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Effects of Deep Vein Thrombosis on Survival in Patients with Epithelial Ovarian Cancer: A Retrospective Study

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Abstract

Objective: The aim of this study was to evaluate the prevalence of Deep Vein Thrombosis (DVT) and the influence of DVT on patients' survival with epithelial ovarian cancer with standard DVT treatment.

Methods: This is a retrospective study from prospectively registered data base of patients who underwent cytoreductive surgery and adjuvant chemotherapy from January 2010 to December 2014 at Seoul St. Mary's Hospital. Electronic medical records and picture archiving and communication system was used to evaluate patient's clinical characteristics, treatment results and the influence of DVT.

Results: Two hundred eighty-four patients were identified. There were 260 patients without DVT and 24 patients with DVT. Among 24 patients, 9 patients had pulmonary embolism. All patients with DVT were treated with anticoagulation. Patients with DVT were older (61.0 vs 51.2 years, P=0.009), and diagnosed at more advanced stages (P for trend: 0.029, Cochran-Armitage trend test) at initial diagnosis than those without. The overall survival was not significantly different between two groups (P=0.14) by using the log rank test. The stage was associated with shorter overall survival (for stage IV: Hazard Ratio (HR) 17.0, 95% CI 3.4-83.6, P<0.05); however, the presence of DVT was not associated with poor prognosis (HR 0.8, 95% CI, 0.1.0-1.06, P=0.61).

Conclusion: The incidence of DVT was 8.5% in patients with epithelial ovarian cancer. DVT can cause a fatal complication. However, patients with epithelial ovarian cancer and DVT can be safely treated with standard treatment of DVT.

Keywords: Deep Vein Thrombosis (DVT), Ovarian cancer, Prognosis, Survival

List of Abbreviations: DVT: Deep Vein Thrombosis; PTE: Pulmonary Thromboembolism; TF: Tissue Factor LMWH: Low Molecular-Weight Heparin

Introduction

Deep Vein Thrombosis (DVT) in malignant disease patients was first described by Trousseau in 1865 [1]. Approximately 20% of all cancer patients experienced DVT, and 20% of patients with DVT have been diagnosed with malignant disease [2,3]. The incidence of DVT was higher in ovarian cancer than in other

cancers (range 2.8%-16.6%) [1,4-6]. Risk factors for DVT include old age, immobility, hyperlipidemia, gynecological cancer, cancer stage, surgery, and anticancer therapy [6,7]. Ovarian cancer, pancreatic cancer, and glioblastoma are common malignancies, with development of DVT. DVT occurs 10 times more frequently in ovarian cancer patients than in normal controls [8]. The incidence of DVT is higher in cancer patients than in normal controls. Pathologic mechanisms for DVT are not well defined. Mechanisms proposed so far are as follows:

1) Cancer cells express hemostatic proteins, such as tissue factor.

2) Microparticles, inflammatory cytokines (TNF-a, IL-1B), and proangiogenic factors (VEGF, bFGF) are produced from both cancer and host cells in cancer patients.

3) Adhesion molecules which are expressed by cancer cells bind to platelets, endothelial cells, and leukocytes [7].

Furthermore, in ovarian cancer, hyperviscosity, vessel wall injury during surgery or chemotherapy, and venous stasis caused by massive ascites or a huge mass are associated with a high incidence of DVT [9]. Tissue factor (TF) is a 47-kDA transmembrane glycoprotein which is important for hemostasis [10]. TF is elevated in patients with epithelial ovarian cancer, especially endometrioid and clear cell carcinoma, who develop DVT more frequently than those without [8].

DVT can cause fatal Pulmonary Thromboembolism (PTE) which may affect survival in patients with epithelial ovarian cancer. However, there have been few studies on the effects of DVT in patients with epithelial ovarian cancer. The aim of this study was to evaluate the prevalence of Deep Vein Thrombosis (DVT) and the influence of DVT on patients' survival with epithelial ovarian cancer with standard DVT treatment.

Material and Methods

Study Patients

After approval by the Institutional Review Board of Seoul St. Mary's Hospital (KC15RISI0858), we reviewed the medical records of patients with epithelial ovarian cancer (International Federation of Gynecology and Obstetrics [FIGO] stage I to IV) who attended Seoul St. Mary's Hospital and underwent primary cytoreductive surgery or staged surgery plus adjuvant chemotherapy between January 2010 and December 2014. All the patients were diagnosed with epithelial ovarian cancer and underwent a staging operation-salpingo-oophrectomy, hysterectomy, lymph node dissection, omentectomy, and multiple biopsy. Patients who were treated in other clinics and referred to our hospital due to recurrences, confirmed non-epithelial cancer, borderline malignancy, and benign tumors were excluded from the study. Written informed consents were obtained from all participants.

Diagnosis of DVT

Patients who complained of leg pain, lower extremity edema, or changes in skin color were examined using D-dimer. When the estimated D-dimer level was over 0.8 mg/L, patients were examined using duplex ultrasound/contrast enhanced DVT and pulmonary artery Computed Tomography (CT) to identify the presence of DVT.

Prevention of DVT

Patients who were scheduled for surgery received intermittent pneumatic compression pre- and intraoperatively. Early ambulation was encouraged after surgery. When patients underwent medical treatment in the postanesthetic care unit, they were also treated with intermittent pneumatic compression and Low Molecular-Weight heparin (LMWH) during hospitalization.

Treatment of DVT

Factor Xa antagonist or LMWH plus warfarin was administered orally to patients with DVT. When patients had a great extent of DVT and PTE, they were treated with an inferior vena cava filter to prevent additional PTE.

Statistical Analysis

Statistical analyses were performed by using the SPSS version 11.0 statistical software program. Cox proportional hazard models were used to analyze the effect of risk factors on survival in patients with DVT. The log rank test was used to compare survival difference between the study groups. Fisher exact and Cochran-Armitage tests were used to compare the characteristics of the study patients. A P value of <0.05 was considered statistically significant.

Results

Two hundred eighty-four patients were identified. There were 260 patients without DVT and 24 patients with DVT, the incidence of DVT was 8.5%. Table 1 shows the baseline characteristics of the study patients. The mean age was older in patients with DVT than in those without (61.0 vs 51.5 years, P=0.009). The prevalence of DVT tended to increase with increasing FIGO stages (P for trend: 0.029, Cochran-Armitage trend test). By using the Fisher exact test, DVT more frequently occurred in patients with cerebrovascular disease (P=0.037) and those with dyslipidemia (P=0.019).

Characteristics	DVT (+) n=24	DVT (-) n=260	P value
Age at baseline (years) Mean (range)	61.0 (46-82)	51.5 (16-82)	0.009
FIGO stage, n (%)			
I	3 (1.1)	89 (31.3)	
II	5 (1.8)	22 (7.8)	0.029†
III	11 (3.9)	135 (47.5)	
IV	5 (1.8)	14 (4.9)	
Cell Type, n (%)			
Serous	13 (4.6)	141 (49.7)	
Mucinous	3 (1.1)	28 (9.9)	
Endometrioid	4 (1.4)	25 (8.8)	0.0013‡
Clear cell	3 (1.1)	32 (11.3)	
Other	1 (0.4)	34 (12.0)	
Type of co-morbidity‡			
Hypertension	7 (2.5)	49 (17.3)	0.224
Diabetes mellitus	2 (0.7)	24 (8.5)	1
Ischemic heart disease	2 (0.7)	4 (1.4)	0.083
Cerebral vascular			
Disease			0.037
Yes			
No	2 (0.7)	2 (0.7)	
History of thrombosis	22 (7.8)	258 (90.1)	1
Dyslipidemia	0	1 (0.4)	0.019
Yes			
No			
	2 (0.7)	1 (0.4)	
	22 (7.8)	259 (91.2)	
†Cochran- Armitage trend test; ‡Fisher Exact test			

Table 1: Characteristics of the study patients.

Among 24 patients, there were 17 iliofemoral DVT, 7 calf vein DVT and 9 PTE. All patients with DVT were treated with anticoagulation. 15 patients were treated with low molecular weight heparin and warfarin and 9 patients with rivaroxaban. There was no PTE related death in this group. Table 2 shows the development time of DVT. Among the total patients, 54.2% were diagnosed with DVT within 6 months postoperatively, and 16.7% were diagnosed with DVT pre-operatively. We analyzed the survival difference between patients with and without DVT (Figure 1). There was no significant difference in survival time between the 2 groups (*P*=0.14). Mean survival time of patients with DVT was 1776 (95% CI 880-2155) days, however that of patients without DVT was not estimable. We analyzed risk factors for survival using Cox proportional hazard models (Table 3). The stage was a good prognostic factor for epithelial cancer (stage II: HR 9.6, 95% CI 1.9-49.0; stage III: HR 7.5, 95% CI 1.8-31.8; and stage IV: HR 17.0, 95% CI 3.4-83.6, P<0.05 for each); however, DVT did not affect the survival rate (HR 0.8, 95% CI 1.0-1.06, P=0.61). The presence of comorbidity did not affect the survival rate.

Time from cancer operation (months)	N (%)
Pre-operation	4 (16.7)
0-6	13 (54.2)
6-12	3 (12.5)
12-18	0 (0)
>18	4 (16.7)

Table 2: Development of deep vein thrombosis from operation.

Parameter	Hazard ratio	95% Confidence interval	P-value
Stage			
I	0		
II	9.6	1.9-49.0	<0.05
III	7.5	1.8-31.8	<0.05
IV	17	3.4-83.6	<0.05
Development of DVT			
(-)	0		
(+)	0.8	1.0-1.06	0.61
Comorbidity			
HBP	1	0.0.5-2.2	0.93
DM	0.9	0.3-2.5	0.83
Ischemic heart disease	2	0.4-9.1	0.4
Cerebral vascular disease	0.6	0.1-5.1	0.7

HBP: Hypertension, DM: Diabetes Mellitus

Table 3: Cox proportional hazard model for patients with deep vein thrombosis.

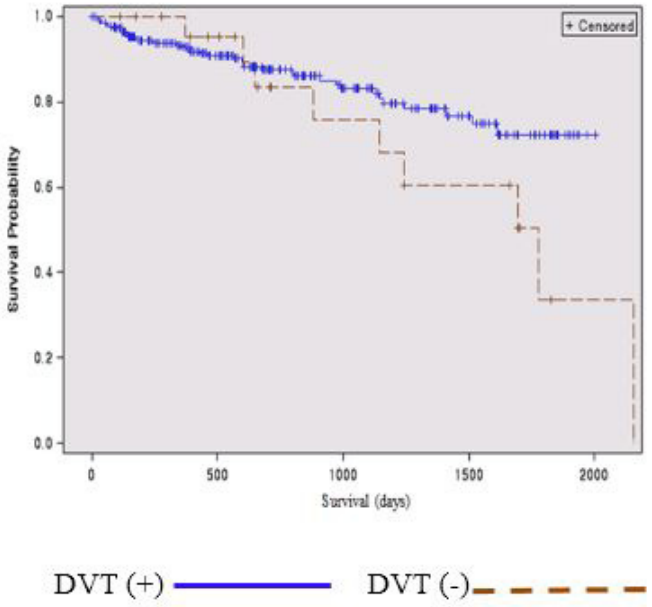

Figure 1: Log rank survival curve of patients with DVT. There was no significant difference in survival between two groups (P=0.14).

Discussion

This study was conducted to evaluate the influence of DVT on survival in patients with epithelial ovarian cancer with standard DVT treatment. 8.5% of patients with epithelial ovarian cancer was diagnosed with DVT during cancer treatment. The incidence of DVT varies according to investigators (1.6%-16.6%) [1,5,11,12]. The incidence of DVT in this study was similar to those of previous studies. The DVT was found most often 1 month after diagnosis, which is consistent with those of previous studies [4,11]. The DVT is associated with the cancer stage [4,13]. The cumulative incidences of DVT are reported to be 1.4%, in patients with local-

stage disease and 6.7% in those with advanced disease [4]. In this study, the incidence of DVT was higher in advanced cancer stage. DVT frequently occurs immediately after surgery [4,13,14]. In this study, DVT occurred in 54.2% of the patients within 6 months of surgery. Tateo, et al. [13] indicated that the rate of developing DVT is highest immediately after surgery and decreases thereafter over time. Rodriguez, et al. [4] demonstrated that DVT occurring within 2 years of surgery reduces OS in patients with epithelial ovarian cancer.

The incidence of DVT in patients with ovarian cancer is well known; however, the effects of DVT on survival in patients with ovarian cancer have not yet been completely elucidated. Morgan, et al. [15] reported that among patients with cervical, endometrial, and ovarian cancer, OS was significantly worse in patients with DVT than in controls (relative risk, RR 2.14; 95% CI 1.47-3.13). Diaz, et al. [5] compared survival difference between clear cell carcinoma patients with and without DVT. Among patients with early-stage disease (FIGO stages I and II), OS times were 98 months in those with DVT and 27 months in those without (P=0.004); however, among patients with advanced disease (stages III and IV), OS time was not significantly different between those with and without DVT (28 vs 16 months, P=0.28). Among colorectal cancer patients, similar results were reported. DVT is a significant predictor of death in patients with local-stage localized (HR 1.8, 95%CI 1.3-1.8) or regional-stage disease (HR 1.5, 95% CI 1.3 - 1.8), but not in those with metastatic disease, (HR 1.1, 95% CI 1.0-1.2) [14]. In this study, after adjustment for confounding factors, including stage, cell type, and comorbidity, OS was not different between patients with and without DVT (HR 0.378, 95% CI 0.32-1.89). Metcalf, et al. [11] documented that development of DVT could affect survival difference in patients with epithelial ovarian cancer, although after adjustment for confounding factors, including stage and performance status, OS time was not statistically different (P=0.91), which is similar to the results of our study.

This study has some limitations. First, this is a retrospective study, so it could have caused selection bias. Secondly, the sample size is relatively small. However, the potential implication of this study is that we analyzed survival differences after adjustment for confounding factors in Korean patients with epithelial ovarian cancer. Malignant disease is a significant risk factor for the development of DVT. Mechanisms underlying thrombosis in cancer patients is complicated and can be associated with patient's own risk factors and history of anti-cancer treatment. In patients with malignant disease, development of DVT seems to be associated with poor survival. After adjustment for confounding factors, such as stage, comorbidity, and cell type, the OS was not affected by the presence of DVT. Further studies are needed to confirm our results.

Conclusion

The incidence of DVT was 8.5% in patients with epithelial ovarian cancer. DVT can cause a fatal complication. However, Patients with epithelial ovarian cancer and DVT can be safely treated with standard treatment of DVT.

Conflict of Interest

The authors have declared that no conflicts of interest exist.

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