Incidence and risk factors of perioperative venous thromboembolism in patients with cervical cancer

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Received March 30, 2020; Accepted March 1, 2022

DOI: 10.3892/mco.2022.2541

Abstract. The aim of this retrospective study was to identify the perioperative incidence and risk factors of venous thromboembolism (VTE) in patients undergoing surgery for cervical cancer. The retrospective medical records of consecutive patients with cervical cancer were collected at the Qianfoshan Hospital affiliated with Shandong University from July 2014 to July 2017. Basic information regarding the patients, as well as tumor and surgery-related factors were compared between the cervical cancer patients with and without VTE. In the present study, a total of 338 patients undergoing surgery for cervical cancer were included. Ten (3.0%) patients were diagnosed with preoperative VTE and 18 (5.5%) with postoperative VTE. Multivariate analyses found that high levels of D-dimer and a larger size of the cervical tumor were independent risk factors for preoperative VTE, whereas the length of surgery and use of chemotherapy were independently associated with VTE development within 30 days after surgery. In conclusion, the major findings of the present study was a significant incidence of VTE in patients with cervical cancer. We also identified the clinical characteristics which can cause cervical cancer patients to have an increased risk for VTE.

Introduction

Venous thromboembolism (VTE) including deep vein thrombosis and pulmonary embolism is a well-recognized common complication associated with malignant tumors. VTE is also a leading reason for the morbidity and mortality of patients with malignant tumors (1). The incidence of VTE has increased during recent years (2). The incidence of VTE in the US is estimated to be 1 to 2 patients per 1,000 people, with 50% of these patients experiencing long-term symptoms of VTE (3). In Japan, Sakuma *et al* reported that 7,864 new patients suffer from pulmonary embolism (PE) every year and the number of new patients with deep vein thrombosis (DVT) is 14,674 each year (4).

Patients presenting with malignancies have a higher risk of VTE. It has been estimated that cancer is an independent major risk factor for VTE with an overall 4- to 7-fold increased risk than the general population. According to estimations, approximately 30% of new VTE patients suffer from cancer (5,6). This in part is due to the pathogenesis of VTE, as malignant tumors can activate the coagulation system and make it a prothrombotic state (7). The incidence of VTE in patients with malignancies range between 3 and 25%. In fact, the incidence is affected by a variety of variables including patient basic information, tumor-related status, and factors associated with treatment (8). The correlation between cancer and VTE was reported for the first time by the famous Parisian physician Armand Trousseau in 1865 (9). Since then, many studies have found that VTE is associated with numerous types of tumors, including hematologic malignancies, brain tumors, ovarian cancer, lung cancer and gastric cancer (10-13).

Cervical cancer is one of the most common gynecologic malignancies worldwide, with an incidence of 26.2 per 100,000 women in Taiwan (14). In the US, there are approximately 12,000 women diagnosed with cervical cancer every year (15). Matsuo *et al* found that the incidence of VTE was 12.3% in American patients with cervical cancer (16). Moreover, Jacobson *et al* utilized a retrospective chart review and reported that the incidence of VTE in cervical cancer patients was 11.7% (17). As these statistics suggest, the risk of VTE is high in patients with cervical cancer. Surgical treatment is a first-line treatment to improve the survival of patients with cervical cancer. However, VTE is a significant complication after surgery in patients with gynecological malignancies, and cancer patients undergoing surgery have twice the risk of developing postoperative VTE (18). In addition, 1 in 12 patients presenting with VTE associated with cancer surgery die within 30 days of their surgery (19). Yet, the incidence of VTE after surgery for cervical cancer remains undefined. The aim of this case-control study was to clarify the incidence and major risk factors of perioperative VTE for both preoperative and postoperative VTE in women undergoing surgery for cervical cancer.

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Key words: cervical cancer, perioperative, incidence, venous thromboembolism, risk factor

Patients and methods

Patients. This retrospective study reviewed the medical records and selected patients who met the criteria.

This was a retrospective analysis and thus no informed consent was required. After this study was approved [(2020) (S514), April 7, 2020] by the Research Ethics Board of Qianfoshan Hospital & The First Affiliated Hospital of Shandong First Medical University (Jinan, Shandong, China), we reviewed the medical records of patients diagnosed with cervical cancer, including general information and clinical pathology. A total of 338 consecutive patients who underwent surgery treatment at our hospital from July 2014 to July 2017 with a clear pathological diagnosis of cervical cancer were considered for admission to the present study. In this analysis, the exclusion criteria included patients with major risk factors such as history of VTE, history of cancer, recent major surgery, long-term immobilization, pregnancy or objectively confirmed deep venous thrombosis or pulmonary thromboembolism and patients under 18 years of age and who underwent no postoperative ultrasonography.

Preoperative parameters that were analyzed and collected included age, body mass index (BMI) (kg/m^2), smoking history, hypertension, hypercholesterolemia, diabetes, cardiovascular complications, Federation International of Gynecology and Obstetrics (FIGO) stage, distant metastasis, adjuvant chemotherapy, pathological type (squamous cell, adenocarcinoma, adenosquamous or others), size of the cervical tumor on MRI, laboratory tests such as platelets ($10^9/l$) and levels of D-dimer (mg/ml). Data collected after surgery included length of operation, surgical method (abdominal or laparoscopic), blood transfusion and adjuvant chemotherapy (adjuvant chemotherapy or radiation). Cancers were staged according to the 2014 FIGO guidelines (20). All cases were grouped into different types and graded according to a revised standard of the WHO (21).

VTE prevention, detection, diagnosis and treatment. In our institution, Doppler study of the extremities, computed tomography (CT) pulmonary artery angiogram, or ventilation-perfusion lung scan were performed by experienced clinical laboratory technologists before and 7 days after surgery to determine the incidence and specific location of VTE both before and after the operation. The possible types of VTE were examined as follows: deep venous thrombosis (DVT) alone, pulmonary embolism (PE) alone, and DVT/PE combined. Mechanical thromboprophylaxis for VTE is as follows: compression stockings and intermittent pneumatic compression. The related medication treatment for VTE is as follows: heparin, low-molecular weight heparin, warfarin, and inferior vena cava filter.

Statistical analysis. General characteristics of the population were described using mean ± standard deviation (SD). Independent-sample t-test and the Chi-square test were used to compare the differences between patients with and without VTE. Univariate and multivariate analyses were performed with logistic analyses to identify the significant risk factors for VTE. Statistical Package for Social Science (SPSS) software (v17.0; SPSS, Inc.) was used to perform statistical analysis. A probability value (P) <0.05 was considered to indicate statistical significance.

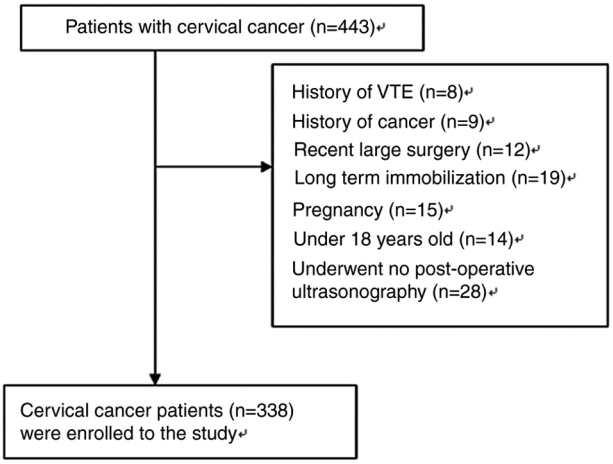

Figure 1. Flow diagram of the cervical cancer patients included in this study. VTE, venous thromboembolism.

Results

There were 443 patients identified who underwent surgery for cervical cancer during the study period. Among the 443 cases of cervical cancer with available medical records, 105 (23.7%) cases were excluded due to various unsuitable factors. Finally, there were 338 patients who met the inclusion criteria for the study. The flow diagram of the patients included in this study is provided in Fig. 1. Among the 338 patients (patients with VTE, 28; patients without VTE, 310), the mean age of the patients was 52.90±12.57 years. The histologic types included in this study included squamous cell (n=272), adenocarcinoma (n=50), adenosquamous (n=14), and other (n=2) types. The patients were divided into two subgroups according to the stage of tumors: stage I+II and stage III+IV. The number of patients with stage I+II disease was 133, and the number of patients with stage III+IV disease was 205. Table I shows the clinical characteristics of the patients with and without VTE. Age, BMI, smoking history, FIGO stage, distant metastasis, pathological type (squamous cell, adenocarcinoma, adenosquamous or others), laboratory data such as platelet count and complications including hypertension, hypercholesterolemia, diabetes, cardiovascular complications were not significant factors for VTE.

Perioperative VTE was detected in 28 (8.3%) of the 338 patients. Ten events (3.0%) occurred in preoperative patients whereas 18 patients (5.5%) had postoperative events. Six of these 28 patients were also diagnosed with pulmonary embolism (PE), 1 with DVT and PE and no patient was deceased. All patients had non-lethal PE. Nine patients had a VTE in the left leg among the 28 patients, 10 in the right leg, and 9 in both legs. Three patients had proximal DVT and the remaining 15 patients had distal DVT. All VTE cases were asymptomatic.

Factors associated with VTE development. The results of the univariate analysis of perioperative risk factors for VTE are listed in Table I. Adjuvant chemotherapy (P=0.009), larger

Table I. Clinical characteristics of the VTE and non-VTE groups.

Preoperative risk factors	VTE group (N=10)	Non-VTE group (N=310)	t/χ^2	P-value
Age[a,b], years, mean ± SD (range)	54.40±12.73 (33-78)	52.87±12.57 (7-80)	0.383	0.859
BMI[a], kg/m^2 (range)	24.63±3.87 (19.1-33)	23.29±3.69 (14-34)	1.131	0.893
Smoking history[b], n (%)	2 (20%)	30 (9.1%)	1.334	0.248
Hypertension[b], n (%)	3 (30.0%)	81 (24.7%)	0.146	0.702
Hypercholesterolemia[b], n (%)	3 (30%)	76 (23.2%)	0.253	0.615
Diabetes[b], n (%)	2 (20.0%)	58 (17.7%)	0.036	0.850
Cardiovascular complications[b], n (%)	2 (20.0%)	64 (17.9%)	0.001	0.969
FIGO stage[b], n (%)			0.490	0.484
I +II	5 (50.0%)	128 (39.0%)		
III+IV	5 (50.0%)	200 (61.0%)		
Distant metastasis[b], n (%)	2 (20.0%)	50 (15.2%)	0.169	0.681
Adjuvant chemotherapy, n (%)	5 (50.0%)	57 (17.4%)	6.895	**0.009**
Pathological type[b], n (%)			1.244	0.742
Squamous cell	7 (70.0%)	265 (80.8%)		
Adenocarcinoma	2 (20.0%)	48 (14.6%)		
Adenosquamous	1 (10.0%)	13 (4.0%)		
Other	0	2 (0.6%)		
Cervical tumor size[b], n (%)			8.941	**0.003**
≥50 mm	7 (70.0%)	79 (25.5%)		
<50 mm	3 (30.0%)	249 (80.3%)		
Platelet count (10^9/l)[a], mean ± SD (range)	290.3±29.94 (230-355)	279.5±32.31 (225-386)	1.040	0.935
D-dimer (mg/ml)[a], mean ± SD (range)	1.33±0.31 (0.4-1.5)	0.67±0.34 (0.1-1.7)	6.054	**<0.001**
Postoperative risk factors	VTE group (n=18)	Non-VTE group (n=310)		
Length of surgery >3 h[b], n (%)	10 (55.6%)	69 (22.3%)	0.316	**0.001**
Blood transfusion[b], n (%)	4 (22.2%)	66 (21.3%)	0.009	0.925
Surgical method[b], n (%)			0.040	0.842
Abdominal, n (%)	16 (88.9%)	280 (90.3%)		
Laparoscopic, n (%)	2 (27.8%)	30 (20.7%)		
Adjuvant chemotherapy[b], n (%)	9 (50.0%)	86 (27.7%)	4.096	**0.043**

[a]t-test; [b]Fisher exact test. BMI, body mass index; FIGO, Federation International of Gynecology and Obstetrics VTE, venous thromboembolism; n, number of patients. Significant P-values are indicated in bold print.

size of the cervical tumor (P=0.003), and high D-dimer levels (P<0.001) were independent risk factors for preoperative VTE. Length of surgery (P=0.001) and adjuvant chemotherapy (P=0.043) were significantly related to postoperative VTE on univariate analysis, but there was no significant difference in regards to type of surgery, and need for blood transfusion.

In the multivariate analysis, larger size of the cervical tumor [odds ratio (OR)=0.118; 95% confidence interval (CI), 0.02-0.56; P=0.007] and high levels of D-dimer (OR=15.092; 95% CI, 8.281-31.353; P<0.001) were independently associated with VTE development within 30 days before surgery (Table II). In the multivariate analysis, length of surgery (OR=19.021; 95% CI, 6.523-55.464; P<0.001) and use of chemotherapy (OR=3.152; 95% CI, 1.08-9.18; P=0.035) were independently associated with VTE development within 30 days after surgery (Table III).

Discussion

Virchow's triad is a well-known factor that contributes to thrombosis and consists of vessel wall injury, hypercoagulability and abnormal venous flow (22). A large number of pathological, experimental and clinical studies have shown that hypercoagulability exists locally or

Table II. Multivariate analysis of the preoperative risk factors for VTE.

Risk factors	OR	95% CI	P-value
Cervical tumor size	0.118	0.025-0.564	**0.007**
D-dimer (mg/l)	15.092	8.281-31.353	**<0.001**

VTE, venous thromboembolism; OR, odds ratio; CI, confidence interval. Significant P-values are indicated in bold print.

Table III. Multivariate analysis of the postoperative risk factors for VTE.

Risk factors	OR	95% CI	P-value
Length of surgery >3 h	19.021	6.523-55.464	**<0.001**
Use of chemotherapy	3.152	1.083-9.178	**0.035**

VTE, venous thromboembolism; OR, odds ratio; CI, confidence interval. Significant P-values are indicated in bold print.

systemically in most cancer patients, for the following reasons. i) Postoperative bed rest and venous compression by the tumor itself cause blood circulation stasis in patients with malignant tumors. ii) Chemotherapeutic drugs and tumors themselves can induce inflammatory mediators that damage the intima of veins. iii) Levels of fibrinogen are higher in cancer patients than in non-cancer patients, and the tumors themselves can release various coagulant substances. The above reasons lead to increased blood coagulation and deep venous thrombosis (DVT).

The incidence of malignant tumors in China is increasing year by year, while the incidence of venous thrombosis caused by malignant tumors is 2.4-12%, which is at least 6 times higher than that of non-cancer patients. Therefore, it is particularly critical to study the risk factors and therapeutic efficacy of DVT in cervical cancer patients undergoing surgery and to prevent its occurrence as early as possible.

In the present study, we found that the incidence of venous thromboembolism (VTE) was 3.0% during hospitalization and 5.5% during postoperative day 30 in female Chinese patients undergoing surgery for cervical cancer when perioperative mechanical thromboprophylaxis was performed, which was similar to previous studies. Satoh *et al* (8) investigated the incidence of VTE before treatment in 272 consecutive patients with cervical cancer and the incidence of VTE was 4.8%. Tsai *et al* analyzed data deposited between 2003 and 2008 in the National Health Insurance Research Database and reported that the 5-year cumulative risk for VTE was 3.3% in the cervical cancer group (23).

Studies have reported that the risk factors of thrombosis associated with gynecological tumors include pelvic surgery, age, race, previous leg edema, presence of venous varicosities, a history of VTE, longer duration of surgery, receipt of adjuvant chemotherapy or radiation therapy, and immobility (24). In the present study, we found that high D-dimer and larger size of the cervical tumor were independent risk factors for preoperative VTE whereas operative time longer than 3 h and postoperative adjuvant chemotherapy were independent risk factors for postoperative VTE.

D-dimer is one of the products of the degradation of crosslinked fibrin. The increase in plasma levels indicates the hypercoagulation state or the activation of fibrinolytic system *in vivo*. Some scholars believe that the value of D-dimer alone in the diagnosis of postoperative DVT of malignant tumors is limited (25). The factors leading to the fluctuation of D-dimer level include disease factors, physical factors and examination methods, thus its specificity is low. Researchers believe that the high negative predictive value of D-dimer makes it unable to be used as a diagnostic tool and is only suitable for the early screening of VTE (26). However, some scholars believe that dynamic detection of D-dimer level may have a certain early warning effect on postoperative VTE of gynecological malignant tumors (27). It has the advantages of rapid, economic, noninvasive and dynamic monitoring for the diagnosis of VTE, and can be popularized and applied in the clinic (28). D-dimer was introduced into the risk assessment system of VTE after malignant tumor surgery, which improved the accuracy of prediction to a certain extent. Research has confirmed that the level of D-dimer is correlated with the prognosis of acute pulmonary thromboembolism (29), and can be used as a predictor of venous thromboembolism, and the cutoff value of D-dimer for predictive VTE is still controversial. Ay *et al* (28) suggested the cutoff for elevated D-dimer was 1.44 mg/ml; however, Kawaguchi *et al* recommended the cutoff value could be more than 1.5 mg/ml in ovarian cancer (30). In the present study, it was found that the median value of D-dimer was 1.33 mg/ml. The results are similar to the above mentioned studies. The occurrence of VTE adverse events in patients with cervical cancer with significantly increased dimer levels should be actively intervened as soon as possible. D-dimer can be used as a primary screening tool for postoperative VTE of gynecological tumors.

Large cervical tumors may compress pelvic vasculature impacting pelvic and lower limb blood circulation, thereby increasing blood viscosity and subsequent thrombus formation. In addition, larger cervical tumors may invade the pelvic wall and damage endothelial cells (31). Satoh *et al* (8) suggested that tumor size >50 mm was an independent risk factors of VTE, which was in keeping with our study. Therefore, chemotherapy drugs may be necessary for patients with larger tumors.

With the use of new chemotherapeutic drugs, the incidence of venous thrombosis in patients with malignant tumors has increased. Studies have reported that the incidence of venous thrombosis can reach 6-30%. Chemotherapeutic drugs lead to injury of vascular endothelial cells, release of procoagulants and destruction of endogenous anticoagulants. Jacobson *et al* reported that the incidence of thrombosis in cervical cancer patients treated with chemotherapy and radiotherapy was approximately 16.7% (32). And in another study, the incidence of thrombosis of 11.7% in patients with the same type of cancer (17).

In the present study, the surgical time of the VTE group was significantly longer than that of the non-VTE patients, which was in keeping with other studies (33). Zhang *et al* recom-

mended that gynecological surgery, unlike general surgery, requires lymph node dissection, which results in prolonged operation time and increased incidence of VTE (34).

In the present study, age, body mass index (BMI), and smoking history, were not associated with the development of VTE, which is consistent with the results of previous studies. In tumor-related factors, FIGO stage and pathological type were not associated with the development of VTE. However, Satoh *et al* recommended that pathological type was not a risk factor for VTE but age >60 years and FIGO stage IV were risk factors for VTE before treatment in patients with cervical cancer (8). Perhaps the reason is that his subjects were patients before treatment and in this study, the subjects were patients undergoing surgery with cervical cancer. In the present study, patient complications were not a risk factor for VTE, and may be less severe in these patients.

In a study by Chen *et al*, the authors investigated the incidence, clinical and pathological characteristics of thrombosis in excised tissues after pneumonectomy, and its association with survival rate in patients with non-small cell lung cancer but not cervical cancer (22). Satoh *et al* investigated the incidence of VTE before treatment in 272 consecutive patients with cervical cancer, and the impact of management on prevention of VTE during and after treatment (8). Tsai *et al* analyzed data deposited between 2003 and 2008 in the NHIRD, provided by the National Health Research Institutes in Taiwan. Strategies to reduce these risks need to be examined (23). Ailawadi and Del Priore found that heparin should not be used with sequential compression devices (SCDs) unless an additional benefit can be demonstrated in a randomized controlled trial (24). D-dimer has a negative predictive value of ≥93% for excluding DVT in symptomatic outpatients and it can be a useful test in the diagnostic work-up of suspected upper extremity DVT. To improve prediction of VTE in cancer patients, Ay *et al* performed a prospective and observational cohort study of patients with newly diagnosed cancer or progression of disease after remission (28). In a review by Barbera and Thomas, the authors focused on the incidence of VTE, patient, tumor, and treatment-related risk factors for VTE, and treatment and prevention of VTE in the setting of cervical cancer (31). Jacobson *et al* noted a high incidence of thromboembolic events (TE) (16.7%) in patients treated at UIHC (University of Iowa Hospitals and Clinics) with chemoradiation for invasive cervical cancer. They did not find a statistical association between age, stage, smoking history, or BMI and risk of TE in this group. Jacobson *et al* found that there was a clear and significant difference in survival between patients with and without TE (32). Kim *et al* found that an increase in surgical duration was directly associated with an increase in the risk for VTE (33). The aim of a study by Zhang *et al* was to assess the major risk factors for venous thromboembolism in Chinese patients with ovarian cancer and to explore optimal methods of prophylaxis and treatment (34).

This study has some limitations including a small sample size, and the fact that it was a single-center, retrospective and non-protocolized study. In particular, the small sample size of the study might have led to false statistical conclusions, and therefore a large-scale, prospective, randomized controlled trial is needed to confirm the results. In addition, all patients enrolled in the current study were Chinese, and there were differences in some basic risk factors, such as BMI.

In conclusion, the present study screened out significant risk factors for prevention of VTE in patients with cervical cancer undergoing surgery. First of all, for patients with cervical cancer, we should choose reasonable treatment and reduce surgical intervention. Secondly, we should evaluate the risk factors of cervical cancer patients with VTE in time and administer early anticoagulation treatment in order to reduce the incidence of VTE.

Acknowledgements

I would like to give my heartfelt thanks to all the people who have ever helped me in this paper.

Funding

The present study was funded by the Key Technology Research and Development Program of Shandong (2017RKB14047).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HZ and SZ made substantial contributions to the conception and design of the work; and the acquisition, analysis, and interpretation of data. YP, ML and YS drafted the manuscript and revised it critically for important intellectual content. All authors gave final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work (including the provided data) are appropriately investigated and resolved.

Ethics approval and consent to participate

This was a retrospective analysis and thus no informed consent was required from the patients. This study was approved by the Research Ethics Board of Qianfoshan Hospital & The First Affiliated Hospital of Shandong First Medical University (Jinan, Shandong, China). The approval number is [2020] (S514), and the date of approval was April 7, 2020.

Patient consent for publication

The patients consented to the publication of their data.

Competing interests

The authors declare no competing interests.

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