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Full Length Article

Venous thromboembolism at time of diagnosis of ovarian cancer: Survival differs in symptomatic and asymptomatic cases

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ABSTRACT

Objectives: To determine the impact on survival of symptomatic and asymptomatic venous thromboembolism (VTE) at time of diagnosis of primary ovarian malignancy.
Materials and methods: The clinical records of 397 consecutive cases of primary ovarian malignancy were studied. Clinical, pathological and survival data were obtained.
Results and conclusions: Of 397 cases, 19 (4.8%) were found to have VTE at diagnosis, of which 63.2% (n = 12) were asymptomatic. VTE was significantly associated with reduced overall median survival (28 vs. 45 months, p = 0.004). Decreased survival was associated with symptomatic VTE compared to patients with asymptomatic VTE (21 vs. 36 months, p = 0.02) whose survival was similar to that of patients without VTE. Decreased survival remained significant in symptomatic patients after controlling for stage of disease at diagnosis, cytoreductive status and adjuvant chemotherapy use. Overall these data suggest for the first time that symptomatic but not asymptomatic VTE prior to primary treatment of ovarian cancer is an independent adverse prognostic factor.

1. Introduction

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is closely associated with malignant disease. The classic triad of vascular endothelial damage, hypercoagulability and venous stasis are the principle mechanisms underlying the pathogenesis of VTE and the malignant process is known to exacerbate all three [1]. Ovarian cancer is associated with a higher incidence of thromboembolic disease compared to other tumour types [2,3,4]. The reasons are multifactorial including; prolonged immobility, chemotherapy, prolonged cytoreductive surgery and factors related to the biology of the tumour such as the release of pro-coagulant factors from ovarian cancer cells [5,6].

The reported incidence of VTE associated with ovarian cancer varies widely. The largest study of over 13,000 ovarian cancer patients found the incidence of VTE within 2 years from diagnosis to be 5.2% [2]. Smaller studies have detected higher rates of VTE with incidences quoted as high as 16.6% [7]. The wide range in these figures is likely to be due to the study of different populations, different treatment regimens and different time points in the disease course (both primary and relapsed disease), as well as different investigations to detect VTE. The presence of VTE at the time of cancer diagnosis is of clinical importance as it has been demonstrated to be associated with decreased survival [8].

VTE can present with classical symptoms but can also be asymptomatic and is detected incidentally during routine imaging investigations. There is a higher prevalence of incidental findings of VTE in asymptomatic cancer patients undergoing CT scans of the thorax compared to all other diagnoses [9]. Evidence from radiological studies indicates that unsuspected PE may also be associated with poorer patient survival outcomes in cancer patients compared to matched controls without PE [10]. However, whether this applies to ovarian cancer patients is not known. Previous reports on VTE with gynaecological cancers and the

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use of inferior vena caval filters in the peri-operative period did not distinguish between symptomatic and asymptomatic VTE [11,12].

The aim of this study is to determine the incidence of asymptomatic and symptomatic VTE in patients with newly diagnosed ovarian cancer and determine whether the impact of asymptomatic and symptomatic VTE on overall survival and disease recurrence is similar or not.

2. Materials and methods

2.1. Patient population

Data were collected from all patients with a primary diagnosis of ovarian cancer (including primary peritoneal and fallopian tube cancers) over a seven year period from January 2006 to December 2012 ensuring a minimum follow up period of 24 months at the Royal Marsden Hospital and St. George's Hospital, London which form a joint centre for the treatment of gynaecological cancers. During the study period, a similar team of surgeons worked at both institutions, the chemotherapy protocols were identical and all new cases with radiological imaging were discussed at a joint weekly multi-disciplinary team meeting. Data were extracted from the electronic patient records. Where details were lacking in the electronic record the history was further clarified by hand searching the paper-based records.

All patients included in the analysis underwent a CT scan of the thorax at the time of diagnosis of ovarian cancer. Patients were excluded if initial staging imaging did not include a CT scan of the thorax, if they had a diagnosis of VTE established prior to the diagnosis of ovarian cancer or if the final histology did not show invasive cancer. In our study having applied these exclusion criteria no subsequent VTE events were detected at later stages of follow-up. However, post-surgery not all patients were exclusively treated in our cancer centre, and we did not undertake routine imaging post-treatment to detect asymptomatic VTE. All patients diagnosed with VTE were treated following the institutions' established guidelines.

2.2. Data collection

Patient age, date of commencement of treatment, date of surgery, date of completion of treatment and date of relapse were recorded. Final histological diagnosis, FIGO stage [13] of disease, grade of disease, serum CA-125 and serum albumin levels at diagnosis were recorded. Surgical procedures were recorded, as were the number of cycles of chemotherapy pre- and post-surgery and the duration of follow-up, as time from diagnosis to last follow-up, or death. The diagnosis of pulmonary embolism was by CT scan of the thorax, and the diagnosis of DVT was made by ultrasonography. In patients diagnosed with VTE an assessment of presenting symptoms was made. Patients reporting dyspnoea, dyspnoea or exertion, cough, chest pain, palpitations, collapse in the preceding 2 weeks were regarded as symptomatic of PE. Patients reporting leg pain, leg swelling and difficulty walking in the preceding 2 weeks to diagnosis were also regarded as symptomatic of DVT. The treatment of patients diagnosed with asymptomatic and symptomatic VTE was identical and patients undergoing upfront surgery had an inferior vena caval filter placed preoperatively, as described previously [12]. The study was approved by the Local Ethics Committee.

2.3. Statistical analysis

All data were recorded in a database. The following variables were evaluated: age, histological type, stage and grade of cancer, chemotherapy, surgical procedure, serum CA-125 and albumin levels at diagnosis, length of follow up, overall survival.

For each variable inter-quartile range and counts were computed to describe continuous and categorical variables, respectively. Differences in variables between patients with and without VTE were assessed using the Chi-squared test for categorical variables or the Mann–Whitney U test as appropriate. Survival curves were generated by the Kaplan–Meier method and compared using the log-rank test. Cox regression analysis was performed to compare differences in survival outcomes between patient groups. All significance testing was two sided and p-values <0.05 was considered significant. All statistical analyses were performed using IBM SPSS Statics Version 20.

3. Results

3.1. Patient characteristics

A total of 432 electronic patient records were reviewed. Thirty-five (8.1%) patients were excluded — 32 patients had not undergone CT imaging of the thorax at the time of diagnosis, one patient had a diagnosis of PE which preceded the diagnosis of ovarian malignancy and two patients had incomplete records. 397 patients were included in the analysis group. The median age of the patients was 62 years (IQR 52-70 years). The majority of patients (69.0%) were diagnosed with FIGO stage 3 disease, 44 (11.1%) had stage 1, 29 (7.3%) had stage 2 and 50 (12.6%) had stage 4. 334 patients (84.1%) were diagnosed with grade 3 tumours, 19 (4.8%) were classified as grade 1 and 44 (11.1%) as grade 2. Histology types were serous (n = 292, 73.5%), mucinous (n = 29, 7.3%), endometrioid (n = 23, 5.8%), clear cell (n = 21, 5.8%), carcinosarcoma (n = 9, 2.3%) and other (n = 23, 5.8%).

Table 1
Patient characteristics for all patients, those with and those without VTE at the time of diagnosis of ovarian cancer. p-Values refer to comparison between VTE and non-VTE groups.

	Cohort	NonVTE group	VTE group	p value
Total number, n	397	378	19	
Age, median (IQR)	62 (52–70)	62 (52–69)	65 (61–71)	0.07
Stage, n (%)				0.36
1	44 (11.1%)	44 (11.6%)	0 (0.0%)	
2	31 (7.8%)	29 (7.7%)	2 (10.5%)	
3	268 (67.5%)	255 (67.5%)	13 (68.4%)	
4	54 (13.6%)	50 (13.2%)	4 (21.1%)	
Grade, n (%)				0.19
1 (low)	47 (11.8%)	47 (12.4%)	0 (0.0%)	
2 (moderate)	10 (2.5%)	10 (2.6%)	0 (0.0%)	
3 (high)	340 (85.6%)	321 (84.9%)	19 (100%)	
Histology				0.63
Serous	292 (73.5%)	275 (72.7%)	17 (89.4%)	
Mucinous	29 (7.3%)	28 (7.4%)	1 (5.3%)	
Endometriod	23 (5.8%)	23 (6.1%)	0 (0.0%)	
Clear cell	21 (5.3%)	21 (5.6%)	0 (0.0%)	
Carcinosarcoma	9 (2.3%)	9 (2.4%)	0 (0.0%)	
Other	23 (5.8%)	22 (5.8%)	1 (5.3%)	
CA125 at diagnosis				0.81
<500 iu	198 (49.9%)	188 (49.7%)	10 (52.6%)	
≥500 iu	199 (50.1%)	190 (50.3%)	9 (47.4%)	
Albumin at diagnosis				0.81
<35	182 (45.8%)	171 (45.2%)	11 (57.9%)	
≥35	215 (54.2%)	207 (54.8%)	8 (42.1%)	
Surgery				0.91
Primary	183 (46.1%)	174 (46.0%)	9 (47.4%)	
Delayed primary	215 (54.2%)	207 (54.8%)	10 (52.6%)	
Cytoreductive status				0.13
Complete	234 (58.9%)	227 (60.0%)	7 (36.8%)	
Optimal	71 (17.9%)	66 (17.5%)	5 (26.3%)	
Suboptimal	92 (23.2%)	85 (22.4%)	7 (36.8%)	
Chemotherapy				0.75
Neo-adjuvant	217 (54.7%)	208 (55.0%)	9 (47.4%)	
Adjuvant	155 (39.0%)	146 (38.6%)	9 (47.4%)	
No chemotherapy	25 (6.3%)	24 (6.3%)	1 (5.3%)	
Relapse				0.75
Yes	174 (43.8%)	213 (56.3%)	10 (52.6%)	
No	223 (56.2%)	165 (43.7%)	9 (47.4%)	
Death				0.001
Yes	129 (32.5%)	116 (30.7%)	13 (68.4%)	
No	268 (67.5%)	262 (69.3%)	6 (31.6%)	