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The survival detriment of venous thromboembolism with epithelial ovarian cancer☆

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HIGHLIGHTS

- Preoperative VTE attenuates overall survival with epithelial ovarian cancer.
- Postoperative VTE compromises progression free and overall survival.
- VTE is a postoperative complication that significantly shortens survival.

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ABSTRACT

Objective. The aim of this study is to evaluate the effect of venous thromboembolism (VTE) chronology with respect to surgery on survival with epithelial ovarian cancer (EOC).

Methods. An IRB approved, retrospective review was performed of patients treated for Stage I–IV EOC from 1996 to 2011. Cox proportional hazards model was used to assess associations between VTE and the primary outcomes of progression free survival (PFS) and overall survival (OS). SAS 9.3 was used for statistical analyses.

Results. 586 patients met study criteria. Median age was 63 years (range, 17–94); median BMI was 27.1 kg/m^2 (range, 13.7–67.0). Most tumors were high grade serous (68.3%) and advanced stage (III/IV, 75.4%). 3.7% had a preoperative VTE; 13.2% had a postoperative VTE. Upon multivariate analysis adjusting for age, stage, histology, performance status, and residual disease, preoperative VTE was predictive of OS (HR 3.1, 95% CI: 1.6–6.1, $p = 0.001$) but not PFS ($p = 0.55$). Postoperative VTE was associated with shorter PFS (HR 1.45, 95% CI: 1.04–2.02, $p = 0.03$) and OS (HR 1.8, 95% CI: 1.3–2.6, $p = 0.001$). When VTE timing was modeled, preoperative VTE (HR 3.5, 95% CI: 1.8–6.9, $p < 0.001$) and postoperative VTE after primary therapy (HR 2.3, 95% CI: 1.4–3.6, $p = 0.001$) were predictive of OS.

Conclusion. Preoperative and postoperative VTE appear to have a detrimental effect on OS with EOC. When modeled as a binary variable, postoperative VTE attenuated PFS; however, when VTE timing was modeled, postoperative VTE was not associated with PFS. It is unclear whether VTE is an inherent poor prognostic marker or if improved VTE prophylaxis and treatment may enable similar survival to patients without these events.

Introduction

Trousseau first described the relationship between cancer and venous thrombosis in 1865 [1]. Since then, malignancy has been widely recognized as a substantial risk factor for venous thromboembolism (VTE) with particular cancer types associated with even higher risk [2]. Moreover, certain authors have reported that ovarian cancer is the solid tumor with the highest rate of VTE [3]. Emerging evidence suggests that proteins involved in VTE formation are influential determinants and contributors to tumor biology [4–6].

When considering cancer patients as a whole, 11% have a clinically evident VTE [7]. Although there is a spectrum of severity, VTE is regarded as the second leading cause of death in cancer patients [8]. Complex mechanisms underlie the pathogenesis of the hypercoagulable state of malignancy involving a combination of thrombin generation due to binding of tissue factor with clotting intermediates, direct procoagulant activity of normal host cells in the presence of tumor, and underlying comorbidities [6,9]. Studies in ovarian cancer and other solid tumors (endometrial, bladder, and a heterogeneous group of cancers) have demonstrated that VTE negatively impacts survival; this data suggests that thrombosis associated with malignancy may

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contribute to a paracrine circuit, ultimately resulting in more aggressive tumor behavior [10–13]. However, a dearth of data is currently available specifically describing the contribution of VTE timing to survival in patients with solid tumors.

The primary objective of our study was to determine whether VTE affects survival in patients with epithelial ovarian cancer (EOC) and to determine how the chronology of VTE events with respect to surgery impacts survival. Secondary objectives were to determine whether the timing of VTE was associated with other EOC characteristics such as stage, histology, and individual surgical procedures.

Methods

A retrospective chart review was performed including 586 consecutive patients treated for epithelial ovarian cancer at The University of Oklahoma Health Sciences Center during the time period of 1/1/1996–6/30/2011. Institutional Review Board approval was obtained prior to study commencement (study #09632). Exclusion criteria were non-epithelial ovarian malignancy and lack of available follow-up data. Demographic, oncologic, and treatment characteristics were recorded. Body mass index and performance status were measured at the time of diagnosis. Patients who underwent debulking surgery (either primary or an interval procedure after neoadjuvant chemotherapy) were classified as having no gross residual disease, residual disease <1 cm, or residual disease ≥1 cm. The performance of lymphadenectomy or radical surgical procedures was recorded, with the latter including splenectomy, diaphragm stripping and/or resection, small bowel resection, or colon resection.

Venous thromboembolic events were classified by timing with respect to surgery. Preoperative VTE was defined as an event noted either concomitant with cancer diagnosis or between this time and the occurrence of surgery. Postoperative VTE was defined as any thromboembolic event occurring after the first surgery until the date of last follow-up. Additionally, postoperative VTE was classified as being perioperative (occurring between surgery and initiation of primary therapy), occurring during primary therapy, and occurring after completion of primary therapy. VTE included deep venous thrombosis (DVT), pulmonary embolus (PE), or both. Remote VTE occurring prior to cancer diagnosis were excluded from analysis due to the lack of consistent and thorough medical records pertaining to these events.

SAS version 9.3 (SAS Institute; Cary, NC) was used for all statistical analyses. Chi squared and Fisher's exact tests were used to compare categorical variables between groups defined by preoperative and postoperative VTE status. Two-sample *t*-tests/non-parametric tests were used to compare continuous variables between the groups. Progression free survival (PFS) was defined as time from completion of primary treatment to time of recurrence. If disease did not recur, PFS was censored at the date of death or last follow-up. Overall survival (OS) was defined as time from date of diagnosis to date of death. If death did not occur within our study period, OS was censored at the date of last follow-up. Median survival time was estimated by using the Kaplan–Meier survival estimator. The association between pre-operative VTE, post-operative VTE (either modeled as yes/no or modeled according to postoperative VTE timing, defined as before initiation of primary therapy, during primary therapy, and after completion of primary therapy) and survival outcomes was examined using the Cox proportional hazards model, adjusting for potential confounding factors including age at diagnosis, stage, histology, performance status, and residual disease status (none versus any). In assessing whether post-operative VTE was predictive of PFS, patients whose VTE events occurred after the time of recurrence were excluded ($n = 17$). Two-way interactions involving the exposure of interest, pre-operative/post-operative VTE, were considered. The Bonferroni correction was applied to adjust for multiple comparisons when VTE timing with 5 categories was modeled. Statistical significance was defined as a 2-sided *p*-value of <0.05 except for analyses of VTE timing, where a *p*-value of <0.0125 defines statistical significance.

Results

During the study period, 586 patients were treated for epithelial ovarian cancer. Table 1 details subject demographics. Median age was 63 (range, 17–94). The majority of patients was Caucasian (88.1%), had advanced stage disease (75.4%), and had high grade serous histology (68.3%). Ninety percent of patients were managed with primary cytoreductive surgery (rather than neoadjuvant chemotherapy), and 83.6% had cytoreduction with <1 cm residual disease (40% no gross residual, 43.6% with residual disease <1 cm). Twenty-nine percent of patients had a radical procedure, and 71.3% underwent pelvic and/or para-aortic lymphadenectomy.

Ninety-four patients experienced VTE events. Twenty-one patients were diagnosed with VTE at the time of diagnosis or during the interval between diagnosis and surgery ("preoperative VTE"). Seventy-four patients had a postoperative VTE. Of the 74 postoperative VTE, 16 (21.6%) had a postoperative VTE before initiation of primary chemotherapy. Fifteen patients (20.3%) had a postoperative VTE during primary chemotherapy, 30 patients (40.5%) had a postoperative VTE occurring after completion of primary chemotherapy, and 13 patients (17.6%) had a postoperative VTE for which the exact timing is unknown. The majority of postoperative VTE ($n = 57$ or 77.0%) occurred prior to disease recurrence. One patient had both a preoperative and a postoperative VTE. Preoperative VTE involved PE either alone or in combination with DVT in the majority of cases (62%), whereas postoperative VTE were typically only DVT (71.6%). Table 2 illustrates the VTE characteristics. Among women who underwent primary surgery ($n = 524$), 93%

Table 1
Subject demographics.

Characteristic	Number of subjects, $n = 586$(%)
Age, years (median)	63 (range, 17–94)
Hypertension	248 (42.3%)
Diabetes mellitus	63 (10.8%)
Race	
Caucasian	516 (88.1%)
African American	19 (3.2%)
Native American	18 (3.1%)
Other	33 (5.6%)
Body mass index (kg/m^2)	
<18.5 (underweight)	11 (2.0%)
18.5–24.9 (normal)	192 (34.5%)
25–29.9 (overweight)	163 (29.3%)
30–34.9 (class I obesity)	100 (18.0%)
35–39.9 (class II obesity)	43 (7.7%)
≥40 (class III obesity)	48 (8.6%)
Performance status = 0	515 (87.9%)
Stage	
I	96 (16.4%)
II	37 (6.3%)
III	361 (61.6%)
IV	81 (13.8%)
Unstaged	11 (1.9%)
Histology	
High grade serous	400 (68.3%)
Endometrioid	79 (13.5%)
Low grade serous	29 (5%)
Clear cell	28 (4.8%)
Mucinous	28 (4.8%)
Mixed/Undifferentiated	22 (3.8%)
Primary treatment modality	
Primary debulking surgery	525 (89.6%)
Neoadjuvant chemotherapy	51 (8.7%)
Quantity of residual disease	
No gross residual disease	234 (40%)
<1 cm residual disease	255 (43.6%)
≥1 cm residual disease	83 (14.2%)

Table 2
Patient characteristics classified by venous thromboembolic events.

Characteristic	Number of subjects (%)	*p*-value
Pre-operative VTE	21 (3.7%)	n/a
DVT	8 (38.1%)	
PE	7 (33.3%)	
Both	6 (28.6%)	
Post-operative VTE	74 (13.2%)	n/a
DVT	53 (71.6%)	
PE	18 (24.3%)	
Both	3 (4.1%)	
Body mass index (median)		0.19
+pre-operative VTE	32.19	
No pre-operative VTE	27.05	
Body mass index (median)		0.48
+post-operative VTE	29.37	
No post-operative VTE	28.70	
HGS histology		0.004
+pre-operative VTE	15 (3.9%)	
No pre-operative VTE	374 (96.1%)	
CCC histology		
+pre-operative VTE	4 (14.3%)	
No pre-operative VTE	24 (85.7%)	
Non-HGS or CCC histology		
+pre-operative VTE	2 (1.3%)	
No pre-operative VTE	149 (98.7%)	
HGS histology		0.003
+post-operative VTE	63 (16.5%)	
No post-operative VTE	318 (83.5%)	
CCC histology		
+post-operative VTE	2 (7.1%)	
No post-operative VTE	26 (92.9%)	
Non-HGS or CCC histology		
+post-operative VTE	9 (6.0%)	
No post-operative VTE	142 (94.0%)	
CA125 level (median)		0.041
+pre-operative VTE	478.00	
No pre-operative VTE	242.50	
CA125 level (median)		0.0009
+post-operative VTE	494.00	
No post-operative VTE	226.25	
Platelet count (median)		0.48
+pre-operative VTE	338.50	
No pre-operative VTE	327.00	
Platelet count (median)		0.16
+post-operative VTE	349.00	
No post-operative VTE	323.00	
No gross residual disease		0.62
+preoperative VTE	8 (47.06%)	
No preoperative VTE	222 (41.11%)	
No gross residual disease		0.08
+postoperative VTE	24 (32.43%)	
No postoperative VTE	206 (43.37%)	
Advanced stage		0.27
+preoperative VTE	17 (89.5%)	
No preoperative VTE	411 (76.3%)	
Advanced stage		<0.001
+postoperative VTE	72 (97.3%)	
No postoperative VTE	348 (73.1%)	
Radical procedures		0.08
+preoperative VTE	2 (10.00%)	
No preoperative VTE	160 (29.36%)	
Radical procedures		<0.001
+postoperative VTE	38 (51.35%)	
No postoperative VTE	119 (24.64%)	
Complete response to primary therapy		0.006
Pre-operative VTE	11 (52.38%)	
No pre-operative VTE	404 (79.68%)	
Complete response to primary therapy		0.22
Post-operative VTE	54 (72.97%)	
No post-operative VTE	356 (79.64%)	

HGS = high grade serous, CCC = clear cell carcinoma.

received adjuvant chemotherapy. VTE did not delay adjuvant chemotherapy as the interval from surgery to initiation of therapy was similar between those with and without VTE (median: 4.27 weeks versus 4.27 weeks, $p = 0.91$). Among patients who received neoadjuvant chemotherapy ($n = 52$), all received post-surgery chemotherapy. Patients who developed VTE after completion of primary therapy ($n = 30$) had all received platinum-based chemotherapy.

Table 2 also shows the comparison between VTE groups in terms of demographic, clinical and treatment characteristics. Platelet count (K cells/mm^3) did not differ with preoperative (median: 338.5 versus 327.0, $p = 0.48$) or postoperative VTE (median: 323.0 versus 349.0, $p = 0.16$). In order to study the effect of preoperative platelet count on postoperative VTE formation, we focused on VTE occurring prior to completion of primary chemotherapy. Additionally, CA125 levels (units/mL) were higher in patients with both preoperative (median 478.0 vs 242.5, $p = 0.041$) and postoperative VTE (494.0 vs 226.3, $p = 0.0009$) as compared to patients without these thrombotic events. Body mass index (BMI, kg/m^2) was similar between preoperative VTE groups ($p = 0.19$) and postoperative VTE groups ($p = 0.48$) in comparison to patients without VTE. Patients with clear cell histology were most likely to have a preoperative VTE ($p = 0.004$), whereas patients with high grade serous histology were most likely to develop a postoperative VTE ($p = 0.003$). However, the timing of postoperative VTE (prior to initiation of primary chemotherapy, during primary therapy, or after primary chemotherapy) was not associated with histology ($p = 1.0$). Advanced stage disease was associated with postoperative (97.3% versus 73.1%, $p < 0.001$) but not preoperative VTE.

Patients with preoperative VTE had a shorter PFS (median: 6.4mo versus 22.5mo) and a shorter OS (median: 18.9 months versus 66.7 months) as compared to patients without preoperative VTE. Also, patients with postoperative VTE had a shorter PFS (median: 14.8 months versus 25.2 months) and a shorter OS (median: 48.0 months versus 83.5 months) as compared to patients without postoperative VTE. Preoperative VTE was an independent predictor of OS (HR = 3.1, 95% CI: 1.6–6.1, $p = 0.001$) but not PFS (HR = 1.2, 95% CI: 0.6–2.4, $p = 0.55$). Postoperative VTE was an independent predictor of both PFS (HR = 1.45, 95% CI: 1.04–2.02, $p = 0.03$) and OS (HR = 1.8, 95% CI: 1.3–2.6, $p = 0.001$). When analyzing PFS according to VTE timing, there was no association between VTE timing and PFS after adjusting for multiple comparisons (all *p*-values >0.0125). When analyzing OS according to VTE timing, preoperative VTE was independently predictive of OS (HR 3.5, 95% CI: 1.8–6.9, $p < 0.001$), and postoperative VTE was independently predictive of OS only when occurring after completion of primary chemotherapy (HR 2.3, 95% CI: 1.4–3.6, $p = 0.001$). In assessing the effect of postoperative VTE on OS, we also conducted a sensitivity analysis excluding patients with postoperative VTE after cancer recurrence; the results were similar (HR: 1.7 vs. 1.8, 95% CI: 1.1–2.5 vs. 1.3–2.6, *p*-value: 0.009 vs. 0.001). Table 3 summarizes the results from the multivariate analyses.

Discussion

Our results demonstrate that both preoperative and postoperative VTE events render a survival detriment with epithelial ovarian carcinoma. The impact of preoperative VTE on overall survival was provocative as this was associated with a ~3-fold increase in the risk of death. This is in accordance with data from Sorensen et al who reported that VTE at the time of cancer diagnosis confers a particularly poor prognosis with a grim 1-year survival rate of 12% ($p < 0.001$). That study included a heterogeneous group of 3135 cancer patients [14]. VTE at the time of diagnosis has previously been noted to have a profound impact on overall survival with clear cell ovarian carcinoma, suggesting that a paracrine circuit involving thrombosis contributes to shortened survival in this select group of patients [11]. However, to our knowledge, this is the first study evaluating the impact of VTE timing with respect to surgery on survival with all histologies of EOC patients. Additionally, we found that postoperative VTE was associated with a 45% increase in the risk of recurrence. VTE occurring in the setting of malignancy is a surrogate of biologically more aggressive disease due to a molecular

Table 3
Progression free and overall survival with venous thromboembolic events.

Multivariate analysis	Hazard ratio	95% confidence interval	*p*-value
Progression free survival			
Pre-operative VTE (yes/no)	1.5	(0.6, 2.4)	0.55
Progression free survival			
Post-operative VTE (yes/no)	1.45	(1.04, 2.02)	0.03
Progression free survival (analyzed by timing)[§]			
Pre-operative VTE	1.5	(0.8, 2.9)	0.262
Post-op VTE: Before primary therapy	1.76	(1.01, 3.10)	0.048
Post-op VTE: During primary therapy	1.6	(0.9, 3.0)	0.120
Post-op VTE: After primary therapy	1.5	(0.7, 2.9)	0.266
Overall survival (yes/no)			
Pre-operative VTE	3.1	(1.6, 6.1)	0.001
Overall survival (yes/no)			
Post-operative VTE	1.8	(1.3, 2.6)	0.001
Overall survival (analyzed by timing)[§]			
Preoperative VTE	3.5	(1.8, 6.9)	<0.001
Post-op VTE: Before primary therapy	1.7	(0.8, 3.5)	0.139
Post-op VTE: During primary therapy	1.5	(0.7, 3.4)	0.327
Post-op VTE: After primary therapy	2.3	(1.4, 3.6)	0.001

Risk factors including stage, performance status, age, histology, and quantity of residual disease (none versus any amount of gross) were considered in constructing the final model; all significant factors in the final multivariate model were adjusted for in computing the hazard ratios.

[§] Patients with no VTE comprised the reference group of the VTE timing variable.

circuit in which thrombosis contributes to tumor propagation [10–13]. However, VTE appears to actually precipitate premature mortality with ovarian cancer. In a SEER analysis of advanced stage ovarian cancer patients, Wright et al reported that postoperative complications (including VTE) increase the risk of delayed receipt of chemotherapy and of disease-specific mortality (with ≥2 complications, HR 1.31, 95% CI: 1.15–1.49) [15]. Additionally, Khuri et al analyzed prospective, multi-center data from the National Surgical Quality Improvement Program encompassing 105,951 patients who underwent a major surgical procedure to identify determinants of survival; their results demonstrated a 42% reduction ($p < 0.001$) in median survival independently attributable to VTE, regardless of preoperative risk assessment. Other postoperative complications were similarly or even more independently predictive of shortened survival [16]. Given this impactful data that postoperative complications impact long-term outcomes, a substantial proportion of deaths could potentially be preventable with improved and tailored thromboprophylaxis. The practice at our institution has been to initiate prophylactic low molecular weight heparin (LMWH) on postoperative day #1 in hemodynamically stable patients with a cancer diagnosis and to continue this for 28 days. This is in accordance with randomized controlled trial evidence demonstrating significantly fewer VTE in patients who underwent laparotomy for an abdominal or pelvic malignancy and were given 28 days of LMWH [17]. However, given that only postoperative VTE occurring after completion of primary therapy were independently predictive of overall survival, research to identify other strategies to reduce morbidity and mortality related to VTE occurring remote from surgery and therapy is necessary.

Patients with postoperative VTE were more likely to have had any radical procedure (51.4% versus 24.6%, $p < 0.001$). This seems physiologically plausible given the greater endothelial damage and possibly longer immobilization due to prolonged operative time. CA125 levels were higher in patients with preoperative VTE and those with postoperative VTE as compared to patients without thrombotic events, again suggesting that development of VTE in ovarian cancer patients reflects a combination of biologic tumor aggression and a defect in host defense mechanisms [10]. The considerable risk of subsequent VTE in patients with a reactive thrombocytosis has previously been demonstrated in other solid tumors. Ho et al reported a 5.3 times greater risk of VTE in intensive care unit patients with thrombocytosis after adjusting for other factors [18]. However, we did not note a significant difference in preoperative platelet count of patients who developed a postoperative VTE either before or during primary chemotherapy.

We did not find that body mass index was related to preoperative or postoperative VTE formation. This is in stark contrast to prior reports in both non-surgical and surgical patients. Parkin et al demonstrated that increasing BMI is an independent risk factor for postoperative VTE; overweight and obese women experienced 1.5-fold greater VTE than their normal weight counterparts [19]. Other authors have similarly demonstrated escalating BMI as a risk factor for VTE [20–25]. However, we feel that we did not have the ideal population to study this association, given the relatively small number of VTE events in our lean group of patients, as 65.8% of subjects had BMI <30.

There are several limitations to this study. First, retrospective data collection lends to incomplete records and ascertainment bias. Next, we did not have information pertaining to underlying thrombophilic disorders or other conditions potentially predisposing to VTE. Third, it is likely that not all VTE were captured as patients may have sought medical care at a facility close to their home. Fourth, we did not have a reliable method to ascertain whether patients were compliant with prescribed postoperative anticoagulation regimens; thus, the observed VTE rate may have been higher than it would have been with perfect use of anticoagulation.

In conclusion, both preoperative and postoperative VTE are independent predictors of poor survival with EOC. The impact on overall survival is more profound in patients with a preoperative VTE, as they experienced almost three-fold greater mortality risk. Additionally, patients who develop a VTE prior to recurrence have a shorter progression free interval. Further study is warranted given the association between VTE and survival in EOC patients, given that VTE is a potentially preventable event. Prospective trials should incorporate the knowledge gained herein to unveil superior thromboprophylactic strategies for patients at particularly high risk.

Conflict of interest

All authors report no relevant conflicts of interest.

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