risk factors such as cancer; so, gynecological oncologists are investigating the best prophylaxis for patients with VTE. This has been shown that 5000 units of low-dose, unfractionated heparin (UFH) given subcutaneously every 8 h, significantly lowers the rate of postoperative thromboembolic events, which is more efficacious than the same dose given subcutaneously every 12 h, because there is no risk of postoperative bleeding. A subsequent investigation revealed that external pneumatic compression and low–molecular weight heparin (LMWH) could provide similar clinical prevention for VTE. In the next section, we will discuss VTE and ovarian, endometrial, and cervical cancers.

VTE and ovarian cancer

Compared with endometrial and cervical cancers, ovarian cancer is probably the one that patients most likely presented with VTE symptoms. Most thromboembolisms occur in the venous system; however, arterial thromboembolism and recurrent VTE also have been reported. The mechanism by which VTE develops in patients with ovarian cancer before or after treatment is not well understood. However, many clinical parameters about coagulation activation have shown that patients with ovarian cancer have an increased susceptibility to VTE. For example, elevated concentrations of cross-linked fibrin degradation products and D dimers were found frequently in the plasma, ascites fluid, and cystic fluid of the ovary in patients with ovarian cancer. Cross-linked fibrin staining has been detected in the tumors and ascites fluid of the peritoneum but has not been observed in the peritoneal wall, diaphragm, mesentry, or bowel serosa of the normal controls. Vascular endothelial growth factor (VEGF) can contribute to extravascular fibrin clotting in a tumor environment by promoting the leakage of plasma fibrinogen into extravascular spaces, where the fibrinogen clots. Fibrin in the tumor or elsewhere in the peritoneum and serosa might help stimulate the new ingrowth of blood vessels. This fibrin gel matrix might also help provide the matrix that facilitates the ingrowth of macrophages and fibroblasts and reorganizes the stroma, preparing it for tumor metastasis to the abdominal cavity. It is interesting that plasma exudates that contribute to ascites, generally remain fluid and do not form an insoluble fibrin gel until they are removed from the patient.

In a recent study, we compared the transcriptional profile of a normal-appearing peritoneum and its adherent and subjacent stroma in patients with epithelial ovarian cancer with that in patients with pathologically benign ovarian disease. Interestingly, some genes included in this study were linked to the coagulation pathway, inflammatory response, activation of macrophages, and endothelial cells (ECs). It has been suggested that the following coagulation factors and regulatory proteins are upregulated in the peritoneum of patients with ovarian cancer: Factor XII, Factor XI, Factor XIII, Factor II–Factor II receptor (thrombin receptor, also called proteinase activated receptor [PAR]), Factor VII, Factor X, Factor I (fibrinogen), fibrin, heparin cofactor II, and endothelial protein-C receptor. These factors are thought to play an important role in tumor cell invasion, metastasis, and the formation of ascites. The reason for the activation of a coagulation cascade in ovarian cancer is not known, but a previous study showed that tumors associated with activated monocytes/macrophages and ECs themselves appear to be capable of initiating thrombin (Factor II) generation and fibrin degradation.

In one retrospective study of VTE and ovarian cancer, two (2/60) patients presented clinically with lower-extremity thrombosis before being diagnosed with ovarian cancer, which is consistent with a previous study in which some patients with VTE had an insidious process of ovarian cancer. Similarly, the incidence of VTE after treatment for ovarian cancer is also not known. In one study, the rate of VTE in the postoperative period was 15%. Only 6.7% of VTEs occurred during the period of heparin administration; whereas after heparin administration, 8.3% of VTEs could occur from the 8th to 29th postoperative day.

Another randomized controlled trial of low-dose heparin prophylaxis showed that the incidence of VTE during the 42 days after major surgery for ovarian cancer was 10.7% (3/28) with prophylaxis and 13.6% (3/22) without prophylaxis. VTE had a later onset and particularly high incidence after the seventh postoperative day. The incidence of VTE during the period of chemotherapy was only 10.6% (5/47), which included four patients between the first and third cycle and one after the fourth cycle of chemotherapy. There were no other data about the incidence of VTE during chemotherapy for ovarian cancer. However, in two studies of breast cancer, the incidence of VTE ranged from 0.8% to 6.8% during therapy with adjuvant cyclophosphamide/methotrexate/fluorouracil and from 2.1% to 10% when anthracycline regimens
were administered\(^{(50)}\). Several mechanisms for chemotherapy-induced thrombosis have been discussed, including reduced levels of antithrombin or protein C\(^{(51)}\) and damage to the endothelium, resulting in the reduced functioning of anticoagulant ECs or release of procoagulants from the destroyed tumor cells\(^{(52)}\).

Because patients with ovarian cancer who are receiving surgery or chemotherapy are susceptible to VTE, one question has arisen: how to monitor the VTE by screening their coagulation test. One study that measured the levels of fibrinogen, D dimer, plasminogen activator inhibitor, antithrombin, and protein in patients with ovarian cancer before and after cancer treatment\(^{(15)}\) found that only the mean levels of D dimer \((P < 0.0001)\) and fibrinogen \((P < 0.05)\) were significantly higher in patients who later died of cancer \((n = 17)\) than in those who remained alive \((n = 41)\). A univariate analysis found that the levels of D dimer and fibrinogen were significant risk factors in reducing OS for these patients\(^{(15)}\).

The D dimer is a very useful hemostatic parameter that can gauge ongoing fibrin formation and degradation in some diseases, including ovarian cancer\(^{(15,35,53–55)}\). The elevated levels of D dimer in plasma and ascites fluid suggested that the fibrin cascade had been activated and that excessive levels of fibrin had been found in the peritoneal cavity of patients with ovarian cancer, which is considered important for tumor metastasis and the development of ascites\(^{(40–42)}\). One study showed that high levels of D dimer were found in the draining vein of an ovarian tumor, which was consistent with the finding of fibrin deposits in the tumor stroma\(^{(56)}\).

Another recent study found that an acute elevation in the level of plasma D dimer was associated with the rupture of an ovarian endometriotic cyst, a usually benign ovarian disease that can sometimes become malignant. Overexpression of the plasma D dimer might reflect the activation of the local coagulation cascade in an ovarian cyst and induce a local inflammatory response in the peritoneal cavity\(^{(57)}\). Inflammation in the peritoneum of patients with ovarian cancer has been considered an important mechanism of tumor metastasis and ascites formation\(^{(58)}\). Therefore, the D dimer was suggested as a prognostic factor that was associated with a poor clinical outcome\(^{(15,35,54,59,60)}\) (Table 1). It seems that the relative levels of CA125 and D dimer, in particular, are very useful diagnostic markers for screening for disease\(^{(53,55)}\) and discriminating benign from malignant ovarian disease\(^{(53)}\). For example, one study observed that the combination of a decrease in CA125 levels with an increase in D dimer levels during treatment makes it possible to identify a subset of patients with a more favorable prognosis\(^{(55)}\).

There were also studies that showed a negative association of the D dimer and ovarian cancer\(^{(61,62)}\). The inconsistent results might be due to different method of detection, samples sites, and patients’ status.

Other coagulation markers, such as fibrinogen, antithrombin, and pv have been associated with ovarian cancer (Table 1). All coagulant markers indicate that the coagulation cascade is activated in a peripheral system and local tumor site, and these markers could play an important role in tumor metastasis, invasion, and the development of ascites because of their association with poor prognosis in patients with ovarian cancer. However, because the above mentioned studies included so few patients, many more randomized studies should be performed to confirm this hypothesis, which could pave the way to targeting coagulation cascade as a strategy for preventing and treating ovarian cancer.

### VTE in endometrial and cervical cancers

No studies have examined the incidence of VTE in patients before they were diagnosed with endometrial or cervical cancers so far. In one review paper, the author stated that the rate of occult uterus cancer in patients with VTE is 2%, but it is not known whether this includes cervical cancer\(^{(11)}\). However, according to some previous studies, some patients with endometrial and cervical cancers could develop VTE after surgery, chemotherapy, hormonal therapy, and radiotherapy\(^{(17,18)}\).

One group that investigated blood rheology and thrombosis preoperatively found that mean pv was significantly higher in patients with endometrial \((P < 0.001; n = 70; pv, 1.37 vs 1.25)\) and cervical cancers \((P = 0.004; n = 52; pv, 1.33 vs 1.26)\) than in patients with the corresponding benign tumor and that pv was a significant risk factor for subsequent thrombosis in patients with cervical cancer \((P = 0.007)^{(17,18)}\). It suggested that patients with endometrial and cervical cancers were also susceptible to VTE.

Unquestionably, surgery is the most significant factor associated with postoperative VTE in patients with endometrial and cervical cancers. In some prospective studies that enrolled patients with cervical and endometrial malignancies who underwent surgery, postoperative VTE was reported in 7.8–17% of patients\(^{(27,63)}\) and accounted for four postoperative deaths in one study\(^{(27)}\). Another study showed that 4% of patients had PEs\(^{(63)}\). The identified risk factors for postoperative VTE in patients with endometrial and cervical cancers were weight in excess of 85.5 kg, advanced clinical stage of malignancy, and radiotherapy within 6 weeks of the operation\(^{(27)}\). Another recent study
Table 1. Common hemostatic markers in ovarian cancer

<table>
<thead>
<tr>
<th>Markers</th>
<th>Expression</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>D dimer</td>
<td>Increased expression in peripheral veins and arteries(^{(56)}), ascites(^{(28)}) and vein of tumor(^{(56)})</td>
<td>Prognostic marker with poor clinical outcome(^{(15,35,54,59,60)})</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Increased expression in plasma(^{(33)}) and tumor stroma(^{(41,139)})</td>
<td>Converted into fibrin and deposited to peritoneum(^{(41)})</td>
</tr>
<tr>
<td>Plasma viscosity</td>
<td>Increased levels in ovarian cancer</td>
<td></td>
</tr>
<tr>
<td>Antithrombin</td>
<td>Decreased expression in peripheral circulation</td>
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</tbody>
</table>

revealed similar risk factors for VTE; these included stage of disease, age more than 40, and length of surgery.\(^{(64)}\) Because pelvic lymphadenectomy for the surgical staging of endometrial cancer is essential, one study evaluated the complications in patients undergoing this surgery: 3.8% (5/133) of patients presented with VTE, including four DVTs and one PE cases.\(^{(65)}\) Therefore, VTE prophylaxis during surgery for gynecological cancer is important. The current strategies for prevention of VTEs include low-dose UFH and external pneumatic compression.\(^{(13,30,31,66)}\)

As a consequence of surgery, the hemostatic system becomes more active; therefore, the following mechanism has been proposed to explain how VTE develops after surgery. Direct surgical action could destroy the endothelium in the vessels, expose them to tissue factors (TFs), and activate the release of procoagulant cytokines, such as tumor necrosis factor \(\alpha\). Restricted postoperative mobility favors venous stasis, which damages the endothelial lining because of the reduced clearance of activated clotting factors and localized endothelial hypoxia. A preliminary study suggested that a thrombosis test, such as measuring the plasma levels of thrombin–antithrombin and fibrinogen \(1 + 2\), may be useful for identifying cancer patients at a particularly high risk of postoperative thrombosis.\(^{(67)}\) Unfortunately, although coagulation abnormalities are relatively common in patients with gynecological cancer, the preoperative predictors of VTE, such as prothrombin time, partial thromboplastin time, and the levels of fibrinogen and fragment D dimer, seem to provide very little useful clinical information.\(^{(64)}\) This may be due to the different cancer types and coagulation tests performed.

Chemotherapy and hormone therapy are the principal strategies for managing endometrial and cervical cancers. There have been so few studies on VTE occurring after chemotherapy so far, but in some recent phase III randomized trials of endometrial cancer, VTE development has been reported as a complication followed by chemotherapy.\(^{(68)}\) There have been no large prospective or retrospective studies to investigate the effect of VTE and chemotherapy on endometrial cancer, and similarly, few studies of cervical cancer and VTE are reported. VTE has also been reported in some clinical trials of hormone therapy for endometrial cancer, with the following incidences: 2/46 in a trial of goserelin\(^{(68)}\), 1/23 in a trial of anastrozole\(^{(69)}\), and 1/25 in a trial of leuprolide.\(^{(70)}\)

Surgery and radiotherapy are the standard care for most patients with cervical cancer, chemoradiotherapy is the current strategy for treating locally advanced cervical cancer (stage IIB–stage IVA), and systemic chemotherapy is used only for patients with recurrent or distant metastases.\(^{(71)}\) One study found that there were abnormalities in blood rheology in patients undergoing postoperative high-dose brachytherapy for uterine cancer, including endometrial and cervical cancers.\(^{(72)}\) Postoperatively, PEs decreased in patients with endometrial cancer and transiently increased in those with cervical cancer. After the third session of irradiation in both groups of patients, pv levels increased, and at the 6-month follow-up, pv levels were higher than those before surgery. Postoperatively, fibrinogen levels were increased and remained at high level throughout high-dose radiotherapy after loading for 6 months.\(^{(72)}\) VTE has been reported in studies of acute morbidity related to brachytherapy for cervical cancer and might be due to the bed rest and immobilization required for low-dose rate brachytherapy. It was estimated that there was a 1.2% incidence of VTE in 327 women receiving brachytherapy for a variety of gynecological
cancer\(^{(73)}\). One study evaluated the perioperative and postoperative complications of low-dose rate intracavitary radiotherapy in 4043 patients with FIGO stage I–III carcinoma of the cervix who received only definitive radiotherapy but not chemoradiation. Only 11 of these 4043 (0.3%) patients had documented or suspected cases of VTE: four died immediately, and the size of tumors of 9 in these 11 patients decreased within 15 months\(^{(74)}\). VTE has not been routinely reported as an adverse event during treatment for cervical cancer with definitive radiation; yet, it can be life threatening and involves significant morbidity. Patients who experience VTE are at risk for chronic postthrombotic syndrome, which is characterized by pain, edema, and venous ulceration in 30\% of cases\(^{(28)}\). Those various incidences of VTE during or after radiation might be due to different group of patients, radiation therapeutic strategy, tumor stage, and patients’ status.

The incidence of VTE in patients treated with chemoradiation has increased considerably. For example, Wun et al.\(^{(16)}\) reported an increased incidence of VTE in patients with cervical cancer who were treated with concurrent chemotherapy, radiation, and EPO. In a group of patients treated with EPO, 28\% (21/75 patients) developed VTE, which occurred mostly in upper-extremity thrombosis; in the group not treated with EPO, 3\% (2/72 patients) had VTE. The patients who received EPO had an OR of 10.3 for developing thrombosis, and multiple logistic regression revealed that the use of EPO alone was associated with an increased risk of thrombosis (OR, 153.3). (VTE induced by EPO will be discussed in a later section.) Most recently, in a retrospective analysis of the use of chemoradiation alone without EPO as a treatment for cervical cancer, a high incidence of VTE was reported (16.7\% [8/48]), but no significant risk factors, such as stage, smoking status, age, or body mass index, were associated with VTE\(^{(75)}\). Because chemotherapy and radiotherapy can result in VTE, susceptibility to VTE will be greatly intensified when these treatments are combined for patients, especially if EPO is added. In practice, we should take care to avoid this kind of complication; however, there is no way to predict whether and when VTE will occur.

The risk factors of VTE developing in gynecological cancer

The mechanism of how VTE develops in cancer patients is not well understood, but several susceptible factors have been identified: certain cancer types, cancer treatments, age, body mass index, and a genetic background of thrombosis. Generally, VTEs are due to both intrinsic and extrinsic factors. “Intrinsic” means that the tumor cells and microenvironment are the source of the prothrombotic status in patients, whereas “extrinsic” means that VTE develops from a therapeutic intervention.

Tumor cells can upregulate many coagulation factors, downregulate fibrinolytic system proteins, and express some cytokines or regulatory proteins associated with the formation of a thrombus, thereby making cancer patients susceptible to prothrombosis (Table 2). These disorders cause an imbalance in the coagulation/anticoagulation system of the body, destroy the endothelium in the vessels, and activate the platelets. One study found that patients with distant metastases had a higher risk of VTE than patients without them (adjusted OR, 19.8\(^{(12)}\)). The profile of the tumor is also an important source of coagulation. Because tumor cells secrete or produce coagulation factors that participate in coagulation cascade, such as the TFs (Factor III) and thrombin (Factor IIa), the monocytes\(^{(45)}\) and the ECs\(^{(46)}\) in the tumor microenvironment can also foster thrombosis. As noted earlier, it has been suggested that the following coagulation factors and regulatory proteins are upregulated in the peritoneum of patients with ovarian cancer: Factor XII, Factor XI, Factor XIII, Factor II–Factor II receptor (thrombin receptor, also called PAR), Factor VII, Factor X, and Factor I (fibrinogen), fibrin, heparin cofactor II, and endothelial protein-C receptor\(^{(44)}\).

Cancer treatments are extrinsic factors that induce VTE in some cancer patients. These antineoplastic therapies can upregulate procoagulant proteins (Table 2), downregulate anticoagulants (antithrombin, protein C, and protein S), suppress fibrinolytic activity, increase platelet activity, enhance adhesion of neutrophils, and induce the release of some cytokines and tumor procoagulants from tumor cell lysis\(^{(76)}\).

The genetic defect leading to thrombosis has been noticed in VTE development in cancer patients recently. The presences of the most common genetic factors for VTE are Factor V Leiden mutation and prothrombin 20210A gene mutation. One study found that individuals with the Factor V Leiden mutation who did not have a malignancy had an OR of 3.3, whereas individuals who did have a malignancy and this mutation had an OR of 5.1 compared with noncarriers without a malignancy. Carriers of the Factor V Leiden mutation who also had cancer had an OR value of 12.1 increased risk compared with persons without cancer and Factor V Leiden mutation. The risk of developing VTE in the presence of a prothrombin 20210A mutation was increased 2.5-fold compared with that of noncarriers (OR, 2.5). Overall, the risk increases approximately 12- to 17-fold for patients with cancer.
who have the Factor V Leiden or the prothrombin 20210A mutation(12). No such data have been reported specifically for patients with gynecological cancer so far.

Until now, no hemostatic markers of coagulation have been shown to predict VTE in individual patients. The prothrombotic state of malignancy is due to complex and not fully recognized interactions between cancer and the hemostatic system that probably create an imbalance of procoagulants versus anticoagulants. Some mechanisms have been partly elucidated (see next section). Another recently recognized possibility that should not be overlooked is that local thrombosis could promote tumor progression (77). TF(77,78), the thrombin (Factor II)-PAR system(79,80), and fibrinogen–fibrin(41,42) are considered to play some key roles in tumor growth, angiogenesis, metastasis, and ascites formation. It could be speculated that a positive feedback loop of cancer and VTE influences tumor progression.

### Anticancer therapeutics based on targeting the coagulation cascade

Currently, our knowledge of the molecular basis of tumor cell prothrombotic properties has greatly improved based on the previous research, and the dual role of coagulation factors and regulatory proteins in cascade (ie, TF, thrombin, PAR, and heparin cofactor II) in both clotting formation and cancer progression is becoming better understood(81). Coagulation factors have been found to have a profound effect on tumor cell behavior in both in vivo and in vitro studies and can enhance tumor cell proliferation, invasion, angiogenesis, and metastasis. Hence, targeting-activated coagulation factors might be a viable strategy for treating cancer. Therefore, it has been postulated that antithrombotic agents, such as aspirin, vitamin-K antagonists (VKA), and heparin, may hinder the progression of malignancies.

### Vitamin-K antagonists

The first report that VKA could reduce mortality in patients with cancer dates back to 1964(82). In 1981, the first, prospective randomized clinical trial that tested warfarin as a treatment for cancer was published by Zacharski et al. (83) and showed that warfarin significantly reduced mortality in patients with small-cell lung cancer (83). However, a systematic review of studies of the effect of VKA on the survival of patients with cancer concluded that there was not enough evidence showing that VKA prolonged survival in patients with malignancies(84).

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**Table 2. Procoagulation factors induced by tumor cells**

<table>
<thead>
<tr>
<th>Coagulation factors</th>
<th>Effects</th>
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<tbody>
<tr>
<td>TF</td>
<td>Upregulated, angiogenesis, invasion, and metastasis</td>
</tr>
<tr>
<td>TF-VII-PAR2(78)</td>
<td>Upregulated, angiogenesis, invasion, and metastasis</td>
</tr>
<tr>
<td>Factor X</td>
<td>Forms complex with TF-VIIa</td>
</tr>
<tr>
<td>Thrombin/PAR1</td>
<td>Upregulated, angiogenesis, invasion, and metastasis</td>
</tr>
<tr>
<td>Fibrinogen/fibrin</td>
<td>Upregulated, metastasis, ascites, and angiogenesis</td>
</tr>
<tr>
<td>Factor XII/XI</td>
<td>Positive feedback on human kallikreins system</td>
</tr>
<tr>
<td>Factor XIII</td>
<td>Form stable fibrin</td>
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<table>
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<tr>
<th>Regulatory proteins</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin cofactor II</td>
<td>Upregulated, degradation of heparin cofactor II promotes inflammation</td>
</tr>
<tr>
<td>Endothelial protein-C receptor</td>
<td>Upregulated, intensify PAR1 signal transduction</td>
</tr>
<tr>
<td>TF pathway inhibitor</td>
<td>Downregulated, loss of control of tumor growth, metastasis</td>
</tr>
<tr>
<td>TF pathway inhibitor-2</td>
<td>Downregulated, loss of control of tumor growth, metastasis</td>
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<table>
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<tr>
<th>Fibrinolytic proteins</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Urokinase plasminogen activator</td>
<td>Downregulated, promote coagulation</td>
</tr>
<tr>
<td>Urokinase plasminogen activator receptor</td>
<td>Downregulated, promote coagulation</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor necrosis factor-α</td>
<td>Upregulated, increase adhesion-molecule expression, induce apoptosis, increase TF expression, and decrease the expression of thrombomodulin and endothelial protein-C receptor</td>
</tr>
<tr>
<td>Interleukin-1β</td>
<td>Upregulated, promote inflammation, angiogenesis</td>
</tr>
<tr>
<td>VEGF</td>
<td>Upregulated, promote coagulation, angiogenesis</td>
</tr>
<tr>
<td>Platelet-derived growth factor</td>
<td>Upregulated, promote angiogenesis, metastasis</td>
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<table>
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<tr>
<th>Inflammatory cells</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophages</td>
<td>Activated, promote coagulation, angiogenesis, inflammation, and metastasis</td>
</tr>
<tr>
<td>ECs</td>
<td>Activated, promote coagulation, angiogenesis, inflammation, and metastasis</td>
</tr>
<tr>
<td>Platelets</td>
<td>Activated, promote tumor metastasis, and local coagulation</td>
</tr>
</tbody>
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Heparins

Heparins are the most extensively used anticoagulants in clinics. In blood coagulation, UFH and LMWH potentiate the activity of antithrombin III, thus inhibiting the activation of the coagulation factors II and X. Heparins also release TF pathway inhibitor, a physiologic inhibitor of the TF pathway, that prevents PE and is used to treat DVT. Since 1980, some retrospective and meta-analytic studies of DVT treatment have shown longer survival among cancer patients with thrombosis who were treated with UFH and LMWH than among cancer patients who did not receive heparin treatment. Thus, the use of anticoagulants in cancer patients might allow them to live longer.

One of the LMWH analogs, enoxaparin, was used in a pilot study in 2003, to treat advanced melanoma, but a positive clinical outcome seemed elusive. Then, a phase-II trial of a combination of chemotherapy and anticoagulant therapy (docetaxel and enoxaparin) was performed in chemotherapy-naïve patients with metastatic non–small-cell lung cancer. The median time to progression was 5 months in term of median follow-up was 11 months. The most frequent toxic effects were neutropenia and asthenia, and no clinically significant bleeding or thrombotic events were observed. This combination treatment was well tolerated in patients with advanced non–small-cell lung cancer, and the results suggested that enoxaparin could prolong the time to disease progression.

Since 2004, four large, prospective randomized, double-blinded studies that investigated the potential value of LMWH therapy in improving survival in cancer patients have been reported (Table 3). The first prospective randomized controlled trial enrolled 385 advanced cancer patients in two arms: the placebo group and the dalteparin (another LMWH) group. The types of advanced cancer included breast, colorectal, ovarian, and pancreatic cancer. Thirty-four percent of the patients in the dalteparin group and 31% of those in the placebo group received chemotherapy while participating in the study, and 8% of each group received radiotherapy. Estimated OS at 1, 2, and 3 years did not differ significantly between groups overall. However, among patients with a better prognosis at enrollment (55 patients in the dalteparin group and 47 patients in the placebo group), estimated OS was significantly longer in the dalteparin group at 2 years (78% versus 60%; \( P = 0.03 \)) and at 3 years (55% versus 36%; \( P = 0.03 \)). A second clinical trial in patients with small-cell lung cancer who were randomly assigned to the chemotherapy or LMWH plus chemotherapy groups showed that the progression-free survival and OS were better in patients who received LMWH for 18 weeks.

In 2005, the follow-up of a long-term study that compared patients who received the LMWH with those who received oral anticoagulant therapy was published. In this study, during the median 12-month follow-up, 602 patients with solid tumors and VTE were randomly assigned to either a dalteparin or a coumarin-derivative (oral anticoagulant) treatment group. Among patients without metastatic disease, the probability of death at 12 months was 20% in the dalteparin group and 36% in the oral anticoagulant group (\( P = 0.03 \)). In the patients with metastatic cancer, no difference in mortality between the treatment groups was observed (72% and 69%, \( P = 0.46 \)). The observed effects of dalteparin on survival were significantly different between patients with and without metastatic disease (\( P = 0.02 \)). The fourth clinical trial showed the value of up to 6 weeks of LMWH therapy compared with placebo in patients with advanced malignant disease that comprised a variety of cancer types; LMWH was associated with significant survival advantage.

The exact mechanism by which heparin mediates antitumor or antimetastatic activity is not known, but this merits further study. UFH and LMWH exert their anticoagulant effects by activating the physiologic coagulation inhibitor antithrombin, which neutralizes many of the serine proteases involved in the coagulation system, particularly thrombin and activated Factor X. In some previous studies of heparin and its antitumor effects, the following profile of antineoplastics was identified: heparin can exert antiproliferative effects on cancer cells by inhibiting the expression of oncogenes, such as c-fos, c-myc, Erb-B2; LWMH can hinder the binding of angiogenic growth factors to their receptors, or heparin can inhibit angiogenesis indirectly by inhibiting the formation of TF, thrombin, and fibrin; heparin might restrain the migration of cells by inhibiting the adhesion of cells to proteins in the extracellular matrix; and heparin can inhibit the proliferation of ECs, induce apoptosis, inhibit tumor cell–derived heparanase activity, and interfere with tumor cell glycosaminoglycans. Heparin also has been implicated in influencing the function of integrins, thus potentially interfering with tumor cell invasion and metastasis.

Aspirin

Another important antithrombotic agent, aspirin, has been investigated for its role in preventing cancer progression and prolonging survival. Two important clinical trials that used aspirin as a preventive agent showed...
against colorectal cancer had very impressive results \(^{(106,107)}\). Although the mechanism is not well understood, aspirin is considered a very useful agent in chemoprevention for patients with a history of colorectal adenomas or colorectal cancer. The use of aspirin is also associated with a reduced risk of esophageal cancer and breast cancer \(^{(108,109)}\), although aspirin does not seem to have chemopreventive activity in ovarian cancer \(^{(110)}\).

In addition to these positive clinical trials of antithrombotic therapies in cancer patients, more clinical trials of these therapies should be performed for other cancer types, such as gynecological cancer; at the same time, much more work needs to be done to identify the mechanisms involved.

### VTE as a complication of antiangiogenic and EPO therapies: friend or foe?

Although the process of angiogenesis in tumor progression and metastasis has been recognized for nearly 70 years, only recently have we been able to show that antiangiogenic therapy is beneficial to cancer patients. Current antiangiogenic therapies target mainly VEGF and VEGF receptors (VEGFRs). Because coagulation system is activated during tumor angiogenesis and VEGF has an indirect role in promoting coagulation, it is reasonable to predict that antiangiogenic therapies targeting VEGF and its receptors might alleviate the prothrombotic tendency associated with malignancies. However, a clinical trial of a combination of antiangiogenic therapy using SU5416, a synthetic small-molecule selective inhibitor of VEGF-mediated Flk-1/KDR receptor signaling, and chemotherapy (cisplatin plus gemcitabine) for colorectal cancer showed an unexpected, serious thrombosis. VTE occurred in both the arterial and venous systems, which led to the abandonment of the trial \(^{(111)}\). Kuenen et al. \(^{(111)}\) suggested that the VEGF pathway was the crucial bridge between the angiogenic process and the coagulation system, potentially giving rise to this adverse effect observed in this study. In addition, cisplatin has been associated with platelet activation in vitro, an elevated von 466 X. Wang et al.

| Table 3. Clinical trials of antithrombotic therapy on cancer |
| Reference | Treatment regimens | Number of patients | Median PFS | Median OS |
| Altinbas et al.\(^{(97)}\) | Chemotherapy (cyclophosphamide + epirubicin + vincristine) | 25 (limited disease) | 8.0 ± 1.21 months | 10.0 ± 1.39 months |
| | Chemotherapy (the same as above) + LMWH (dalteparin) 5000 U daily IC on day 1 every 3 weeks for 6 cycles | 23 (limited disease) | 11.0 ± 1.44 months; \((P = 0.025)\) | 16.0 ± 3.91 months; \((P = 0.007)\) |
| | Median follow-up, 10 months | 17 (extensive) | 6.0 ± 0.81 months | 8.0 ± 0.95 months |
| | | 23 (extensive) | 10.0 ± 0.95 months; \((P = 0.012)\) | 13.0 ± 1.62 months; \((P = 0.012)\) |
| Kakkar et al.\(^{(100)}\) | LMWH (dalteparin) 5000 U daily IC | 190 | 78% at 2 years | 1.44 months (P = 0.025) |
| | Placebo (0.9% saline) | 184 | 55% at 2 years | 36% at 3 years |
| Lee et al.\(^{(98)}\) | LMWH (dalteparin) 150–200 U/kg daily for 6 months | 75 without mets | 20% death probability at 12 months |
| | Coumarin derivative (warfarin or acenocoumarol). Median follow-up, 12 months | 75 without mets | 36% death probability at 12 months |
| | LMWH (dalteparin) 150–200 U/kg daily for 6 months | 221 with mets | 72% death probability at 12 months |
| | Coumarin derivative (warfarin or acenocoumarol). Median follow-up, 12 months | 231 with mets | 69% death probability at 12 months |
| Klerk et al.\(^{(99)}\) | LMWH (nadroparin) 0.4–0.8 mL IC during 14 days and once daily for another 4 weeks | 148 | 8.0-month survival at median 1-year follow-up |
| | Placebo | 154 | 6.6-month survival at median 1-year follow-up |

IC, intracutaneous; mets, metastatic disease; PFS, progression-free survival.
Willebrand’s factor (vWF), and hypomagnesemia-induced vasospasm, which has been proposed as a potential mechanism for VTE progression\(^{112}\).

Another antiangiogenic therapy uses bevacizumab (Avastin, Genentech Inc., South San Francisco, CA) to block the binding of human VEGF to its receptor\(^{114}\). Bevacizumab is a recombinant humanized monoclonal antibody to VEGF (rhuMAb-VEGF) that is composed of human immunoglobulin G1 framework regions and antigen-binding, complementarity-determined regions from a murine antibody (A.4.6.1)\(^{113}\). Bevacizumab can inhibit several VEGF activities, including endothelial cell growth, vascular permeability, and angiogenesis\(^{114,115}\). The combination of bevacizumab with chemotherapeutic agents has also been successful in treating colorectal\(^{116,117}\) and lung cancers\(^{118}\). In addition to its antiangiogenic effects, bevacizumab might play an even more profound role in antitumor response. For example, the hypoxia-induced production of VEGF is believed to be important in mediating tumor resistance to radiotherapy and chemotherapy, and bevacizumab could significantly augment antitumor effects\(^{119,120}\).

VTE with grade 3–4 is a common outcome of treatment with bevacizumab in patients with colorectal or lung cancer, and its incidence has been reported as 8.6%\(^{117}\), 12.5%\(^{116}\), and 9.4%\(^{118}\) in these patients. These studies indicated that different combinations of angiogenic and chemotherapeutic agents make patients susceptible to different degrees of VTE.

**VEGF–VEGFR and thrombosis**

Antiangiogenic therapies target mainly the VEGF–VEGFR system and play multiple roles in antineoplastic strategies, and the disruption of this system might be why VTE occurs. VEGF has a role not only in increasing vascular permeability and angiogenesis but also in maintaining the integrity of the endothelium. If the endothelium is damaged, locally produced VEGF probably contributes to repairing the ECs. On the one hand, VEGF might affect hemostasis; on the other hand, VEGF can enhance the expression of TF and thrombomodulin\(^{121,122}\). The fibrinolysis system is also activated because VEGF can stimulate the expression of tissue plasminogen activator, urokinase plasminogen activator, plasminogen activator inhibitor-1, and the receptor for the urokinase plasminogen activator\(^{123}\).

A clinical trial of SU5416 showed that it induced VTE; in that thrombosis and endothelium activation were found in patients given SU5416\(^{111}\). These authors found that EC activation was further associated with the finding of significant increases of soluble TF, vWF, and soluble E-selectin in plasma. The elevated levels of soluble E-selectin reflected the activation of the ECs, and the elevated levels of vWF and s-TF reflected the activation of circulating ECs that was caused by the damage to the ECs\(^{124}\). In the mean time, the level of endogenous thrombin was increased in all patients\(^{124}\). These results indicated that blockade of the VEGF–VEGFR system by SU5461 stimulated the procoagulant status and activation of the ECs. However, little is known about the exact connection between angiogenic factors and the coagulation cascade.

The endothelium has multiple physiologic functions, including secretory, metabolic, and immunologic functions. When ECs are damaged by injury or inflammation, they become activated and form a prothrombotic surface\(^{125}\). One important event that occurs upon EC activation is the release of vWF. When cultured ECs are stimulated with VEGF, vWF expression is increased. Elevated levels of vWF in plasma are associated with an increased risk of thrombosis\(^{126}\), and, similarly, the elevated levels of circulating soluble TF have been found to correlate with increased thrombogenicity in some diseases\(^{127}\). From VEGF's physiologic role, an appropriate or low level of VEGF is essential for maintaining the function of ECs that are not in tumors, which act as protective factors for ECs. However, antiangiogenic therapy could abrogate the action of VEGF and VEGFR in the microenvironment of tumor or nontumor tissues, thereby activating ECs and increasing the potential for coagulation. At the same time, activated factors of the endothelial system and coagulation cascade could also promote tumor cell growth, invasion, and metastasis.

**EPO and thrombosis**

EPO, a small molecule with a glycoprotein structure that is produced by the kidneys in response to hypoxia, regulates the production of erythrocytes. Recombinant human EPO (rHuEPO) was first introduced for the treatment of anemia in end-stage renal disease\(^{128}\). EPO has been used in cancer medicine recently, primarily for palliative care or combination with chemoradiotherapy. Because cancer-related anemia is often a contributing factor to fatigue and the reduced health-related quality of life for patients with metastatic or advanced cancer and because tumor hypoxia contributes to the resistance to the above-mentioned antineoplastic therapies, the administration of EPO can increase the patient's sensitivity to
chemotherapy and radiotherapy by enhancing oxygen delivery to the tumor tissues\(^\text{25}\). Most recently, however, thrombotic events have been noted as a potential complication of EPO treatment. One clinical trial of palliative therapy in patients with metastatic cancer had to be terminated early because of a significantly increased incidence of thrombotic events in the rHuEPO arm of the trial (rHuEPO was begun at 40,000 U subcutaneously, per week); that is, 28.5\% (4/14 patients) developed a DVT or PE\(^\text{129}\). In 2005, a Southwest Oncology Group study analyzed the extent to which rHuEPO with oral iron corrected anemia in patients receiving chemoradiotherapy for locally advanced cervical cancer (stage IIB–IVA)\(^\text{130}\). There was a higher incidence of VTE in those patients; 13\% (7/53) of patients presented with symptomatic DVT\(^\text{130}\). According to previous studies, there has been a high incidence of VTE in patients receiving rHuEPO combined with chemoradiotherapy for several types of cancer, that is, VTE developed in 23\% (17/75) of patients with stage IB–IVA cervical cancer who were given rHuEPO during chemoradiotherapy\(^\text{116}\), 27\% (4/15) of patients with stage I–III cervical cancer who were given rHuEPO during cisplatin/radiotherapy\(^\text{131}\), and 29\% (4/14) of patients with metastatic breast cancer who were given rHuEPO\(^\text{132}\). Wun et al\(^\text{16}\) reported that patients with cervical cancer who received EPO had ten times the likelihood of developing a thrombosis in comparison with patients who had not received EPO\(^\text{16}\). One Gynecologic Oncology Group, phase III protocol 191 of chemoradiotherapy both with and without rHuEPO was terminated in 2003 because of the high rate of DVT in the patients receiving rHuEPO. As a result, some authors suggested that rHuEPO should not be used routinely, because it was associated with a high incidence of VTE in patients receiving chemoradiotherapy for cervical cancer\(^\text{130}\).

The mechanism by which thrombosis is induced by EPO is being investigated. The administration of RHuEPO led to about a threefold increase in the content of platelets in the thrombi in an atrioventricular shunt model. At the same time, rHuEPO-induced platelet aggregation and activation\(^\text{133}\); the level of P-selectin, which is a marker for platelet activation, was observed to be elevated\(^\text{134}\), and Factor VIII and thrombin were also found after rHuEPO therapy\(^\text{135}\). However, low levels of proteins C and S were also observed in patients given rHuEPO\(^\text{133}\). These alterations in hemostasis could contribute to a prothrombotic status in patients. There is evidence that the endothelium is activated in vivo following intravenous rHuEPO administration\(^\text{134}\). One study found that the exposure of ECs to rHuEPO resulted in tyrosine phosphorylation of the JAK-2/STAT5 pathway; simultaneously, rHuEPO-induced long-lasting phosphorylation of MAPK P42/44\(^\text{136}\). The activation of these two pathways was followed by changes in the expression of TF on the underlying extracellular matrix, which suggested a prothombotic effect of rHuEPO\(^\text{136}\). Another study proved that cultured ECs exposed to rHuEPO could release plasminogen activator inhibitor-1, which showed that rHuEPO promotes a prothrombotic status\(^\text{137}\). rHuEPO could also inhibit the production of nitric oxide from ECs by selectively suppressing endothelial nitric oxide synthase activity\(^\text{138}\).

Clinically, the targeting antiangiogenesis and added EPO therapies were most likely the source of the VTE. So that more can be known about the etiology of VTE and its relationship to cancer, the design of clinical trials should ensure that while the preclinical data are being collected, any evidence of complications in the patients is also recorded.

In summary

Factors in the extrinsic and intrinsic coagulation cascades have complex and important roles in cancer progression. In the microenvironment of cancer (eg, ECs, platelets, fibroblasts, leukocytes, and the extracellular matrix), altered gene expression affects the key intracellular signaling events. Certain signaling pathways may facilitate thrombus formation in the peritumoral environment and promote localized angiogenesis. Retrospective analysis and clinical trials have confirmed the advantage of antithrombotic therapy for patients with malignancies. However, no such studies of patients with gynecological cancer have been performed so far. Therefore, more clinical trials that investigate new approaches to chemoprevention and therapeutics targeting coagulation cascade in patients with ovarian, cervical, or endometrial cancers are warranted. In summary, the interaction between the coagulation system and cancer progression is a novel promising area to be explored in the study of VTE in gynecological cancer.

References


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Venous thromboembolism syndrome in gynecological cancer


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