Venous thromboembolism in women with ovarian cancer undergoing neoadjuvant chemotherapy prior to cytoreductive surgery: A retrospective study

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Abstract

Introduction: Ovarian cancer is associated with a venous thromboembolism risk of at least 7.2% by 2 years from diagnosis, and although patients undergoing surgery benefit from routine thromboprophylaxis, those undergoing neoadjuvant chemotherapy do not. This study aims to determine the venous thromboembolism incidence in patients with ovarian cancer undergoing neoadjuvant chemotherapy, and explore whether any subset is at higher risk, in order to evaluate whether thromboprophylaxis is justified in some or all of these patients.

Material and methods: This was a retrospective review of all women undergoing neoadjuvant chemotherapy for FIGO radiological stages III and IV primary ovarian, fallopian tube, and primary peritoneal cancer, between 2000 and 2015, in a London tertiary cancer center. The primary outcome was venous thromboembolism rate among women undergoing neoadjuvant chemotherapy. The secondary outcomes were patient or treatment factors associated with venous thromboembolism risk, including age, body mass index, smoking status, performance status, and tumor stage.

Results: We identified 278 eligible women from the ovarian cancer database. Fifty-eight women (20.9%) developed venous thromboembolism between initial presentation and the immediate postoperative period, of which 45 (77.6%) developed a pulmonary embolism. In all, 15.1% of women developed venous thromboembolism from the start of neoadjuvant chemotherapy. Age, body mass index, smoking, or other comorbidities were not significantly associated with venous thromboembolism risk.

One woman died from massive pulmonary embolism, 27 women underwent inferior vena cava filter insertion, and 10 had surgery delayed.

Conclusions: This study demonstrates an unacceptably high rate of avoidable venous thromboembolism including pulmonary embolism in these women, which complicates and delays treatment. Thromboprophylaxis during neoadjuvant chemotherapy should now be assessed prospectively.
1 | INTRODUCTION

Patients with cancer have a high risk of developing venous thromboembolism (VTE), and this incidence has increased over recent years, possibly as the result of increased detection, thrombogenicity of current treatments, and the use of indwelling venous catheters. Chemotherapy is a significant risk factor for VTE, which commonly causes substantial morbidity, including delays to cancer care, and is a leading cause of mortality in ambulatory chemotherapy patients. Ovarian cancer has one of the highest VTE incidences among solid tumors, with a 2-year cumulative incidence of 7.2% in a Danish national cohort study. This is likely due to a combination of widespread disease at diagnosis, venous stasis from pelvic masses, and chemotherapeutic agents, all of which are known to promote coagulation.

Epithelial ovarian cancer typically presents with advanced disease, and management involves either upfront debulking surgery followed by adjuvant chemotherapy, or neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS), which is non-inferior for selected patients. Current practice in many countries is for women undergoing ovarian cancer surgery to have extended thromboprophylaxis for up to 30 days with low-molecular-weight heparin (LMWH). This was found to have a number-needed-to-treat to prevent one VTE of 13–39 by a recent systematic review of major abdomino-pelvic cancer surgery.

However, there are no such recommendations for thromboprophylaxis for women with ovarian cancer undergoing NACT before IDS. For women having upfront surgery, this heightened postoperative VTE risk was found to extend into the perioperative period of adjuvant chemotherapy, demonstrating the thrombogenicity of this disease across the treatment timeline. Silent or subclinical VTE frequently occurs before surgery, and this may account for the high incidence of VTE detected immediately following ovarian cancer surgery. There is therefore good reason to expect a heightened risk of VTE during NACT for ovarian cancer, which may manifest before or immediately after IDS.

Several studies have looked at thromboprophylaxis in ambulatory cancer patients with a variety of solid tumors. A recent Cochrane review found high-quality evidence that LMWH reduced the risk of all VTE compared with placebo by 43% (relative risk 0.57, 95% CI 0.46–0.71). Factor Xa inhibitors, a class of direct oral anti-coagulants, have been studied in two major relevant placebo-controlled trials: Apixaban in the AVERT trial, which contained 25.8% of patients with ovarian cancer, and Rivaroxaban in the CASSINI trial, which contained a lower proportion of patients with ovarian cancer (6.4%). Each of these trials demonstrated a significant reduction in the rates of VTE in the intention-to-treat population, and pooled analysis found that direct oral anti-coagulants significantly reduced the risk of VTE (5.2% on treatment vs. 9.3% on placebo (relative risk 0.55, 95% CI 0.34–0.90; $p = 0.02$).

Key message

This study provides evidence that patients undergoing neoadjuvant chemotherapy for advanced epithelial ovarian cancer face an unacceptably high risk of venous thromboembolism, including pulmonary embolism. Consideration should now be given to strategies to reduce this risk, including evaluation of thromboprophylaxis.

However, in order to establish whether one or more of these agents should be offered to ovarian cancer patients during NACT, either routinely or as an ongoing trial, it is necessary to reliably estimate the incidence of VTE in these patients.

The aims of this study were therefore to identify the risk of VTE in patients with Stage III or IV epithelial ovarian cancer undergoing NACT before IDS, and to conduct an exploratory analysis as to whether this entire cohort, or a particular subset based on demographic or tumor characteristics, had an elevated VTE risk. This informs an evaluation of whether these patients may benefit from thromboprophylaxis during NACT.

2 | MATERIAL AND METHODS

A local database of prospectively collected, anonymized, ovarian cancer patient records was retrospectively searched for all women diagnosed with advanced (Stage III/IV) primary epithelial ovarian, fallopian tube, or peritoneal cancer, who underwent NACT prior to planned IDS, in a single tertiary center between January 2000 and December 2015. Patient demographic data included age, body mass index (BMI), comorbidities, smoking status, menopausal status, Eastern Cooperative Oncology Group performance status, as well as tumor histology and FIGO (International Federation of Gynecology and Obstetrics) stage.

We examined a time period from diagnosis, through NACT, pre-operative imaging, and the immediate postoperative period (within 3 days). This perioperative period was included in light of evidence that major immediate postoperative VTE arises from undetected pre-existing VTE. Information about VTE diagnosis was obtained from the clinical data repository; we recorded the date of VTE diagnosis and the need for an inferior vena cava (IVC) filter and any modification of the surgical date. A diagnosis of VTE was suspected clinically or identified incidentally on routine imaging (including pre-IDS imaging), and then confirmed by Doppler ultrasound or computed tomography pulmonary angiography in all cases. No routine screening was performed.
2.1 | Statistical analyses

Data were analyzed using SPSS version 23 (IBM). To identify the association between VTE risk and patient demographics or tumor subtype, the odds ratios and 95% CI were calculated. Mann-Whitney U test was used and all analyses were two-sided with a significance level of \( p = 0.05 \).

2.2 | Ethical approval

This project was registered and approved by the University College London Hospitals National Health Service Foundation Trust’s Department of Women’s Health internal review board as an audit and evaluation of routine service provision on February 4, 2016.

3 | RESULTS

3.1 | Demographics

Three hundred and two women were identified; 24 of these were subsequently excluded because of pre-existing anti-coagulation or a lack of sufficient data about VTE outcomes, leaving 278 women suitable for analysis.

Demographic information and tumor characteristics are shown in Table 1. The median age was 67 years for the VTE group and 63 years for non-VTE group, the median BMI was 24.1 kg/m\(^2\) for the VTE group and 25.0 kg/m\(^2\) for the non-VTE group. There were no statistically significant differences between the VTE and non-VTE groups for any of the underlying clinical and demographic features recorded. Although there was no statistically significant difference for most tumor subtypes, two out of three patients with clear-cell histology (odds ratio 7.80, 95% CI 0.69–87.8, \( p = 0.10 \)), and three out of four patients with carcinosarcoma (odds ratio 11.7, 95% CI 1.19–115, \( p = 0.035 \)) developed a VTE.

3.2 | Venous thromboembolism

Fifty-eight patients (20.9%) developed a VTE. The most common site was pulmonary embolus, which occurred in 45 patients (77.6%); 12 of these patients also had a deep venous thrombosis (20.7% of VTE patients). An additional 13 patients (22.4% of VTE patients) developed a deep venous thrombosis alone (Figure 1), at sites including major vessels in the lower limb, iliac veins, infra-renal IVC, and splenic and hepatic veins, as well as the upper limb in conjunction with a peripherally inserted central catheter.

Nineteen patients (6.83%) were diagnosed with VTE at initial presentation, 33 (11.9%) developed VTE between starting NACT and undergoing IDS, with 20 of these (40%) diagnosed based on new symptoms during chemotherapy and 13 (26%) diagnosed incidentally during their interval computerized tomography scan before surgery. Six patients (2.16%) were diagnosed with VTE at other times, including the immediate postoperative period (Figure 2).

One patient died from massive pulmonary embolism (0.36% of total) during NACT. Twenty-seven patients (46.6% with VTE) underwent insertion of an IVC filter before surgery, and 10 patients (17.2%) had surgery delayed because of their VTE. No patients required modification of their surgery as a result of their VTE.

### Table 1: Demographics and tumor characteristics, characterized by presence of venous thromboembolism (VTE)

| Characteristic                  | VTE \((n = 58)\) | No VTE \((n = 220)\) | Odds ratio (95% CI) | \( p \) |
|-------------------------------|----------------|----------------------|---------------------|--------|
| Age (y)                       |                |                      |                     |        |
| Under 60                      | 17             | 80                   | 1.38 (0.74–2.58)    | 0.32   |
| 60 and older                  | 41             | 140                  |                     |        |
| Smoking status                |                |                      |                     |        |
| Non-smoker                    | 17             | 66                   | 0.55 (0.11–2.68)    | 0.46   |
| Smoker                        | 2              | 14                   |                     |        |
| Body mass index (kg/m\(^2\)) |                |                      |                     |        |
| Under 30                      | 33             | 136                  | 1.33 (0.59–2.98)    | 0.49   |
| 30 and over                   | 10             | 31                   |                     |        |
| Premenopausal                 | 7              | 5                    | 0.88 (0.36–2.18)    | 0.79   |
| Postmenopausal                | 43             | 174                  |                     |        |
| Previous malignancy           |                |                      |                     |        |
| Yes                           | 9              | 30                   | 1.16 (0.52–2.61)    | 0.79   |
| No                            | 49             | 190                  |                     |        |
| Stage                         |                |                      |                     |        |
| III                           | 30             | 106                  | 0.83 (0.45–1.52)    | 0.55   |
| IV                            | 23             | 98                   |                     |        |
| Histology                     |                |                      |                     |        |
| High grade                    | 49             | 191                  |                     |        |
| Serous                        | 0              | 4                    | 0.43 (0.02–8.12)    | 0.57   |
| Mucinous                      | 0              | 6                    | 0.30 (0.01–5.37)    | 0.41   |
| Endometrioid                  | 2              | 1                    | 7.80 (0.69–87.8)    | 0.10   |
| Clear cell                    | 3              | 1                    | 11.7 (1.19–115)     | 0.035  |
| Carcinosarcoma                |                |                      |                     |        |
| Site of origin                |                |                      |                     |        |
| Ovary                         | 46             | 171                  |                     |        |
| Peritoneum                    | 24             | 92                   | 0.88 (0.56–1.69)    | 0.91   |
| Fallopian tube                | 0              | 9                    | 0.19 (0.01–3.40)    | 0.26   |
| Carboplatin and paclitaxel    |                |                      |                     |        |
| No                            | 11             | 31                   |                     |        |
| Yes                           | 47             | 189                  | 0.70 (0.33–1.50)    | 0.36   |

4 | DISCUSSION

These results demonstrate high rates of VTE in women undergoing NACT for ovarian cancer; with 20.9% of patients affected, of
which the majority developed a pulmonary embolism, and others had thromboses in major pelvic and abdominal vessels. VTE that occurs after the time of tumor diagnosis and NACT decision can be considered as potentially avoidable, and so excluding those patients with VTE diagnosed around the time of cancer presentation leaves 15.1% of patients diagnosed with VTE from the decision for NACT. Although mortality was relatively low, any VTE causes distress to patients, interrupts and often delays therapy, and almost half required additional procedures such as an IVC filter insertion before surgery. In our study, individual patient characteristics were not significantly associated with VTE risk. This leads to an inability to identify a higher-risk subgroup from these results, and we therefore conclude that the entire cohort is at risk.

To our knowledge, this study constitutes the largest review of VTE risk in patients with ovarian cancer undergoing NACT. Although baseline patient data were collected prospectively our analysis was retrospective, so some data were missing, primarily for those patients before 2010. However, we do not consider that this affected the overall analysis, with a generally high degree of detail available in the individual patient medical records. We were not able to analyze whether laboratory results such as anemia, elevated platelet or leukocyte counts were associated with VTE in our groups. These are known to be associated with VTE in ovarian and other cancers, with reactive thrombocytosis being a common occurrence in ovarian cancer, associated with ascitic interleukin-6 levels, so the omission of these data is a potential limitation.

We did not identify patient characteristics associated with VTE diagnosis in our exploratory analysis, which may be a result of the numbers in our series. Of note, BMI was not associated with VTE in our study, although an association is well known. We speculate that this is due to the low number of patients with recorded raised BMI in our study, along with the possibility that disease and treatment-related prothrombotic mechanisms may outweigh the effect of patient-related factors such as BMI. Patients undergoing NACT have a high (usually unresectable) tumor burden with ascites, both significantly associated with VTE risk, likely due to a combination of reduced blood flow from pelvic venous compression, and the ectopic secretion of procoagulant material including tissue factor, membrane-derived microparticles, and cytokines such as interleukin-6 and tumor necrosis factor-α. In addition, NACT can lead to VTE via pathways including reduced protein C and S expression (from reduced vitamin K absorption), increased factor V expression, and direct injury to vascular endothelium.

In our study, clear cell and carcinosarcomas were associated with VTE, although the numbers are small and do not reach statistical significance in the case of clear cell disease. This reflects their at least 2.5-fold greater VTE risk, which is known from larger studies, most likely because of increased ectopic production of tissue factor and factor VII.

Our data add to results from other smaller retrospective studies in the field. Chavan et al found a VTE incidence of 13.6% in a population of 147 patients with ovarian cancer undergoing multimodal curative treatment; however, only 16 patients received NACT with a VTE rate of 20%. They did not find that NACT significantly increased this risk (p = 0.16), but in their study VTE occurred more commonly in postmenopausal women (p = 0.04). The study by Greco et al of 112 patients with ovarian cancer undergoing NACT found a VTE incidence of 11.6%, with no significant association with patient demographics. In this patient group, a further 10.4% developed a VTE around the time of diagnosis (before NACT), and a further 9.9% during adjuvant chemotherapy.

The current study is the largest to date, and focuses on the period from diagnosis until immediately post IDS; our findings therefore endorse and enhance existing data by demonstrating a comparable VTE rate of 15.1% in all ovarian cancer patients receiving NACT, regardless of demographic characteristics. In our view this represents a very high avoidable complication rate, with a significant impact on patients who already have the burden of their disease and treatment. We recommend that thromboprophylaxis must now be considered for all of these patients.

Various risk stratification tools have been developed for the prediction of VTE in ambulatory cancer patients starting...
Primary thromboprophylaxis with LMWH is routine in the extended postoperative period, where the number-needed-to-treat to prevent one VTE is 13–39. LMWH can be expected to have benefit in this group, with no greater risk of harm. Neither LMWH (relative risk 1.49, 95% CI 0.86–2.59) nor prophylactic dose direct oral anticoagulants (relative risk 1.95, 95% CI 0.88–4.30) are known to be associated with a significant increase in major bleeding. In our view, both LMWH and anti-Xa inhibitors would be justified during NACT at prophylactic doses: both have a short half-life and their effects cease quickly after stopping in the presence of bleeding or before debulking surgery, after which they would be recommended postoperatively, as is usual practice for LMWH.

5 | CONCLUSION

We demonstrate evidence of an unacceptably high avoidable VTE rate during NACT for ovarian cancer, from the time of diagnosis through to the immediate postoperative period. Patients with clear-cell and carcinosarcoma histology are likely at even higher risk. Thromboprophylaxis should now be assessed prospectively, preferably via a randomized controlled trial, to assess the impact on VTE rate and complications, along with a formal cost-benefit analysis.

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AUTHOR CONTRIBUTIONS

SO contributed to data collection and analysis, manuscript drafting and, critical revision. YA contributed to design of the work, data collection, and manuscript drafting. NS contributed to design of the work and data collection. DH contributed to data collection. MT and ML contributed to critical revision of the manuscript. AO contributed to conception of the work and to critical revision of the manuscript. All authors approved the final manuscript for publication.

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