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Full Length Article

Venous thromboembolism in epithelial ovarian cancer. A prospective cohort study

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ABSTRACT

Objective: To determine the incidence of symptomatic and incidental venous thromboembolism (VTE) at time of diagnosis and throughout the first year, in patients with suspected epithelial ovarian cancer (EOC).
Methods: Patients were recruited consecutively in the gynecological outpatient clinic at Aalborg University Hospital, Denmark from December 2014 to May 2017. All patients underwent a whole leg compression ultrasound scan (CUS), Computed Tomography (CT) of the thorax in arterial phase at time of inclusion, to be able to diagnose deep vein thrombosis (DVT) and pulmonary embolism (PE), respectively. Patients were followed and systematically screened for VTE throughout 12 months.
Results: Ninety-seven patients with suspected EOC were enrolled in the study and followed up. Within the group of EOC patients ($N = 53$) eleven were diagnosed with VTE during the first year from EOC diagnosis, the incidence of VTE at time of diagnosis was low (2/53–3.8%). No patients with borderline or benign ovarian neoplasms were diagnosed with VTE. One EOC patient had a VTE during the postoperative period and further eight EOC patients were diagnosed with VTE within the first year, during periods undergoing non-surgical cancer treatment. Median time to VTE was 87 days.
Conclusions: The one year cumulative incidence of VTE in EOC patients was 20.8% with a low incidence at time of diagnosis. A substantial number of VTE cases (73%) appeared during periods of non-surgical oncologic treatment. Future research should focus on risk factors and timing of VTE in EOC patients, as this could have important implications for future prophylaxis guidelines.

1. Introduction

Cancer is a major risk factor for the development of venous thromboembolism (VTE), and ovarian cancer is among the solid cancer types that carry the highest risk [1]. The importance of VTE in cancer was demonstrated by Sørensen et al. in a retrospective cohort study reporting that cancer diagnosed at the same time as a VTE episode, was associated with a factor 3 increase in 1-year mortality [2]. In accordance with this finding, Heath et al. recently showed that VTE at time of diagnosis significantly reduced survival in epithelial ovarian cancer (EOC) patients [3]. A prospective study from our research group, including 193 consecutive patients with colorectal cancer, revealed a prevalence of preoperative asymptomatic VTE of 7.8% [4]. Previous reports on VTE rates in EOC have primarily been based on retrospective cohort studies, with an immense variation in incidence rates and time of diagnosis. A retrospective study of 13,031 ovarian cancer patients from the Californian Cancer Registry reported a 2-year incidence of 5.2% of symptomatic VTE [5]. Tateo et al. found 16.6% symptomatic VTE cases in a retrospective study of 253 EOC patients with a median observation time of 31 months [6].

In a prospective study from Germany by Tempelhoff et al., 60 patients with EOC and borderline malignancies were screened with

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impedance plethysmography at time of diagnosis and followed up till 41 months (median 26.5 months) [7]. Only two patients (3.3%) presented with a VTE, whereas further 15 developed VTE throughout the study period. A few recent prospective cohort studies from Japan, with systematic screening for both symptomatic and asymptomatic cases, focused on VTE at time of EOC diagnosis. These studies reported incidences between 22.7 and 31% [8–10].

International guidelines recommend that prolonged thrombosis prophylaxis is considered for four weeks following major abdominal or pelvic surgery, for cancer with high-risk features [11]. It can be questioned whether this is the most beneficial approach in EOC patients, as high incidence rates are reported even prior to surgical treatment, as well as during neoadjuvant chemotherapy (NACT) [12]. Previous reports on VTE incidence are difficult to interpret, due to confusion concerning definition of VTE and differing baseline characteristics. We aimed to determine the incidence of both symptomatic and asymptomatic VTE in EOC patients, at time of diagnosis and during a one year follow up period in a Danish cohort, in order to evaluate possible risk factors for VTE, including chemotherapy.

2. Materials and methods

Study design and patient population: data were collected in a single center prospective cohort study, in order to estimate the incidence of symptomatic and asymptomatic VTE at time of diagnosis and during a one year follow up period. All patients referred to the Department of Gynecology and Obstetrics, Aalborg University Hospital in the period December 2014 to May 2017 were evaluated for inclusion in the study. Inclusion criteria were: Presentation with a pelvic mass and concurrent Risk of Malignancy Index (RMI) ≥ 200. Calculation of RMI was described by Tingulstad et al. and include; menopausal status (score 1 or 4), ultrasonography findings (score 1 or 4) and serum CA 125 level [13]. Exclusion criteria were previous (within the past three years) or concomitant cancer, connective tissue disease, current prophylactic or therapeutic anticoagulation, or lack of informed consent. Patients with malignant sex cord-stromal or germ cell ovarian tumors were excluded from the final study cohort.

All included patients provided oral and written informed consent. With these inclusion criteria, the expected study population should comprise of one third benign ovarian tumors and two thirds with malignant ovarian disease [14].

Clinical data on non-participants were found in the patient files, and evaluated in order to assess whether the included cohort was representative of the whole cohort of patients with suspected EOC at our department during the study period.

The study was approved by the local Committee on Health Research Ethics, Region Northern Jutland (re: N-20140009) and The Danish Data Protection Agency (re: 2008-58-0028). The study is registered at ClinicalTrials.gov (identifier: NCT02480790).

The present report adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [15].

Data collection: Patients were enrolled at the outpatient clinic at time of first referral. Medical history and clinical data on each patient were obtained by the gynecologic oncologist. Patients underwent systematic screening for VTE on the day of first referral or within a few days after. The day of VTE screening was set as the starting point of follow up.

Blood samples were drawn by venipuncture according to the European Concerted Action on Thrombosis (ECAT) procedures [16]. Compression ultrasound scan (CUS) including the femoral, popliteal and calf veins according to standard procedure (grey scale, color Doppler, B-mode), was performed in order to screen for deep vein thrombosis (DVT). Blood sampling was repeated on day 1 or 2 after surgery and 1, 3, 6 and 12 months after inclusion. Compression ultrasound scan was repeated on day 1 or 2 after surgery and again at 1, 6 and 12 months after inclusion. Additional CUS and/or CT-thorax were performed on suspicion, e.g. clinical symptoms or elevated D-dimer levels. Some pulmonary embolisms (PEs) were incidental findings on Computer Tomography (CT), performed in order to document disease response and status.

Staging classification followed the International Federation of Gynecology and Obstetrics (FIGO 2014) [17]. Every patient was routinely examined with a ^{18}F-labeled Fluoro-2-deoxyglucose Positron Emission Tomography and Computed Tomography (^{18}F-FDG PET-CT) of the abdomen and thorax (GE-Discovery Multi-Slice PET CT). The CT-thorax included an arterial phase to be able to diagnose PE. Patients with symptomatic and asymptomatic VTE were treated equally in accordance with American Society of Clinical Oncology guidelines [11]. VTE episodes occurring within the first month after major surgery were considered postoperative.

Thrombosis prophylaxis with low-molecular weight heparin (LMWH) and graduated elastic compression stockings was initiated 12 h before surgery, and continued throughout the hospital stay in patients with suspected ovarian cancer.

Frozen section was performed for initial diagnosis, and several fractions of fresh frozen tumor tissue were obtained for storing in The Danish Cancer Biobank. Fractions of these were used for BRCA-analysis. Pathological examination was conducted by experts in gynecopathology, the cases of EOC were classified according to WHO 2014 [18]. Epithelial ovarian cancer treatment adhered to international guidelines [19]. Neoadjuvant chemotherapy comprising of three cycles of carboplatin/paclitaxel was used for down staging in cases of primary inoperability, prior to interval debulking surgery. Six cycles of adjuvant chemotherapy with carboplatin/paclitaxel was offered to patients with stage IA-IB grade 2/3 tumors, all patients with stage IC-IIA disease and all patients with clear cell carcinomas.

Patients with advanced stage of disease were offered 6 cycles of carboplatin/paclitaxel after primary surgery and four cycles after neoadjuvant chemotherapy and secondary surgery. Bevacizumab was added in cases of remaining visible tumor after debulking surgery, or in cases of inoperability. Based on BRCA mutation status, some patients were offered treatment with Poly ADP Ribose Polymerase (PARP) inhibitors, or inclusion in protocol trials with PARP inhibitors or placebo.

2.1. Statistics

Data from previous studies were used in power calculations even though the difference in VTE incidence before and after surgery is not known when a systematic approach is used. Sample size was calculated assuming a prevalence of VTE at first referral in the benign group of maximum 3.5% and in the malignant group of 20% (null hypothesis) [9,20]. Using Fisher's exact test with a two-sided significance level of 0.05 and a power of 0.80, the required sample size was calculated to be 94 patients in the malignant group and 47 patients in the group with benign tumors. Inclusion was discontinued after the inclusion of 97 patients due to logistic reasons. Differences between EOC patients with/without VTE events were tested using Wilcoxon rank sum for continuous variables and Fisher's exact test for categorical variables. A p-value < 0.05 was considered statistically significant. The diagnostic accuracy of the Khorana score [21] was tested by calculating sensitivity, specificity, positive and negative predictive values. Cumulative incidence calculations took into account the competing risk of death. Statistics was carried out using Stata version 13 and R version 3.4.0 (R Core Team, 2017) [22].

3. Results

A total of 221 patients with suspected ovarian cancer were evaluated for inclusion into the study in the period November 2014 to May 2017. We included 97 patients; 33 patients with benign ovarian tumors, 11 with borderline tumors and 53 with EOC (including primary ovary-, fallopian tube- or peritoneal cancer) (Fig. 1 - flowchart). Baseline

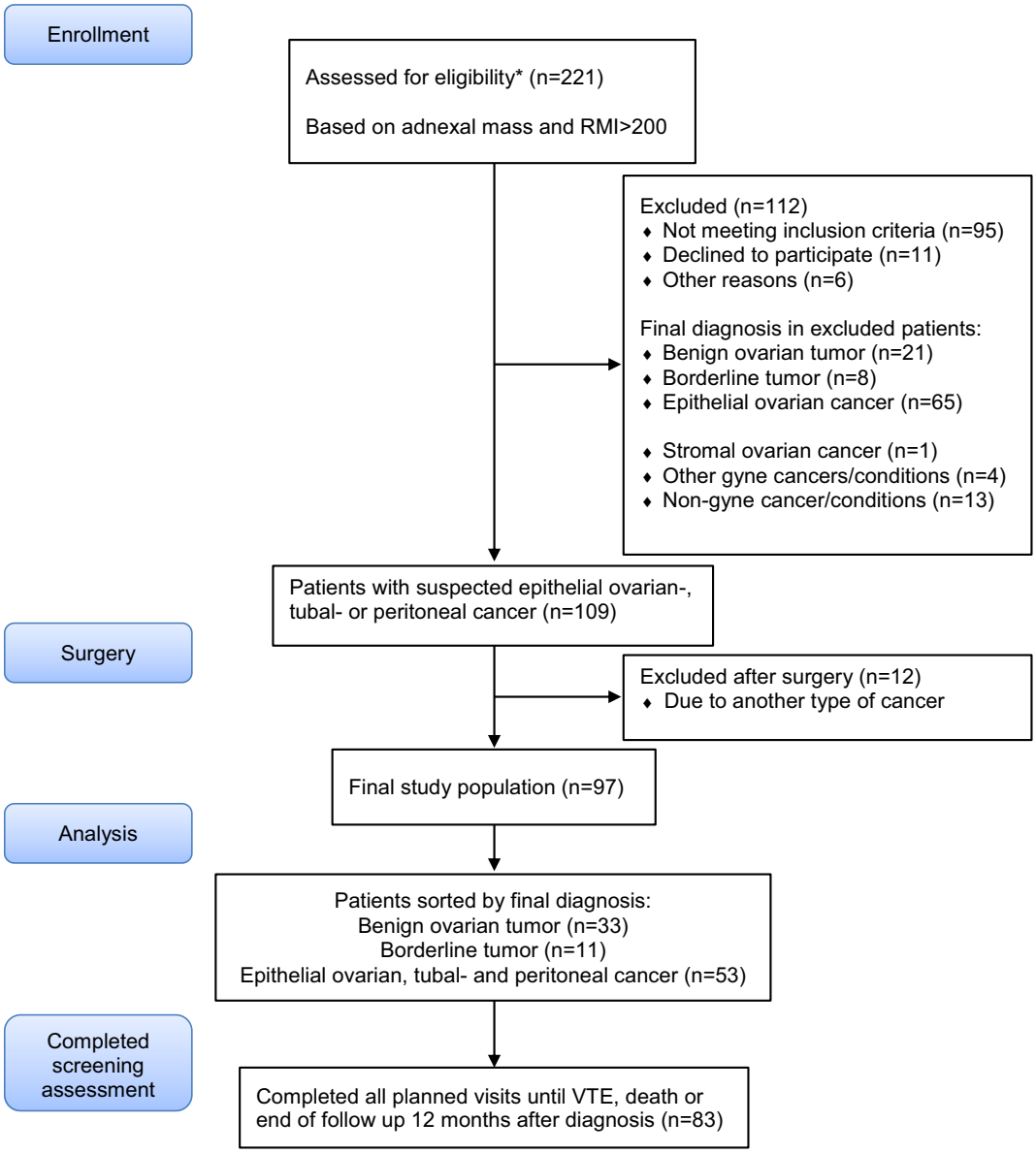

Fig. 1. Flowchart presenting the selection of study population.
*7 patients with ovarian cancer were not assessed for eligibility due to RMI < 200 (3 epithelial -, 1 germ cell -, 3 stromal cell ovarian cancers). Another type of cancer was expected in 4 patients. Consequently, they could not be included at time of diagnosis.

characteristics are provided in Table 1.

Fourteen patients were lost to follow-up, none of these patients had symptomatic VTE registered in the patient records. The remaining 83 patients attended all follow up visits. An overview of the incidence and timing of VTE events and death is provided in Fig. 2. Two patients were diagnosed with PE on the initial PET-CT scan at time of diagnosis, one patient had a postoperative PE on day one after primary surgery. Eight patients developed VTE during medical anticancer treatment > 28 days following surgery. Three developed VTE during neoadjuvant chemotherapy, three during adjuvant chemotherapy, one during palliative chemotherapy initiated due to recurrent disease. The last patient had a symptomatic PE in a protocol trial receiving PARP inhibitor or placebo.

No patients included in the clinical trial experienced any bleeding complications.

Of patients that experienced a VTE event, two had endometrioid histopathology, two were clear cell, and the remaining seven patients had high-grade serous carcinomas. Details on case characteristics, including location of VTE are provided in Supplementary Table 1. Five patients (9.4%) with EOC died during the first year after diagnosis, two of these patients were previously diagnosed with VTE, which was reported to be a likely cause of death. Two EOC patients had a history of VTE and one of them experienced a recurrent VTE during follow-up. No patients with borderline or benign ovarian tumors were diagnosed with VTE. There was no statistical significant difference between cancer patients with and without VTE events according to age, BMI (Body Mass Index), stage of disease, histologic type of EOC or Khorana score (Table 2). Two EOC patients who developed VTE were classified as intermediate risk, they both had clear cell carcinomas. We calculated the sensitivity (81.2%) and specificity (45.2%) for the Khorana score to correctly categorize patients at high risk of VTE. The positive and negative predictive values were 28.1% and 90.5%, respectively.

The cumulative incidence of VTE from EOC diagnosis through one year of follow up was 20.8% in all patients undergoing screening for VTE. The time of VTE and death measured in days after first referral is illustrated in Fig. 3, which also illustrates a low influence of death as competing risk to VTE. Data on EOC patients treated at our department

Table 1
Baseline characteristics and variables related to treatment (n = 97).

Variable[a]	Benign n = 33(34%)	Borderline n = 11(11.3%)	Carcinomas n = 53(54.7%)	Totals N = 97
Age, mean ± SD, years	62.7 ± 13.5	65.2 ± 9.8	65.2 ± 9.8	64.3 ± 11.2
BMI, median (range)	27 (16–41.5)	25.5 (18.8–31.5)	24 (18.1–46.4)	25.4 (16–46.4)
Cytoreductive status				
Complete/optimal	33 (100)	11 (100)	39 (73.6)	83 (85.6)
Suboptimal[b]			4 (7.5)	4 (4.1)
Inoperability			10 (18.9)	10 (10.3)
Oncologic treatment[c]				
Neoadjuvant CT			22 (41.5)	22 (22.7)
Adjuvant CT			20 (37.7)	20 (20.6)
Primary palliative CT			4 (7.5)	4 (4.1)
Bevacizumab			9 (17)	9 (9.2)
PARP/placebo			7 (13.2)	7 (7.2)
No chemotherapy			7 (13.2)	7 (7.2)
Histopathology				
Serous	9 (27.3)	6 (54.5)	38 (71.7)	53 (54.6)
Mucinous	3 (9.1)	5 (45.5)	1 (1.9)	9 (9.3)
Endometrioid			8 (15.1)	8 (8.2)
Clear cell			2 (3.8)	2 (2.1)
Other tumor type[d]	2 (6.1)		4 (7.5)	6 (6.2)
Ovarian fibroma	11 (33.3)			11 (11.3)
Dermoid cyst	3 (9.1)			3 (3.1)
Endometriosis	5 (15.2)			5 (5.2)
FIGO stage				
I		7 (63.6)	8 (15.1)	15 (15.5)
II		1 (9.1)	5 (9.4)	6 (6.2)
III		3 (27.3)	30 (56.6)	33 (34)
IV			10 (18.9)	10 (10.3)
ASA score				
ASA 1	11 (33.3)	8 (72.7)	16 (30.2)	35 (36.1)
ASA 2	17 (51.5)	2 (18.2)	19 (35.8)	38 (39.2)
ASA 3	5 (15.2)	1 (9.1)	18 (34)	24 (24.7)
Previous VTE			2 (3.8)	2 (2.1)

Abbreviations: BMI, Body mass index; CT, Chemotherapy; PARP, Poly ADP Ribose Polymerase; FIGO, International Federation of Gynecology and Obstetrics; ASA score, American Society of Anesthesiologists (ASA) score classification.

[a] Data are expressed as No. (%) unless otherwise indicated.

[b] Tumor tissue > 1 cm left.

[c] Column percent does not add up to 100 as one patient would receive both CT and PARP-inhibitor.

[d] The following histologic subtypes were each present in one patient: Carcinosarcoma concomitant with high grade serous carcinoma, primary Plano cellular carcinoma, primary Choriocarcinoma, undifferentiated carcinoma. Benign hydro salpinx, benign torsio adnexorum uteri with no histologic subtype due to necrosis.

in the study period, but not included in the clinical trial (non-participants), were found in the patient files. Demographic data are provided in supplementary material. Thirteen of 72 (18%) non-participants with EOC developed VTE, three patients had VTE at time of cancer diagnosis. Cases of VTE were symptomatic in 54% of the patients and incidental findings on CT status in 46%. Sixteen (22.2%) patients with EOC among non-participants died within the first year after cancer diagnosis. Rate of VTE, time of appearance and anatomical location of VTE in non-participants, was comparable to what was observed in patients participating in the clinical trial (Table 3).

4. Discussion

The main finding of this study was a low incidence (3.8%) of symptomatic and asymptomatic VTE in EOC patients at time of diagnosis. The cumulative incidence of VTE from diagnosis and throughout the first year was 20.8%.

The incidence of VTE at time of diagnosis was lower than the rate observed by Satoh et al. (3.8% vs. 25%) [9]. Based on previous publications from Japan with similar VTE screening programs, most events were expected at time of diagnosis, but 8 (73%) of 11 VTE cases in our study were diagnosed later than 30 days after referral for suspected EOC.

Epithelial ovarian cancer is characterized by significant tumor heterogeneity: Three possible sites of origin (ovary, fallopian tube and peritoneum), a broad variation in histologic subtypes and differences in grading, all influencing prognosis and the risk of complications including VTE [23,24]. Clear cell ovarian carcinoma in particular, is associated with a significantly increased risk of VTE. An American retrospective case-control study comparing risk of VTE in clear cell carcinomas versus non-clear cell found an adjusted Odds Ratio of 2.5 (CI 1.15–5.60, p = 0.024) [25]. Elevated interleukin-6 and increased expression of tissue factor in clear cell carcinomas are risk factors correlated with VTE [26,27]. The influence of histologic subtype on VTE risk could account for some of the difference in the observed incidences, since clear cell histology represents only 4.5% of all EOCs in Denmark compared to 24% in Japan [28,29]. The fact that the incidence of clear cell carcinomas is higher in Japan compared to most other countries was considered when the present study was conducted, and given that VTE events are more common in this tumor type, sample size calculation was adjusted according to this. Two patients with clear cell carcinomas (FIGO stage IC and IIIB) were included in the present study, both developed VTE.

The Khorana score categorizes all gynecologic cancers at intermediate or high-risk of developing VTE events. We tested the performance of Khorana score in our cohort and found a positive predictive value at 28.1% and a negative predictive value at 90.5%. Two patients with VTE and clear cell carcinomas were classified as intermediate risk which demonstrates the impact of the histopathological tumor type which should be considered when risk of VTE is predicted in EOC patients. Because of low power these results add little to the existing knowledge [21,30].

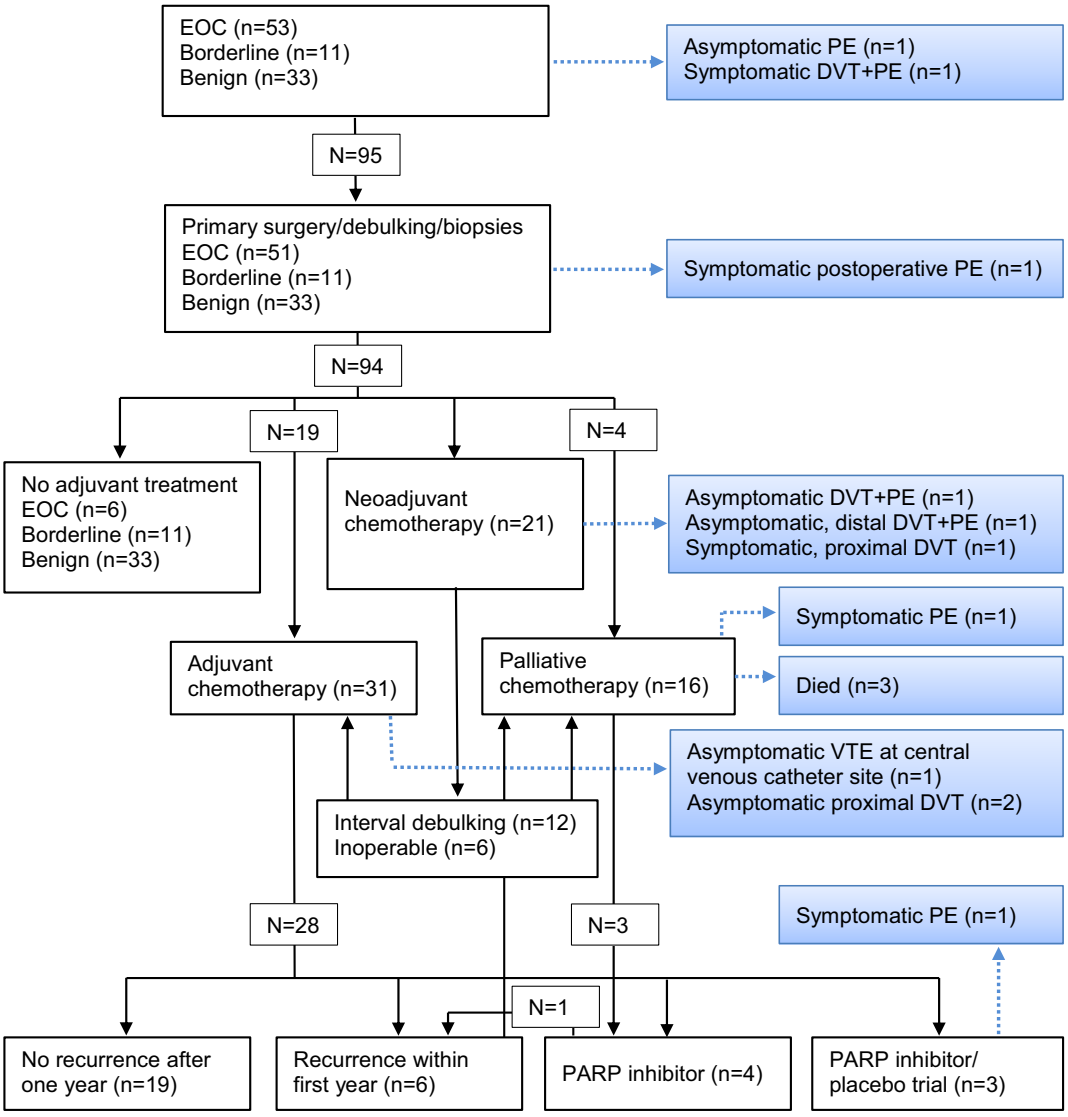

Fig. 2. Study flow illustrating number and timing of thromboembolic events and death within the first year after EOC diagnosis.
Venous thromboembolic events and death are depicted in the blue boxes.
Abbreviations: EOC, epithelial ovarian cancer; PE, pulmonary embolism; DVT, deep vein thrombosis; PARP, poly ADP ribose polymerase. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Comparison of characteristics in Epithelial Ovarian Cancer (EOC) patients with and without VTE events within the first year after diagnosis.

Variable[a]	EOC without VTE *n* = 42(79.2)	EOC with VTE n = 11(20.8)	*P*-value
Age, Mean ± SD, years	65.4 ± 9.6	64.4 ± 11	0.957
BMI, median (range)	25.5 (18.8–31.5)	23.9 (18.1–46.4)	0.114
Histopathology			
Serous	31 (73.8)	7 (63.6)	0.714
Non-serous	11 (26.2)	4 (36.4)	
FIGO stage			
I–II	10 (23.8)	3 (27.3)	1.000
III–IV	32 (76.2)	8 (72.7)	
Khorana score			
1–2 (Intermediate risk)	19 (45.2)	2 (18.2)	0.167
≥3 (High risk)	23 (54.8)	9 (81.8)	

Abbreviations: VTE, Venous thromboembolism; BMI, Body mass index; FIGO, International Federation of Gynecology and Obstetrics.
[a] Data are expressed as No. (%) unless otherwise indicated.

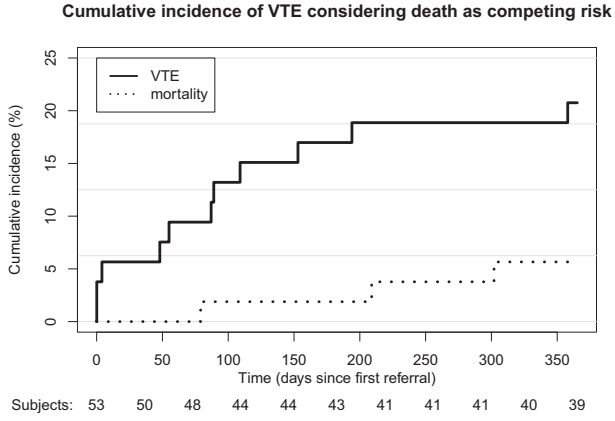

Fig. 3. Twelve-month cumulative incidence of venous thromboembolism following epithelial ovarian cancer diagnosis accounting for the competing risk of death.

Table 3
Characteristics on epithelial ovarian cancer patients developing VTE within first year of diagnosis; comparing patients participating in the clinical trial with non-participants.

Variable[a]	Patients participating (11)	Non-participants (13)[b]
VTE location		
Proximal DVT	4 (36.3)	4 (30.7)
Central PE	–	1 (7.7)
Segmental PE	–	1 (7.7)
Subsegmental PE	3 (27.3)	3 (23.1)
DVT + PE	3 (27.3)	2 (15.4)
VTE at central vein catheter site	1 (9.1)	1 (7.7)
Ovarian vein thrombus		1 (7.7)
Symptomatic vs. asymptomatic		
Symptomatic	5 (45.5)	7 (53.8)
Asymptomatic	6 (54.5)	6 (46.2)
Timing of VTE		
Median time to VTE, days (range)	87 (0–358)	71 (0–184)
Before treatment[c]	2 (18.1)	3 (23.1)
Postoperative VTE	1 (9.1)	1 (7.7)
During adjuvant chemotherapy	3 (27.3)	2 (15.4)
During neoadjuvant chemotherapy	3 (27.3)	4 (30.8)
During palliative chemotherapy	1 (9.1)	3 (23)
During randomized trial with PARP-inhibitor/placebo	1 (9.1)	

Abbreviations: VTE, Venous thromboembolism; DVT, Deep vein thrombosis; PE, Pulmonary embolism.

[a] Data are expressed as No. (%) unless otherwise indicated.

[b] Concomitant disease in non-participants with possible influence on risk of VTE (each disease was present in one patient): FIGO stage I endometrial cancer, relapsed small cell lung cancer, rheumatoid arthritis. One patient developed PE + DVT during hospitalization with neutropenic fever.

[c] Two non-participants with VTE diagnosed within a year (92 and 279 days respectively) before cancer diagnosis are not included in the table.

Inconsistent reports on the prevalence of VTE at time of diagnosis between different clinical trials could partly be due to misclassification of DVT. In the present study, DVT is defined as a thrombus arising in a deep vein of the body and deep veins of both legs were screened with CUS consistent with previous literature [31,32]. In two studies, patients underwent systematic screening for VTE, which was present in > 20% at the time of EOC diagnosis, however, more than half of these cases were either intramuscular or superficial vein thrombosis(SVT) (9 of 16 and 14 of 25 cases respectively) [9,10]. Superficial vein thrombosis should not be classified as DVT, since only 3.4% of SVT progress to DVT or PE [33].

Seventy-three percent of the VTE cases in the present study, were observed during non-surgical oncologic treatment in both patients with active cancer, but also following optimal cytoreductive surgery. These results indicate that EOC patients would probably benefit from thrombosis prophylaxis during outpatient oncologic treatment. However, the PROTECHT trial did not show any statistical significant difference in VTE risk (RR 0.5, CI: 0.22–1.14) comparing LMWH vs. placebo prophylaxis in a mixed cohort of outpatients receiving chemotherapy for metastatic or locally advanced cancers [34,35]. In a retrospective analysis of the PROTECHT population, Barni et al. aimed to identify subgroups of patients at higher risk of thromboembolic events according to the type of chemotherapy [36]. The results indicated that outpatients in carboplatin-containing regimens had a high incidence of thromboembolic events (5.5%), which was reduced with 85% if LMWH was administered, but the study was insufficient in statistical power.

Treatment regimens of EOC have changed over the last decade with the implementation of neoadjuvant chemotherapy with delayed debulking surgery for selected patients, as well as introduction of targeted therapies, such as angiogenesis inhibitors for patients with residual disease and PARP inhibition in BRACA mutated tumors. All of these factors contribute to further heterogeneity of the EOC population. In a retrospective cohort study, Greco et al. followed patients with advanced EOC scheduled for interval debulking surgery and found that 11.6% developed VTE during neoadjuvant chemotherapy [12]. Three out of twenty-one (14.3%) patients in the present study were diagnosed with VTE during neoadjuvant chemotherapy, which increased comorbidity and preoperative risk assessment.

The median time to occurrence of VTE of 87 days in the present study, suggests that selected EOC patients might benefit from an increased duration of thrombosis prophylaxis longer than 28 days after debulking surgery. This is supported by Sweetland et al. who found an increased risk of VTE up to 12 weeks following surgery, but information on adjuvant therapy following cancer surgery was lacking [37]. Furthermore, the benefit of 28 days prolonged prophylaxis was questioned by Schmeler et al. as the decrease in 30-day VTE incidence induced by 28 days of prophylaxis was not sustained after 90 days in a retrospective analysis of EOC patients undergoing surgery before and after implementation of extended prophylaxis [38]. The lack of a randomized controlled trial, to determine the impact of different EOC treatment modalities on VTE risk, was addressed by Swier et al. in a recent review [39]. Previous studies are mostly observational and divergent in study design and follow up methods and time, which makes it difficult to compare the results, and distinguish between cancer and treatment related risk factors.

The strength of our study is the consecutive inclusion of patients and consequent objective examination with CUS by the same experienced physician, as well as initial CT-angiography in all patients. This enables a more exact indication of the time where EOC patients develop VTE. We did not find any evidence to support the hypothesis suggested by Satoh et al., that asymptomatic VTE cases arise prior to surgery and become clinically evident during the postoperative period [9]. The prospective design of the study enabled us to exclude patients with known risk factors that could increase incidence of VTE regardless of EOC diagnosis or treatment.

A limitation of this study, was that a large number of EOC patients treated at our department were not included and 14% of the included patients did not complete the planned follow up. Lack of inclusion could in part be explained by selection bias, as morbidity and mortality was higher among non-participants compared with patients participating in the clinical trial [40]. For this reason, we would expect at least equivalent rates of VTE's among non-participants if they underwent the same VTE screening program. Another limitation is that we did not reach our calculated sample size. Retrospectively, we realized that the initial sample size calculation was based on a histologically different background population and misclassification of DVT. The actual statistical analysis was limited by the small sample size and we did not attempt to use multivariable regression analysis to reveal specific significant risk factors, since the study was statistically underpowered for this type of analysis. Observational studies with larger cohorts and landmark analyses during the period of treatment for EOC are needed, in order to draw conclusions on the exact incidence and significant risk factors associated with VTE.

This present study shows that EOC patients are at high risk of a VTE event not only in the first month following debulking surgery, but throughout their anticancer treatment. Our results indicate that VTE prophylaxis should be extended throughout the entire treatment period. Interventional studies should be conducted with the aim of clarifying the optimal treatment regimens of VTE prophylaxis.

Conclusion: The incidence of VTE at time of EOC diagnosis, was lower than previously reported (3.8%). We found that patients were at risk of developing VTE throughout the whole study period of one year, resulting in incidence rates of 20.8% and 87 days median time to event. This indicates that duration of VTE prophylaxis should extend previous recommendations, in selected patients. An interesting finding was that 73% of all VTE cases occurred during non-surgical oncologic treatment.

A larger cohort is needed to define risk factors of VTE, which could have significant implications on future VTE prophylaxis policies.

Authorship

Contribution: HSK, AAK and OTU designed the study. OBC, CTP, AG, VI were involved in planning the project. HSK and AAK enrolled the patients. HSK performed compressive ultrasound scan at enrollment and follow up visits. AG contributed to histopathological examination of tumor tissue. VI scheduled and interpreted the PET-CT scan including CT-thorax in arterial phase. HSK analyzed and interpreted the data and wrote the manuscript. AAK, OTU, OBC, CTP, AG, VI interpreted the data and reviewed the manuscript.

Source of the study

Observational consecutive single center cohort study with 12 months follow up.

Declaration of competing interest

The authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.07.027.

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