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Recurrence of venous thromboembolism in patients with gynaecological malignancies: incidence, risk factors, and impact on survival

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Summary

Purpose: The purpose of this study was to define the incidence, risk factors, and impact on survival of venous thromboembolism (VTE) recurrence in patients with genital tract malignancy. *Materials and Methods:* This was a retrospective cohort study of patients with gynaecological malignancies treated in the Tertiary Gynaecological Cancer Centre Hospital between 2006 and 2017. Patients with cancer- related VTE were identified. Demographic data, histology, stage, surgery, chemotherapy, co-morbidities, and timing of primary and recurrent VTE episodes were recorded. *Results:* One hundred and twenty-four gynaecological malignancies were diagnosed with cancer associated VTE. The incidence of recurrent VTE was 22% (n=27). Patients were at highest risk of recurrent VTE if their first VTE had occurred before commencement of primary cancer treatment (OR 2.2, 95% CI 1.1-4.2 $p = 0.018$). Seventeen (63%) patients were on a therapeutic dose of low molecular weight heparin at the time of recurrent VTE. Patients with recurrent VTE had significantly higher monocyte (p=0.03) and eosinophil count ($p \leq 0.01$) compared to the non-recurrent VTE group. There was no difference in progression-free and overall survival between patients who suffered a single VTE and those who had recurrent VTE. *Conclusions:* Patients with gynaecological malignancies treated for VTE remain at high risk of recurrent VTE despite standard anticoagulant treatment.

Key words: Venous thromboembolism; VTE recurrence; Gynaecological malignancies; Gynaecological cancer; Cancer associated venous thromboembolism.

Introduction

Patients with active cancer have 4- to 6.5-fold higher risk of developing venous thromboembolism (VTE) compared to the general population [1, 2]. Reports suggest that VTE can be found in up to 50% of cancer patients on autopsy [3]. The risk factors for VTE in cancer patients have been broadly divided into three groups as: patient-related, cancer-related, and treatment-related [4]. Variables such as age, ethnicity, increased BMI or previous VTE history affect the risk of VTE [5-7]. The risk of VTE also depends on cancer type, disease stage, histology, and interval from cancer diagnosis [8, 9]. Active cancer treatments including surgery, systemic chemotherapy, and anti-angiogenic agents have all been found to increase the risk of venous and arterial thromboembolism [10, 11]. Diagnosis of VTE in cancer patients has been linked to a reduction in short- and long-term survival [12].

Genital tract cancers are a diverse group of diseases. Ovarian cancer carries the highest risk of VTE within this group of cancers, with an interval of 5.2% to 16% [13]. Clear cell cancer has the highest risk, reported to be as high as 27% [14]. Patients with ovarian cancer who undergo chemotherapy have an 11% incidence of VTE [8]. The risk of VTE associated with the uterine cancer varies between 1.5% in localised and 10.5% in advanced disease [15]. Cervical cancer associated VTE was estimated to be around 12% [16]. Treatment of gynaecological cancers involves complex surgery and often chemotherapy and/or radiotherapy. Shuang *et al.* found that the incidence of VTE in gynaecological cancer peaked in perioperative (35.1%) and preoperative (29.1%) periods [17]. In a previous study in the present centre, one-third of ovarian cancer associated VTE were diagnosed within 28 days of surgery or during chemotherapy [14]. Current practice guideline suggests that cancer associated thrombosis should be treated with low molecular weight heparin (LMWH) for minimum of three to six months [18]. However VTE recurrence frequently occurs despite standard treatment. Chee *et al.* reported adjusted ten-year cumulative VTE recurrence rate of 28.6% in patients with active cancer [19]. In that cohort, patients with ovarian cancer had three-fold increased hazard of VTE recurrence compared to other types of cancer.

Although gynaecological cancers are associated with one of the highest rates of cancer associated VTE, few studies have investigated VTE recurrence in these women. This study aimed to investigate the rate of recurrence of VTE in

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the gynaecological cancer population, the factors that influence recurrence of VTE, and the impact of recurrent VTE on patient survival.

Material and Methods

This was a retrospective cohort study on patients with gynaecological cancer treated in St. James's Hospital Gynaecological Cancer Centre, a tertiary referral centre for gynaecological cancer patients in Ireland, between January 2006 and March 2017. Data from all patients diagnosed and treated for gynaecological malignancy in this unit was extracted from hospital records. Patients with a first episode of cancer-related VTE were identified and the accuracy of records was verified through the general practice/community records. Cancer-related VTE was defined either as a VTE diagnosed within six months prior to, or at any time following the cancer diagnosis, during treatment while the malignancy was active, following cancer related surgery, during chemotherapy or radiotherapy. The diagnosis of VTE was based on a documented objective testing, such compression ultrasonography, venography, or computed tomography, and pulmonary angiogram in case of a pulmonary embolism (PE). Patients were excluded if they had a history of VTE (more than six months prior to their cancer diagnosis), a personal history of VTE unrelated to cancer, and documented thrombophilia or family history of VTE. Recurrent (second episode) of VTE was defined according to the international standards [20]. This defines recurrent VTE as "thrombosis of a site that was either previously uninvolved or had interval documentation of incident DVT or PE resolution". Patients were followed up for at least six months following the diagnosis of cancer associated VTE or until death.

Pre cancer treatment white cell count (WCC), hemoglobin (Hb), platelet count (PLT), creatinine (Cr), albumin, D-dimers. and fibrinogen levels were extracted from laboratory records. D-dimers and fibrinogen levels from patients on anticoagulation were excluded from final analysis.

The Khorana score was calculated for all patients. All patients were scored as follows, 1 for gynaecological cancer, 1 for PLT $\geq$ $350x10^9$/L, 1 for Hb < 10 g/L or use of red cell growth factors, 1 for WCC $\geq$ $11x10^9$/L and 1 for BMI $\geq$ 35kg/m^2 [21]. Patient comorbidities were quantified and calculated according to Charlson Comorbidity Index [22, 23].

Descriptive statistics were used to describe patient demographics. Median and interquartile ranges were calculated for continuous variables. Categorical variables were expressed as counts and percentages. Differences in variables between the patients with and without recurrent VTE were assessed using the chi-square test in case of categorical variables. Continuous variables were assessed using Student's *t*-test or Mann-Whitney test as appropriate. Progression-free and overall survival were estimated with Kaplan-Meier method and compared with log-rank test. Cumulative incidence of VTE recurrence was analysed using Cox regression analysis. In all cases $p < 0.05$ was considered significant. All data was analyzed using SPSS v.23 programme.

Results

One hundred and twenty-four gynaecological cancer patients diagnosed with gynaecological cancer associated VTE met the inclusion criteria (Table 1). The median (IQR) age of the patients was 60 (54-68) years. BMI was higher than 30 in 49 (40%) patients. Women were postmenopausal in 100 (81%) cases and did not smoke in 97 (78%) cases. Open surgery was performed in 96 (77%) patients. Twenty-four patients had a second primary malignancy either prior to (n=21), or at the time of gynaecological cancer diagnosis (n=3).

Cancer sites included: ovary (n=62, 50%), corpus uteri (n=39, 31%), cervix (n=13, 11%), vulva (n=3, 2%), and more than one site (n=7, 6%). The most common histological subtypes were: high-grade serous (n=54, 43%), endometrioid (n=32, 26%), and squamous (n=13, 10%). The majority of the cancers were advanced stage. Median (IQR) Charlson Comorbidity Index was 8 (6-10). There were no significant differences between the recurrent and non-recurrent groups with respect to the demographics recorded.

One hundred and twenty-four index VTEs are described in Table 2. Ninety-three (75%) patients were diagnosed with first VTE while ambulatory and not on any form of anticoagulation. Thirty-three (27%) patients were diagnosed with VTE prior to any form of cancer treatment (surgery, chemotherapy or radiotherapy). Within this group, 18 (15%) patients presented with symptomatic VTE and occult gynaecological malignancy, nine (7%) had incidental finding of VTE at cancer diagnosis, and six (5%) developed VTE in the interval between cancer diagnosis and treatment.

Thirty-eight (31%) patients developed VTE within six weeks after surgery; 21 while in hospital and 22 on VTE prophylaxis. Twenty-six (21%) patients developed VTE during chemotherapy or radiotherapy, six (5%) patients developed VTE following completion of cancer treatment, and 21 (17%) at the time of cancer recurrence. In 15 (12%) patients the first VTE was the heralding sign of cancer recurrence.

The median follow up time was 25 (range 1–120) months. The first VTE was: PE (n=46, 37%), DVT (n=58, 47%), PE+DVT (n=14, 11%), and other (n=6, 5% (which included catheter related thrombosis in five cases and inferior vena cava thrombosis in one case) (Table 2).

Anticoagulants were prescribed for the first VTE for a median (IQR) time of six months (3-8). Twenty-seven (22%) patients had VTE recurrence in this cohort. Recurrent VTE were: PE (n=12, 10%), DVT (n=12, 10%), PE, and DVT (n=2, 2%) and catheter related VTE (n=1). Eleven (24%) patients with index PE experienced recurrent VTE, as PE (six), DVT (four), and catheter related VTE (one). Ten (17%) patients with index DVT experienced recurrent VTE, as PE (three), DVT (six), PE, and DVT (one). Six (43%) patients with first PE and DVT had recurrent VTE, as PE (three), DVT (two), PE, and DVT (one). Patients with first catheter related VTE or vena cava VTE did not experience recurrence.

The median time to VTE recurrence was four (range: 1–90) months. Fourteen (11%) patients had recurrent VTE within three months following first event, 18 (15%) within six months, and 22 (18%) within one year following first VTE.

Table 1. — *Demographics and baseline characteristics of patients with gynaecological cancers with recurrent and non-recurrent VTE.*

Variable	All patients	Recurrent VTE	Non-recurrent VTE	p-Value
Number (%)	124	27 (22%)	97 (78%)	
Age, median (IQR)	60 (54-68)	62 (54-66)	60 (54-70)	0.924
BMI (kg/m^2)				0.327
<30	65 (52%)	17 (65%)	48 (55%)	
>30	49 (40%)	9 (35%)	40 (45%)	
Cancer Site (%)				0.939
Ovary	62 (50%)	14 (52%)	48 (49%)	
Corpus uteri	39 (31%)	7 (26%)	32 (33%)	
Cervix	13 (11%)	3 (11%)	10 (10%)	
Vulva	3 (2%)	1 (4%)	2 (2%)	
More than one site	7 (6%)	2 (7%)	5 (5%)	
Histology (%)				0.526
High Grade Serous	54 (43%)	12 (44%)	42 (43%)	
Clear Cell	7 (6%)	2 (7%)	5 (5%)	
Endometrioid	32 (26%)	5 (19%)	27 (28%)	
Mucinous	1 (1%)	1 (4%)	0	
Squamous	13 (10%)	3 (11%)	10 (10%)	
Sarcoma	10 (8%)	3 (11%)	7 (7%)	
Other	7 (6%)	1 (4%)	6 (6%)	
Stage (%)				0.483
I	37 (30%)	5 (18%)	32 (33%)	
II	7 (6%)	2 (7%)	5 (5%)	
III	52 (42%)	13 (48%)	39 (41%)	
IV	27 (22%)	7 (26%)	20 (21%)	
Surgery (%)	113 (91%)			0.563
Open	96 (77%)	22 (88%)	74 (84%)	
Laparoscopic	14 (11%)	2 (8%)	12 (14%)	
Vulvectomy	3 (2%)	1 (4%)	2 (2%)	
Duration of hospital stay				0.617
Median (IQR)	10 (8-18)	13 (9-21)	10 (7-16)	

Table 2. — *Characteristics of index or first VTE.*

Variable	All patients	Recurrent VTE	No recurrent VTE	*p*-value
First VTE site (%)				0.125
PE	46 (37%)	11 (41%)	35 (36%)	
DVT	58 (47%)	10 (37%)	48 (50%)	
PE+DVT	14 (11%)	6 (22%)	8 (8%)	
Other	6 (5%)	0	6 (6%)	
Inpatient at the time of first VTE (%)				0.900
Yes	31 (25%)	7 (26%)	24 (25%)	
No	93 (75%)	20 (74%)	73 (75%)	
Anticoagulation at the time of index VTE event (%)				0.706
Yes	31 (25%)	6 (22%)	25 (26%)	
No	93 (75%)	21 (78%)	72 (74%)	
Treatment of the index VTE				0.175
LMWH	99 (82%)	19 (70%)	80 (85%)	
Oral VKA	11 (9%)	4 (15%)	7 (7%)	
IVC filter+LMWH	9 (7%)	3 (11%)	6 (6%)	
IVC filter+oral VKA	1 (1%)	1 (4%)	0	
NOAC	1 (1%)	0	1 (1%)	

Recurrent VTE events occurred within seven days after surgery in five (19%) patients, despite LMWH treatment. Recurrent VTE occurred during chemotherapy or radiotherapy (n=8, 30%), at the time of cancer recurrence or progression (n=8, 30%), following completion of cancer treatment (n=3, 11%) and prior to cancer treatment (n=3, 11%) (Figure 1) . In two of these cases, recurrent VTE was the heralding sign of cancer; a third patient developed recur-

Table 3. — *Laboratory biomarkers in patients with gynaecological cancers with recurrent and non-recurrent VTE.*

Variable, median (IQR)	Normal values	All patients (n)	Recurrent VTE (n)	Non-recurrent VTE (n)	*p*-value
Fibrinogen	1.9-3.5 (g/L)	4.1 (3.2-4.9) n=39	4.8 (4.2-4.9) n=7	3.9 (3.2-4.7) n=32	0.141
D-Dimer	<500 (ng/ml)	1536 (780-5472) n=35	1385 (1224-4302) n=7	2343 (693-5924) n=28	0.643
WCC	4.0-11.0 (10^9/L)	7.7 (6.3-9.3) n=120	8.2 (7.0-12.3) n=26	7.7 (6.1-9.1) n=94	0.146
Neutrophils	2.0-7.5 (10^9/L)	5.1 (4.0-7.0) n=120	5.3 (4.3-7.6) n=26	4.9(3.6-6.8) n=94	0.208
Lymphocytes	1.5-3.5 (10^9/L)	1.6 (1.1-2.1) n=120	1.5 (1.1-2.2) n=26	1.6 (1.1-2.1) n=94	0.757
Monocytes	0.2-0.8 (10^9/L)	0.6 (0.5-0.7) n=120	0.7 (0.5-0.9) n=26	0.6 (0.5-0.7) n=94	0.037
Eosinophils	0-0.4 (10^9/L)	0.1 (0.1-0.2) n=120	0.2 (0.1-0.3) n=26	0.1 (0.05-0.2) n=94	0.012
Basophils	0-0.1 (10^9/L)	0	0 (0-0.1) n=26	0 n=94	0.627
Hb	11.5-16.4 (g/dL)	12.0 (10.8-13.4) n=120	12.0 (10.8-13.3) n=26	12.0 (10.8-13.5) n=94	0.426
PLT	140-450 (10^9/L)	330 (261-441) n=120	384 (275-464) n=26	325 (260-411) n=94	0.354
Urea	3.0-7.0 (mmol/L)	4.9 (4.0-6.3) n=119	4.6 (3.9-5.6) n=26	5.1 (3.9-6.4) n=93	0.405
Creatine	44-80 (μmol/L)	70 (59-81) n=119	68 (53-78) n=26	71 (61-82) n=93	0.112
Albumin	35-50 (g/L)	40 (35-44) n=119	38 (33-42) n=26	40 (35-44) n=93	0.117

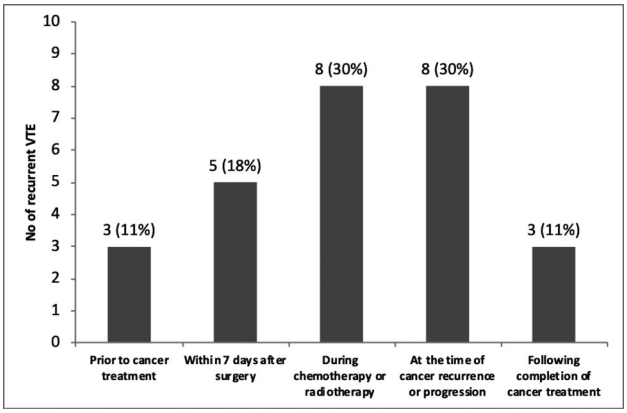

Figure 1. — Distribution of recurrent VTE events (n=27, Y-axis) according to the timing of occurrence (X-axis), percentages refer to the total number of recurrent VTE events.

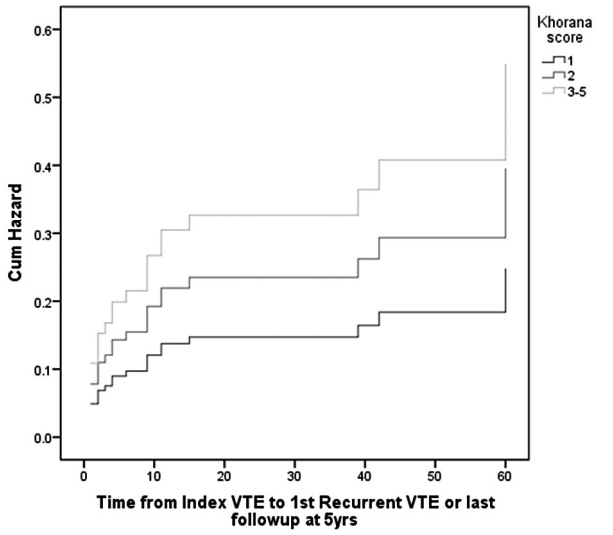

Figure 2. — Cumulative incidence of recurrent VTE (n=27) in the first 5 years following index VTE according to the Khorana score.

rent VTE between cancer diagnosis and treatment.

Nineteen (70%) patients with a recurrent VTE event, were diagnosed in the community setting, 15 were symptomatic, and four asymptomatic for VTE.

Twenty-one (78%) patients were receiving anticoagulation when recurrent VTE occurred. Seventeen patients (63%) were on a full therapeutic dose of LMWH, one patient was on oral vitamin K antagonist (VKA), and three were on prophylactic LMWH. Ten patients had inferior vena cava (IVC) filter inserted following their index VTE, and four of them experienced recurrent VTE, three of whom still had IVC filter in situ. Four patients (15%) had a third VTE within 12 months of the second VTE (PE, DVT, IVC thrombosis, cerebral venous sinus thrombosis). Twelve (36%) of 33 patients who experienced first VTE before their primary treatment for gynaecological cancer experienced VTE recurrence. They were more likely to have recurrent VTE than the patients who experienced first VTE after primary treatment for gynaecological cancer (OR 2.2, 95% CI 1.1-4.2).

Age, BMI, smoking, menopausal status, presence of prior malignancy, cancer characteristics (site, histology, stage), surgery type, duration of hospital stay, and Charlson Comorbidity Index were similar in both non-recurrent and recurrent VTE group.

Khorana score was available for 112 (90%) patients. The results were as follows: score 1 (n=48, 43%), score 2 (n=32, 29%), score 3 (n=23, 20%), score 4 (n=6, 5%), and score 5 (n=3, 3%). There was no statistical difference between recurrent and non-recurrent VTE group in regards to the score recorded. 28% of patients who scored 3 or more suffered a recurrent VTE compared with 17% of patients who scored 1. The cumulative incidence of recurrent VTE following the index VTE according to the Khorana score is demonstrated in Figure 2. Patients who scored 3 or more had a greater cumulative incidence of recurrent VTE compared with those who scored 2 or less but this was not significant (HR = 2.2, 95% CI 0.84-5.84).

Patients with recurrent VTE had significantly higher pre-

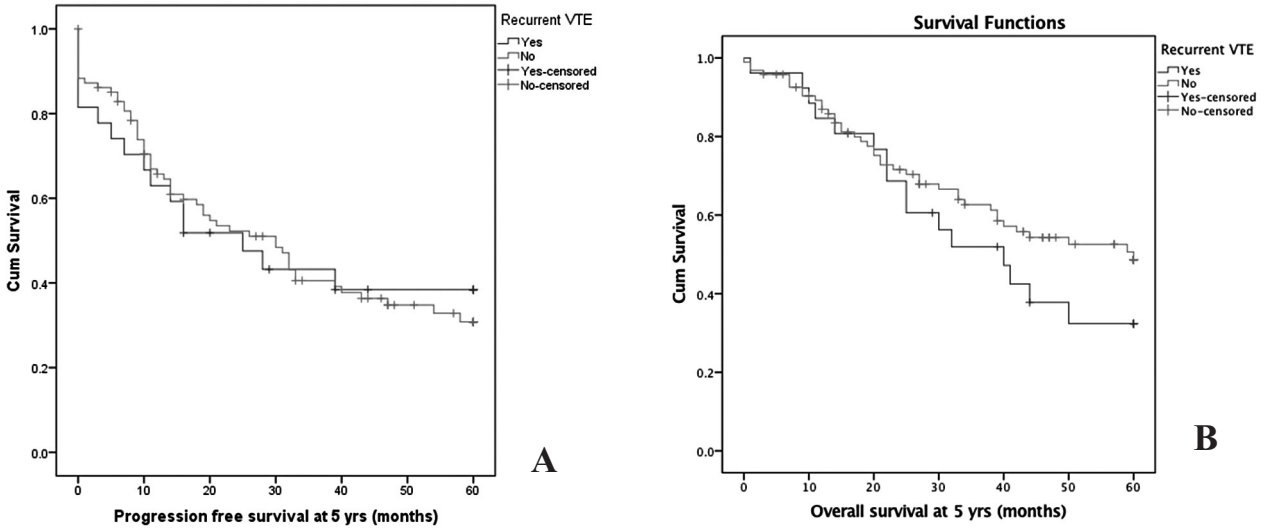

Figure 3. — Kaplan-Meier cancer progression-free survival (A) and overall survival (B) curve for women with recurrent VTE versus women without recurrent VTE.

cancer treatment monocyte (p = 0.037) and eosinophil counts (p = 0.012) compare to the non-recurrent group (Table 3). Fibrinogen and D-dimer levels were available for 48 and 47 patients respectively. Following exclusion of patients on anticoagulants there was no difference between recurrent and non-recurrent VTE group in regards to fibrinogen and D-dimer levels. There was also no difference in other routinely tested pre cancer treatment blood parameters.

Sixty-three (51%) patients in the study died between January 2006 and September 2017. VTE was not the labelled cause of death in any patient within this cohort. One patient died due to severe upper gastro-intestinal bleeding while on therapeutic dose of LMWH. Median five-year progression-free survival was 25 months for recurrent and 30 months for non-recurrent VTE group (Figure 3a).

Median five-year overall survival was 40 months for those with recurrent VTE and 60 months for those without recurrent VTE (Figure 3b). Neither of them reached statistical significance.

Discussion

The present authors found that the incidence of recurrent VTE in patients with genital tract malignancies was 22%. This is similar to findings from previous studies on recurrent VTE in mixed cancer populations. Prandoni *et al.* found that the 12-month cumulative incidence of recurrent thromboembolism in cancer patients was 20.7% (95% CI, 15.6%-25.8%) *vs*. 6.8% (95% CI, 3.9%-9.7%) in patients without cancer [24]. A similar VTE recurrence rate (19.4%) was reported in patients with leukaemia [25]. In a recent study, the overall incidence rate for recurrent VTE in mixed cancers was 9.6 per 100 person-years [26]. The peak at 22.1 per 100 person-years was noted in the first six months, which fell to 7.9 between six and 12 months. Similar findings were demonstrated by Martinez *et al.* [27]. They showed that the incidence rate for recurrent VTE peaked in the first six months at 11 per 100 person years. The present findings are in agreement with both of these studies.

Most recurrent VTE events in this cohort occurred within six months of first VTE (67%) and the majority within 12 (81%) months. These findings confirm that the highest risk of VTE recurrence is early and suggest that anticoagulation should be continued for at least six months.

The majority of patients were receiving anticoagulation at the time of their recurrent VTE event (63% therapeutic and 11% prophylactic dose of LMWH). This has been reported by previous researchers. In Schulman *et al.*'s cohort of 212 patients with recurrent VTE, 70% were on LMWH and 27% on a vitamin K antagonist at the time of the recurrent VTE event [28]. This raises questions regarding the efficacy, dosage, and compliance with current standard anticoagulation regimes. Antithrombotic benefit of LMWH must to be balanced against the risk of bleeding in cancer patients. The 12-month cumulative incidence of major bleeding was 12.4% (95% CI, 6.5%-18.2%) in patients with cancer compared to 4.9% (95% CI, 2.5%-7.4%) in patients without cancer in previous studies [24]. The present authors had one bleeding associated mortality; a 73-year-old women with high grade serous ovarian cancer and above knee DVT treated with LMWH. During her second cycle of neo-adjuvant chemotherapy (single agent carboplatin) she had a fatal upper gastro-intestinal bleed.

Surgery and chemotherapy are known to exacerbate the risk of VTE in cancer patients, however, in this study the authors showed that the highest incidence of VTE recurrence was in patients who had suffered their first VTE before primary treatment for cancer. This reflects the highly thrombogenic nature of the primary tumour. Classically,

three main factors contribute to the formation of a thrombus: hypercoagulability, haemodynamic changes (stasis), and vessel injury or dysfunction. Cancer cells interact with haemostatic system through different pathways [29]. These include expression of hemostatic factors [tissue factor (TF), cancer procoagulant], microparticles, inflammatory cytokines, and proangiogenic factor production. Individuals who experience VTE prior to any cancer treatment may be more susceptible to the thrombotic effect of the malignancy and therefore remain at high risk of further VTE. Previous studies conducted in the present institution showed that expression of TF in clear cell and endometrioid type ovarian cancer is significantly higher in patients who develop VTE [30]. This indicates the important role that tumour derived procoagulants play in thrombosis risk. Further work is required to determine whether tumour derived TF plays a role in the risk of recurrent VTE in cancer patients.

The present authors did not find any differences in age, BMI, presence of secondary malignancy, smoking, menopausal status, type of surgery or Charlson Comorbidity Index - between this recurrent group and this non-recurrent VTE group. BMI, surgical complexity, and comorbidities are all risk factors for VTE, however these did not appear to play a role in VTE recurrence in this study. In agreement with this, Chee *et al.* found that only cancer type (ovarian, pancreatic, brain, lung), myeloproloferative or myelodysplastic disorders, Stage 4 disease, and leg paresis were predictive of recurrence in a cancer population [19]. The adjusted ten-year cumulative VTE recurrence rate in active cancer in their population was 28.6%. Lack of long term anticoagulation and the presence of a second primary malignancy were significant contributors to VTE recurrence in patients with glioblastoma multiforme [31]. These risk factors were non-contributory in the present study of gynaecological related VTE recurrence.

In the cancer population, several biomarkers have been proposed to predict VTE recurrence. Elevated D-dimer level at cancer diagnosis or progression and at the time of VTE event was shown to be useful in predicting both the risk of index VTE and recurrent VTE respectively by others [32, 33]. High fibrinogen levels are associated with arterial thrombosis and VTE in non-cancer patients [34, 35]. D-dimer and fibrinogen levels were available in a subgroup of the present patients prior to the start of cancer treatment. However there was no statistical difference in levels between the recurrent and non-recurrent VTE groups.

Monocytes count and eosionophil count were numerically higher in the recurrent VTE group. Monocytes are known to express tissue factor and to significantly contribute to procoagulant activity [36-38]. Vieira *et al.* showed that the levels of monocyte bound TF are significantly elevated in patients with VTE and suggested their use as a marker for DVT detection [39]. Monocytosis has been associated with risk of DVT in the general population [40]. Its role in initiation and propagation of thrombosis has been demonstrated in mice in vivo [41]. Together with neutrophils they were the predominant leukocyte subsets that actively accumulated at the vessel lining during thrombus formation in veins. Eosinpohils have been found to be a main source of preformed TF in blood [42]. Increased monocyte and eosinophil counts in patients with recurrent VTE is an interesting finding but requires further study as their values fell within normal clinical range.

Khorana risk score is a prediction model used to assess cancer-associated thrombosis before initiation of chemotherapy [20]. Although it is not designed to predict recurrence of VTE, the present authors used it to classify their patients accordingly to low (1), intermediate (2), and high (≥ 3) risk group. There was no difference between the groups with regards to the VTE recurrence. However, there was a trend towards higher cumulative VTE recurrence with Khorana scores of 3-5.

Conclusion

In conclusion, the present authors found that the incidence of recurrent VTE in patients with genital tract malignancies was 22%. They were not able to demonstrate significant differences between recurrent and non-recurrent VTE groups in terms of potential risk factors, demographics, and survival, but this may be due to retrospective nature of the study and low number of events. In addition, the authors do not perform routine post-mortem examination on patients with cancer in this institution. Patients who experienced index VTE prior to any form of cancer treatment were more likely to experience recurrent VTE. Patients with gynaecological cancer treated for VTE remain at high risk of recurrent venous thrombosis despite standard anticoagulation treatment.

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