Outcomes for Epithelial Ovarian Cancers Diagnosed with Concomitant Venous Thromboembolism

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Abstract

Background and Significance

Most large studies on venous thromboembolism (VTE) incidence in gynecologic cancer focus on prevention and management of postoperative VTE. Treatment for preexisting VTE at the time of diagnosis of epithelial ovarian cancer (EOC) includes careful risk assessments, weighing the benefits of debulking and risks of anticoagulation in the setting of a new VTE and new EOC diagnosis, respectively. We aimed to describe perioperative and cancer survival outcomes associated with concomitant diagnoses.

Research Question

To describe short-term perioperative outcomes and overall survival (OS) among women who present with VTE at initial EOC diagnosis.

Methods

Women presenting with VTE within 30 days prior to EOC diagnosis between 1/2/2003 and 12/30/2011 who had primary debulking surgery (PDS) or chemotherapy (CT) alone were included. Descriptive statistics and the Kaplan-Meier method were used to estimate OS from time of EOC diagnosis, with patient characteristics and process-of-care variables retrospectively abstracted.

Results

Of the 36 women with VTE within 30 days prior to EOC diagnosis, 28 (77.8%; mean age 64.2 years) underwent PDS and 8 (22.2%; mean age 61.4 years) received CT alone. Eastern Cooperative Oncology Group (ECOG) performance status (PS) was ≤2 in 85.7% (n=24) of PDS patients compared to 62.5% (n=5) of CT patients. Advanced stage (III/IV) disease was diagnosed in 71.4% (n=20) of PDS group; all CT patients were advanced stage. Among those who underwent PDS, 26 (92.9%) had a preoperative IVC filter placed; 1 (12.5%) in the CT group received an IVC filter. Perioperative bleeding complications were 7.2% in the PDS group. Within the PDS group, median OS was 25.6 months while the CT group had median OS of 4.5 months.

Conclusions

Preoperative VTE in EOC patients can be safely managed with low rates of bleeding complications. Poor OS in CT group may reflect worse overall health or more aggressive cancer. Median OS was notably shorter than previously published; IVC filter utilization on oncologic outcomes in EOC warrants further investigation.

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Introduction

Advances in technology and therapy have improved our ability to diagnose and treat deep venous thrombosis (DVT) and pulmonary embolus (PE) (collectively referred to as venous thromboembolism (VTE) events). In the setting of cancer, the risk of VTE is increased and the mortality rate associated with VTE development is highest among cancer patients who undergo surgery. Postoperative VTE most often occurs in the setting of advanced breast, hepatic, pancreatic, lung, and, importantly, epithelial ovarian cancer (EOC) (1). The rate of VTE at the time of EOC diagnosis has been reported to range from less than 1% for clinically evident VTE (2) up to 40% for asymptomatic or symptomatic postoperative VTE (3). The rate of VTE in gynecologic cancer is high (4). In fact, among acute deaths after cancer surgery, nearly 50% are secondary to VTE (3) (5). It has been estimated that approximately 25% of women with newly diagnosed EOC also have a subclinical VTE and prevention of life-threatening VTE-associated complications is important (6). Fatal PE occurs in 1% of women diagnosed with concomitant EOC and VTE, and is often preceded by an asymptomatic DVT (7). In addition to immediate perioperative VTE risk, women who have gynecologic cancer surgery appear to remain at higher risk for VTE up to, and perhaps beyond, 3 months after surgery (8). VTE can be the initial presenting symptom of an underlying malignancy and the likelihood of a cancer diagnosis is substantial within the first few months following a thromboembolic event (2). Additionally, well-documented risk factors for VTE development—age >60 years, previous VTE, surgery lasting >2 hours, bed rest >3 days, and advanced stage cancer (9)—are often present in women diagnosed with EOC and most can occur prior to surgical intervention for EOC.

While aggressive surgical cytoreduction is associated with improved survival in the setting of primary EOC (10), management of a concomitant VTE requires balancing anticoagulation and prevention of perioperative bleeding. One strategy to reduce the likelihood of perioperative life-threatening PE is preoperative placement of an inferior vena cava (IVC) filter. In general, survival from a perioperative VTE does not appear to be negatively influenced by utilization of an IVC filter and, among patients who cannot receive therapeutic anticoagulation, IVC filter placement alone improves VTE-associated survival (11).

Most studies on VTE in gynecologic cancer concentrate on prevention and management of postoperative VTE (8) (12) (13) (14). Women presenting with preexisting VTE at the time of diagnosis of EOC represent a unique population and challenges to treatment. Given the delicate balance between the risks and benefits of both anticoagulation and debulking in the setting of a new VTE and new EOC diagnosis, respectively, we aimed to describe perioperative and cancer survival outcomes associated with concomitant diagnoses in a tertiary referral center.

Methods

Study Population and Data Collection

Women diagnosed with primary EOC, peritoneal carcinoma and fallopian tube carcinoma (collectively referred to henceforth as "EOC"), were identified at Mayo Clinic in Rochester, Minnesota between January 2, 2003, and December 30, 2011. Using both surgical and medical indices and the International Classification of Diseases, Ninth Revision (ICD-9), codes for ovarian, primary peritoneal and fallopian tube carcinoma as well as VTE (either DVT or PE) were used to identify all women diagnosed with both primary EOC and VTE within 30 days prior to EOC treatment. Patients were excluded if they were diagnosed with non-epithelial ovarian cancer, recurrent EOC, non-ovarian cancer, or did not consent to their medical record being used for research.

Patient characteristics, risk factors, and perioperative variables as defined by the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP), were retrospectively abstracted. VTE was defined as any clinically diagnosed thrombus identified by imaging, including portal vein and IVC thrombi. Variables abstracted included, but were not limited to, age, body mass index (BMI), past medical history and comorbidities, smoking status, mode of EOC diagnosis, International Federation of Gynecology and Obstetrics (FIGO) stage and grade, histology, VTE type and location, ascites, primary cancer treatment, IVC filter placement, Eastern Cooperative Oncology Group performance status (ECOG PS), American Society of Anesthesiologists (ASA) score, pre-treatment laboratory data, postoperative complications, cancer progression/recurrence, and vital status. If a patient had less than 6 months of follow-up within the electronic medical record, a survey was sent to the patient or their next of kin (in cases of known patient death). Past medical history of VTE was defined as a separate diagnosis of VTE occurring more than 30 days prior to the EOC treatment initiation.

A multidisciplinary team of gynecologic oncologists and medical oncologists determined the primary EOC treatment for each patient as part of their clinical cancer care. Primary treatments included primary debulking surgery (PDS) with adjuvant chemotherapy (PDS group) and chemotherapy alone (CT group). Among the PDS group, the date of treatment initiation

was defined as the date of PDS and all cases were histologically confirmed to be EOC based on pathology review of surgical specimens. Among the CT group, diagnosis was made via diagnostic paracentesis, thoracentesis, or fine needle aspiration and date of treatment initiation was the date that chemotherapy was started or planned to start. This study was approved by the Mayo Clinic Institutional Review Board.

Statistical Analyses

Descriptive statistics were utilized to summarize the PDS and CT groups. The Kaplan-Meier method was used to estimate overall survival (OS) from the time of EOC treatment initiation for each group.

Results

Patient Characteristics and Clinical Management

Between January 2, 2003 and December 30, 2011, 888 patients underwent PDS for EOC at Mayo Clinic in Rochester, Minnesota. Of those, 28 (3.2%) were diagnosed with VTE within 30 days prior to their PDS. During the same time period, 8 additional women were diagnosed with both biopsy-proven EOC and a new VTE within 30 days prior to the start of CT alone. Baseline characteristics of those who underwent PDS and those who received CT alone are presented (Table 1).

Among those who underwent PDS, 20 (71.4%) had advanced stage disease (III/IV), 13 (46.4%) had serous histology, and 5 (17.9%) had either grade 1 or 2 disease. Debulking to no residual disease was achieved in 19 (67.9%) and 2 (7.1%) patients had suboptimal disease resection. Twenty (71.4%) patients had documented receipt of adjuvant chemotherapy following PDS.

All who received CT alone were presumed to have advanced stage disease based on imaging, thoracentesis, or biopsy site. All had grade 3 disease. Platinum-based chemotherapy was front-line therapy for 7 out of the 8 in the CT cohort. One patient was scheduled to initiate chemotherapy, however, had rapid cardiovascular decline prior to initiation of CT and received supportive care only. Among the 7 women in the CT group, a median of 9 (interquartile range (IQR) 1, 12) cycles were completed. No patient treated with CT underwent interval debulking surgery (IDS).

Of note, 6 (21.4%) within the PDS group had a past history of VTE (diagnosed >30 days prior to their EOC diagnosis), whereas none in the CT group had a past history of VTE.

Table 1. Patient characteristics among women diagnosed with concomitant VTE and primary EC treated with primary debulking surgery (PDS) and primary chemotherapy (CT).

Characteristic	**PDS** (N=28)	**CT** (N=8)
Age (years), mean (SD)[†]	64.2 (11.5)	61.4 (5.0)
BMI (kg/m^2), mean (SD)	28.2 (5.4)	30.3 (7.3)
Mode of EOC diagnosis, N (%)		
Surgical debulking	28 (100.0)	0 (0.0)
Paracentesis	-	2 (25.0)
Thoracentesis	-	1 (12.5)
Image-guided biopsy	-	5 (62.5)
Advanced FIGO stage (III/IV), N (%)	20 (71.4)	8 (100.0)
FIGO grade, N (%)		
1	3 (10.7)	0 (0.0)
2	2 (7.1)	0 (0.0)
3	23 (82.1)	8 (100.0)
Histology, N (%)		
Serous	13 (46.4)	1 (12.5)
Endometrioid	4 (14.3)	0 (0.0)
Mucinous	1 (3.6)	1 (12.5)
Clear cell	6 (21.4)	0 (0.0)
Carcinosarcoma	1 (3.6)	1 (12.5)
Adenocarcinoma, not defined	0 (0.0)	4 (50.0)
Mixed[‡]	3 (10.7)	1 (12.5)
Ascites, N (%)	13 (46.4)	6 (75.0)
Number of primary CT cycles, median (IQR)	-	9 (1, 12)
IVC filter placed, N (%)	26 (92.9)	1 (12.5)
ECOG PS > 2, N (%)	4 (14.3)	3 (37.5)
ASA score, N (%)		
1	1 (3.6)	0 (0.0)
2	6 (21.4)	0 (0.0)
3	21 (75.0)	0 (0.0)
Unknown	0 (0.0)	8 (100.0)

Smoking status, N (%)		
Current	4 (14.3)	2 (25.0)
Past	2 (7.1)	0 (0.0)
Never	22 (78.6)	6 (75.0)
Past medical history/comorbidities, N (%)		
Previous VTE, N (%)^	6 (21.4)	0 (0.0)
Coronary artery disease	0 (0.0)	1 (12.5)
Myocardial infarction	1 (3.6)	1 (12.5)
Hypertension	10 (35.7)	5 (62.5)
Hyperlipidemia	12 (42.9)	4 (50.0)
Peripheral vascular disease	0 (0.0)	1 (12.5)
Type II diabetes	3 (10.7)	2 (25.0)
Hypothyroidism	5 (17.9)	3 (37.5)
Inflammatory bowel syndrome	1 (3.6)	0 (0.0)
GERD	5 (17.9)	1 (12.5)
Irritable bowel syndrome	1 (3.6)	0 (0.0)
Anemia	10 (35.7)	2 (25.0)
Stroke/TIA	0 (0.0)	1 (12.5)
Asthma/COPD/emphysema	3 (10.7)	0 (0.0)
Laboratory data*		
Hemoglobin (g/dL), mean (SD)	12.0 (1.4)	11.3 (2.1)
Platelets (x10^9/L), mean (SD)	342 (126)	297 (132)
Creatinine (mg/dL), mean (SD)	0.9 (0.3)	0.9 (0.2)
Albumin (g/dL), mean (SD)	3.6 (0.6)	3.2 (0.7)
CA-125 (U/mL), median (IQR)	463 (210, 1155)	510 (408, 862)
Residual disease, N (%)		
None	19 (67.9)	-
Measureable (≤1 cm)	7 (25.0)	-
Suboptimal (>1 cm)	2 (7.1)	-

Abbreviations: ASA, American Society of Anesthesiologists; CA-125, cancer antigen 125; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; GERD, gastroesophageal reflux disease; IQR, interquartile range; PE, pulmonary embolism; SD, standard deviation; TIA, transient ischemic attack.

† Age for the PDS group is age at surgery and age for the CT group is age at tissue diagnosis.

^ History of VTE defined as previous VTE event >30 days before concomitant VTE and primary EOC treatment.

** Data for the PDS group is preoperative laboratory data and lab data for the CT group is laboratory data at EOC diagnosis.*

‡ PDS: endometrioid and clear cell (n=1), serous and clear cell (n=1), serous and endometrioid (n=1); CT: serous and clear cell (n=1).

Table 2. Locations of clinically diagnosed VTEs.

Characteristic	**PDS** (N=28)	**CT** (N=8)
Type of VTE, N (%)		
DVT	13 (46.4)	3 (37.5)
PE	8 (28.6)	2 (25.0)
DVT and PE	7 (25.0)	3 (37.5)
DVT location, N (%)		
Calf	4 (20.0)	1 (16.7)
Knee	4 (20.0)	1 (16.7)
Thigh	8 (40.0)	2 (33.3)
Pelvis	3 (15.0)	0 (0.0)
Unknown/unclear	1 (5.0)	0 (0.0)
Abdominal vessels	0 (0.0)	2 (33.3)

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

VTE Location and Treatment

PE was diagnosed in 15 (53.6%) of the PDS group and in 5 (62.5%) of the CT group. Two (25.0%) patients within the CT group were diagnosed with VTE within an abdominal vessel—one within the inferior vena cava and one within the portal vein. These patients were retained in the study as the VTE diagnosis influenced their EOC management. Details of VTE locations for each group are listed (Table 2).

Among the PDS group, 26 (92.9%) had an IVC filter placed while only 1 (12.5%) in the CT group received an IVC filter. The single patient who had an IVC filter placed in the CT group had large bilateral PEs, a dilated pulmonary artery, residual large DVT, and required interruption of her full anticoagulation for a CT-guided omental biopsy.

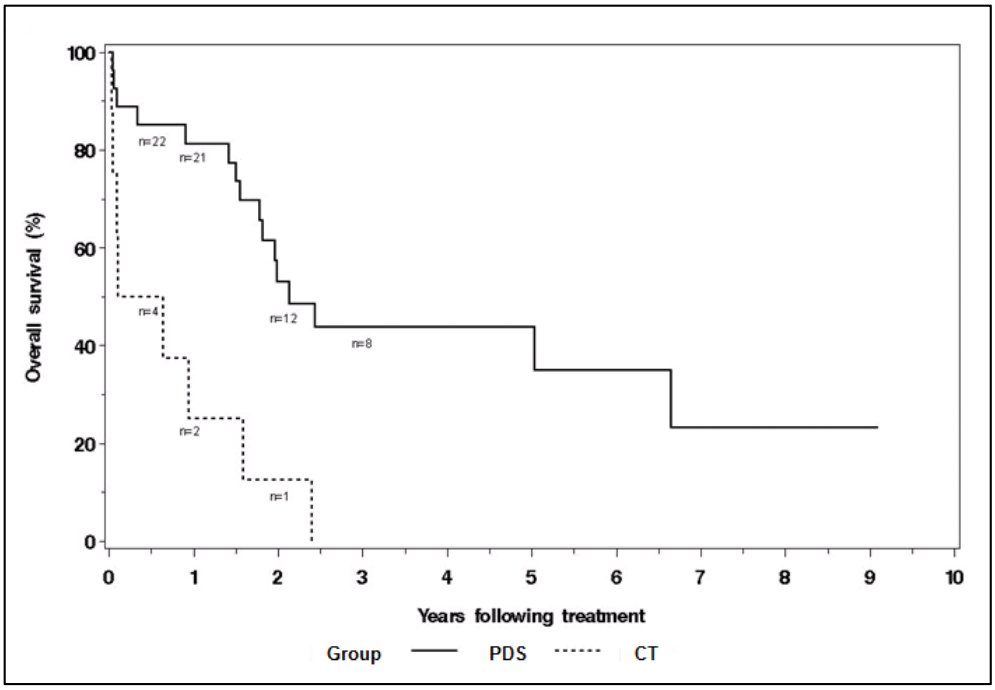
Perioperative bleeding complications within the PDS group were rare. One patient (3.6%) developed an intra-abdominal hematoma that was surgically evacuated and 1 (3.6%) developed rectal bleeding secondary to supratherapeutic anticoagulation and the presumed site of bleeding was a fresh colorectal anastomosis. There were no bleeding complications within the CT group.

Overall Survival & Perioperative Outcomes

Among those who underwent PDS, overall survival was 81.3% at 1 year after surgery, (95% CI 67.8, 97.5), 53.0% (95% CI 36.6, 76.7) at 2 years, and 43.7% (95% CI 27.7, 69.0) at 5 years with median OS of 25.6 months (Figure 1). Median OS was 25.6 months. As of the last follow-up (range 0.02-9.1 years), 12 patients remained alive. Among the 8 patients with early stage (I/II) disease, 7 (87.5%) were alive at last follow-up (range 1.7-9.1 years); among the 20 patients with advanced stage (III/IV) disease, 5 (25.0%) were alive at last follow-up (range 0.02-6.3 years). While 71.4% in the PDS group received chemotherapy, administration of adjuvant chemotherapy was unknown for 5 (17.9%) patients. Three (10.7%) patients did not receive adjuvant chemotherapy: one patient had a stage IA, grade 1 mixed endometrioid and serous EOC and she was treated with surgery alone and 2 died within 30 days of PDS (postoperative days 16 and 21). The 30-day mortality rate was 7.1% (2/28) in the PDS group.

Thirty-day mortality for the CT group was 25% (2/8). At 1 year, OS in the CT group was only 25.0% (95% CI 7.5, 83.0), median OS was 4.5 months, and all patients died within 3 years of EOC diagnosis (Figure 1).

Figure 1. Kaplan-Meier estimate of overall survival among patients diagnosed with concomitant VTE and primary EOC who underwent PDS or CT. Thirty-day mortality for the CT group was 25% (2/8). At 1 year, OS in the CT group was only 25.0% (95% CI 7.5, 83.0), median OS was 4.5 months; all patients died within 3 years of EOC diagnosis.



Discussion

Overall, the median OS was much shorter than other studies find (15) (16). Perhaps IVC filter utility on oncologic outcomes in EOC should be further investigated since one study had found an association with filters and a significant increase in metastatic dissemination, considered to be a direct cause from the filter (17). Poor OS in the CT group may be due to clinically worse overall health or more aggressive cancer. The bleeding complication rate is low among the patients who have a newly-diagnosed EOC and VTE, so surgery is a safe option.

Cytoreductive surgery for EOC often requires a high complexity operation (10) which can be complicated even further by the presence of an active VTE. Fortunately, concomitant diagnosis of EOC and clinically evident VTE in the preoperative setting represents a small proportion of the EOC patient population. Nevertheless, the ideal cancer management in the setting of a new VTE requires care in balancing the surgical risks of bleeding and/or additional clotting and the benefit of therapeutic cancer extirpation.

In our study, we observed a median OS of 25.6 months among women diagnosed with concomitant EOC and VTE who underwent PDS, while median OS was only 4.5 months among those treated with CT alone. Clinically, the CT group all had evidence of advanced stage disease and nearly 40% had ECOG PS >2. As such, the clinical decision-making regarding primary treatment took into consideration the overall health status of each patient. And the fact that none of those who received primary CT underwent IDS, suggests that the health among this group did not improve throughout chemotherapy and chemotherapy may not have positively impacted survival. Given the overall poor survival among those clinically triaged to primary CT, quality of life, palliative care, and the option of supportive care should be considered and discussed.

Interestingly, despite cytoreduction to ≤1 cm residual disease in 92.9% of the PDS group and nearly 30% of the PDS group being diagnosed with early stage disease (I-II), median OS was notably lower than median OS, which ranges from 35 to 50 months, reported in cohorts similar in stage distribution and residual disease (15) (16). Indeed the median OS in our PDS group was lower than a previous report of suboptimally debulked cases and cases who did not receive

adjuvant chemotherapy from our own institution (10). Perhaps this finding reflects the impact of the concomitant VTE on survival or that the development of VTE is a sign of worse prognosis EOC. Or perhaps an intervention to manage the VTE directly impacted survival.

Since preoperative DVT can lead to a life-threatening PE, the utilization of IVC filters has become common among patients undergoing surgery in the setting of a DVT. IVC filters appear to reduce acute VTE-related mortality in the setting of EOC debulking and the procedural risks of placement are low (7) (11). An IVC filter was placed in 92.9% of patients in our PDS group. Although there are reports of an increased long-term risk of recurrent VTE with their use, IVC filters may also be associated with worse long-term oncologic outcomes. Matsuo, et al. reported a 5-fold higher incidence of hematogenous dissemination associated with permanent IVC filter utilization in women undergoing surgery for EOC. Additionally, among those with an IVC filter, both progression-free survival and OS were worse compared to women undergoing EOC debulking who did not have an IVC filter in place (17). Interestingly, the median OS of 25.6 months in our PDS group was similar to the median OS of 22.1 months in the IVC filter group reported by Matsuo, et al (17). Whether there is a directly causal relationship or whether this finding represents an inherently poorer prognosis EOC remains unanswered. Additionally, the impact of retrievable IVC filters on oncologic outcomes in EOC has not been explored.

Despite lower than expected OS among those who underwent PDS, a proportion had excellent outcomes. In the PDS group, nearly 30% had stage I/II disease; the one patient who died of her disease died 5 years after her stage IC clear cell EOC diagnosis and her recurrences were intraperitoneal. Among the remaining 7 patients with early stage disease, 2 were alive with disease (follow-up 1.7, and 2.4 years) and 5 were without evidence of disease recurrence at the time of this study (follow-up 3.0, 3.2, 3.6, 7.0, and 9.1 years). Given the great potential for cure among early stage EOC, the chance these cancers may not require chemotherapy, and the possibility that imaging findings represent borderline or even benign disease, primary surgical resection should remain the standard of care. Additionally, DVTs among early stage EOC may be secondary to the bulk of the ovarian tumor compressing the lower extremity venous return and, as such, removal of the ovarian tumor may alleviate the primary DVT nidus.

In our PDS group, there was also one long-term survivor initially diagnosed with advanced stage disease that has had no evidence of recurrence at 6.3 years from her initial diagnosis. As such, while perioperative therapeutic anticoagulation has been shown to increase the risk of bleeding and hematoma formation in abdominopelvic surgery with rates of 3% when bridged with low molecular weight heparin up to 10% in the setting of long-term warfarin use (18) (19), the postoperative bleeding complication rate of 7% in our PDS group may be an acceptable risk in the setting of early stage or fully-resectable EOC.

Limitations of this study include the small sample size and that it was retrospective in nature. During the study period, women presenting acutely with a VTE and pelvic mass without histologic evidence of invasive EOC were not included in the study and only those with clinically diagnosed VTEs were included. Additionally, quality of life data is lacking for all patients included in the study.

Strengths of the study include the utilization of a comprehensive electronic medical record and ACS NSQIP-defined variables. VTEs were confirmed by imaging in all patients and those treated with CT alone had biopsy-proven EOC. Additionally, while EOC patients referred to our tertiary care center often receive their chemotherapy closer to their primary referral source, we utilized surveys to either the patient or their next of kin to generate the most complete follow-up data.

In conclusion, a concomitant VTE diagnosis in the setting of newly-diagnosed EOC presents a clinical situation that requires a balance between surgical risks of bleeding and/or additional clotting and potential oncologic benefits. In the setting of resectable or early stage EOC, the potential for a curative outcome likely outweighs the modest bleeding risk. Among those patients who are clinically deemed suboptimal surgical candidates, OS is substantially short and quality of life should be considered in the setting of treatment counseling. IVC filters are associated with improved short-term acute VTE-associated mortality; however, the impact of IVC filters on oncologic outcomes in EOC and whether retrievable filters mitigate hematogenous cancer dissemination requires further investigation.

Future Directions

Our study found an increased mortality rate in PDS patients with concomitant VTE diagnosis compared to other studies of comparable population except for VTE. Since Matsuo, et al. had reported a 5-fold higher incidence of hematogenous dissemination among IVC filter users within their EOC surgical cohort, the impact of retrievable IVC filters within oncologic or even gynecological malignancies should be further explored.

Conclusions

Median OS was notably shorter than previously published. IVC filter utilization on oncologic outcomes in EOC warrants further investigation. However, poor OS in CT group may reflect worse overall health or more aggressive cancer. Perioperative management of a preoperative VTE in the newly-diagnosed EOC patient can be safely done with low rates of bleeding complications. In the setting of concomitant new EOC and VTE diagnoses, if PDS is not clinically feasible, quality of life outcomes should be addressed.

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