EJGO European Journal of Gynaecological Oncology

Poor prognosis associated with venous thromboembolism in Asian patients with ovarian clear cell carcinoma

Ka Yu Tse[1], Philip Pun Ching Ip[2], Suk Kwan Lau[1], Tong Yow Ng[1], Kar Fai Tam[1], Annie Nga Yin Cheung[2], Hextan Yuen Sheung Ngan[1]

[1]Department of Obstetrics and Gynaecology, [2]Department of Pathology, Queen Mary Hospital, the University of Hong Kong, (Hong Kong)

Summary

Purpose of Investigation: To evaluate the incidence and prognostic implications of venous thromboembolism (VTE) in Asian patients with ovarian clear cell carcinoma (CCC). *Materials and Methods:* Between July 1987 and December 2005, 144 CCC patients were identified. The clinical outcomes of those with (case) and without (control) VTE were analyzed retrospectively. *Results:* After a mean follow-up of 131.2 ± 52.2 months, 11.1% (16/144) developed VTE and only one occurred in the perioperative period. Compared to the control, the case group was less responsive to chemotherapy (57.1% *vs*. 85.1%, $p = 0.01$) with shorter duration of response to chemotherapy (4.7 months *vs*. 83.6 months; $p < 0.001$), higher recurrence / progressive disease rate (100.0% *vs*. 37.2%, $p < 0.001$), shorter median disease-free survival (DFS) (0 months *vs*. 70.8 months; $p < 0.001$), and overall survival (OS) (16.5 months *vs*. 88.0 months; $p < 0.001$). The median interval from the diagnosis of VTE to death was 43.0 (range 1–394) days, and the 60-day mortality rate was 56.3%. Multivariate analysis showed that duration of chemotherapy response for more than one year was independently correlated with the DFS, while VTE, stage, and the chemotherapy response duration were independent prognosticators for OS. *Conclusion:* VTE is rare in Asian patients with CCC and care is needed when giving it to these patients in view of possible haemorrhagic complications. When VTE occurs, it is associated with high mortality.

Key words: Ovarian carcinoma; Clear cell; Venous thromboembolism.

Introduction

Venous thromboembolism (VTE), deep vein thrombosis (DVT), and pulmonary embolism (PE) are well-known complications of malignancy. These were first reported by Trousseau in the 1860s [1]. Their pathophysiology is unclear but is postulated to be due to the stasis of blood flow as a result of immobility or compression by tumor, as well as hypercoagulability related to the release of procoagulant factors such as tissue factor [2, 3] and other inflammatory cytokines [4, 5]. VTE can lead to significant morbidity such as recurrent thromboembolism, bleeding, venous gangrene, and even death. Amongst gynecological cancers, VTE is commonest in epithelial ovarian carcinomas (EOC) compared with other primaries, with an incidence that ranges between 5.2% and 16.9% [6-8].

Ovarian clear cell carcinoma (CCC) accounts for 2.5–12.2% in EOC and is the second most common histological type after high-grade serous carcinoma (HGSC) [9, 10]. It is more common in Asian countries like Japan where the prevalence is up to 15–25% [11, 12], and the incidence of VTE is 10.8–42% [6, 9, 13-17].

It is recommended that routine thromboprophylaxis with either unfractionated heparin or low molecular heparin should be administered to all patients before and for at least seven days after major pelvic surgery [18]. Also, several authorities such as the American Society of Clinical Oncology (ASCO), American College of Chest Physicians (ACCP), and National Institute for Health and Clinical Excellence (NICE) also advocated extended prophylaxis for up to four weeks after pelvic surgery for malignancy for those with low risk of bleeding [18-20]. This recommendation has been supported by some cost-effective analyses [21, 22]. Nevertheless, this practice is not commonly implemented in Asian population because the incidence of thromboembolism in Asians is lower than that reported in the Western countries [23]. This study aims to discover the incidence of thromboembolism in a group of Asian patients with ovarian CCC, and to investigate its clinical implications in these patients.

Materials and Methods

This retrospective study was performed in the Division of Gynaecological Oncology of the Queen Mary Hospital, a tertiary cancer referral center in Hong Kong. Approval of the Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster was obtained. Between July 1987

Revised manuscript accepted for publication October 18, 2016

and December 2005, 144 patients with CCC were identified from the departmental registry and pathology database. All available clinical details including the demographic data, information on the disease, treatment, recurrence, and survival were collected. All specimens were reviewed by present gynecological pathologists.

All full staging procedures were performed or supervised by accredited gynaecological oncologists. Stage I and II were classified as early-stage diseases while Stage III and IV were regarded as late-stage diseases. Optimal debulking was defined as having residual diseases less than 1 cm in diameter in this study. It had been estimated that the annual incidence of DVT and pulmonary embolism in Hong Kong was 17.1 and 3.9 per 100,000 population, respectively [24], and thromboprophylaxis was not a routine practice [23]. Only simple measures like early mobilization, intermittent pneumatic compression, and graduated compression stockings were used, unless if the patients had risk factors like heavy smoking, Caucasians or high body mass index. DVT was detected by clinical signs and ultrasound Doppler, while PE was detected by clinical signs and ventilation / perfusion scan, computed tomography or pulmonary angiogram. Clinical data were compared between those with (case) and without VTE (control). Overall survival (OS) was defined as the time interval from the date of primary surgery to the date of death or being censored at the date of the last follow-up. Disease-free survival (DFS) was defined as the time interval from the date of primary surgery to the date of recurrence or last follow-up. Patients' survival distribution was analyzed by the Kaplan-Meier method and the results were compared with log rank test. Multivariate analysis was performed using Cox regression. Categorical variables were analyzed by Chi-square test or Fisher's exact test and means or medians of continuous variables were compared using independent *t*-test or Mann-Whitney U test where appropriate. A *p*-value of less than 0.05 was considered as significant. These statistics were analyzed using SPSS software version 20.

Results

One hundred forty-four patients with CCC were identified during the study period, accounting for 20.1% of all EOC patients. The mean follow-up interval was 131.2 (range 10.7–301.3) months, and the mean age of the whole cohort was 48.1 ± 9.8 (range 26–81) years. All were Hong Kong Chinese, except one Filipino, one Singaporean and one Indonesian. For patients with CCC, 16 (11.1%) had symptomatic VTE in comparison to only 1.7% (eight out of 468) in non-CCC ovarian cancer patients. Only one out of 13 patients was a smoker. The mean body mass index was 23.7 ± 4.1. None of them had previous history or family history of VTE. The mean white cell count was 11.3 ± 5.6, absolute neutrophil count was 10.0 ± 5, platelet count was 293.0 ± 144.8, haematocrit was 0.30 ± 0.03. All had thrombosis in the lower limb vessels, with five involving iliac veins, one involving inferior vena cava up to the renal vein, and one with co-existing pulmonary embolism. Apart from one patient who developed VTE before the diagnosis of cancer and another one the next day after primary surgery, the rest (87.5%) were diagnosed at the time of recurrence or progression. The median time interval between the date of primary surgery and the development of VTE was 409 (range 36–2,373) days.

The median CA 125 level before treatment was 87.5 (range 4–16,174) U/ml. Apart from one patient who refused treatment, all patients had undergone upfront surgery and 12 (8.4%) of which were conservative surgery. As the practice of lymphadenectomy was not standardized in the earlier years, 71 patients (49.3%) did not have complete staging procedure and 55 (77.5%) of them had apparently Stage I disease. Overall, 92.8% patients had an optimal cytoreduction. The demographic features, treatment details, and outcomes of the case and control groups are outlined in Table 1. Fewer patients in the case group presented at early stage (50.0% *vs*. 71.0%, $p = 0.247$), although it was not statistically significant, and 132/144 (91.7%) patients received adjuvant chemotherapy and 112 (84.8%) of them were platinum-based. Compared with the control group, significantly smaller proportion of the patients with VTE was responsive to chemotherapy (57.1% *vs*. 85.1%, $p = 0.01$) including platinum-based therapy (30.8% *vs*. 80.2%, $p = 0.001$). The median duration of response to chemotherapy was 4.7 (range 0.9–31) months in the case group and 83.6 (range 0–218) months in the control group ($p < 0.001$). Sixty-eight out of 137 (49.6%) had either relapse, persistent or progressive disease. The recurrence / progressive disease rate was significantly higher in the case group compared to the control (100.0% *vs*. 37.2%, $p < 0.001$).

The five-year OS rate and DFS rate of the whole cohort was 69.8% and 62.3% respectively, for early-stage diseases, and dropped to 12.5% and 8.3%, respectively, for those with late-stage diseases. None of the 16 patients in the case group survived, compared with 81 out of 128 patients (63.3%) in the control group ($p < 0.001$), and all patients of the case group died of progressive disease rather than complications of VTE or its treatment. The five-year DFS and OS rates of the case group were 0% and 6.2%, compared with 52.0% and 63.0% in the control group, respectively. The median DFS (0 months, range 0–0 months *vs*. 70.8 months, range 0–222.8 months; $p < 0.001$) and OS (16.5 months, range 3.1–77.7 months *vs*. 88.0 months, range 0.1–301.3 months; $p < 0.001$) were all significantly worse in the case group than the control group. The median interval between the diagnosis of VTE and death was 43.0 (range 1–394) days, and the mortality rate was 56.3% within three months after the diagnosis of VTE.

Survival analysis was performed to evaluate the relationship between different clinical parameters with CCC, and those significant factors for DFS and OS are shown in Figures 1 and 2, respectively.

Cox regression was performed using those parameters found to be significant in the Kaplan-Meier analyses. Duration of chemotherapy response, including partial and complete response, for more than one year was independently correlated with the DFS (hazard ratio (HR) 4.0, 95% confidence interval (CI) 1.5 – 10.3; $p = 0.005$), while VTE (HR 4.3, 95% CI 1.2–15.0; $p = 0.02$), Stage (HR 0.2, 95%

Table 1. — *Demographic features, treatment details, and outcomes of patients with and without VTE.*

		Thromboembolism		*p*-value
		Yes	No	
Age (years)		43.6 ± 12.0	48.7 ± 9.4	0.049
	Range	30 - 79	26 - 81	
	Number of patients	16	128	
Parity	Nulliparity	11 (73.3%)	61 (47.7%)	0.099
	Multiparity	4 (26.7%)	67 (52.3%)	
	Number of patients	15	128	
Presentation	Abdominal distension	5 (33.3%)	38 (29.7%)	0.773
	Abdominal discomfort / pain	1 (6.7%)	31 (24.2%)	0.306
	Mass	4 (26.7%)	20 (15.6%)	0.486
	Post-menopausal or irregular vaginal bleeding	2 (13.3%)	16 (12.5%)	1.000
	Constitutional symptoms	0 (0%)	3 (2.3%)	1.000
	Incidental finding	0 (0%)	17 (13.3%)	0.216
	Ankle edema +/- calf pain	2 (13.3%)	1 (0.78%)	0.030
	Pleural effusion	0 (0%)	1 (0.78%)	1.000
	Acute retention of urine	0 (0%)	1 (0.78%)	1.000
	Pyrexia	1 (6.7%)	0 (0%)	0.106
	Number of patients	15	128	
Median pre-treatment		177.9	84	0.763
CA125 (U/ml)	Range	5.9 - 1209	4 - 16174	
	Number of patients	10	74	
Stage	Stage 1	2 (25.0%)	40 (58.0%)	NA
	Stage 2	2 (25.0%)	9 (13.0%)	
	Stage 3	3 (37.5%)	16 (23.2%)	
	Stage 4	1 (12.5%)	4 (5.8%)	
	Number of patients	8	69	
Primary treatment	Nil	0 (0%)	1 (0.8%)	NA
	Surgery alone	2 (12.5%)	8 (6.2%)	
	Surgery and adjuvant chemotherapy	14 (87.5%)	119 (93.0%)	
	Number of patients	16	128	
Lymphadenectomy	Yes	7 (43.8%)	55 (43.3%)	0.973
	No	9 (56.2%)	72 (56.7%)	
	Number of patients	16	127	
Yield of pelvic lymph nodes		11.5 ± 8.7	18.9 ± 11.0	0.204
	Range	3 - 20	1 - 45	
	Number of patients	4	35	
Yield of para-aortic lymph nodes		23.7 ± 5.5	10.6 ± 8.4	0.02
	Range	20 - 30	1 - 30	
	Number of patients	3	17	
Lymph node involvement	Positive	2 (28.6%)	5 (8.8%)	0.166
	Negative	5 (71.4%)	52 (91.2%)	
	Number of patients	7	57	
Capsular involvement	Capsular involvement	6 (50.0%)	30 (36.6%)	0.372
	No capsular involvement	6 (50.0%)	52 (63.4%)	
	Number of patients	12	82	
Rupture of tumour	Rupture	4 (50.0%)	60 (72.3%)	0.231
	Intact	4 (50.0%)	23 (27.7%)	
	Number of patients	8	83	
Peritoneal cytology	Negative	6 (66.7%)	52 (61.2%)	1.000
	Positive	3 (33.3%)	33 (38.8%)	
	Number of patients	9	85	
Residual disease	≤1cm	12 (100%)	104 (92.0%)	0.598
	>1cm	0 (0%)	9 (8.0%)	
	Number of patients	12	113	
Platinum-based chemotherapy	Platinum-based	13 (92.9%)	99 (83.9%)	0.694
	Non-platinum-based	1 (7.1%)	19 (16.1%)	
	Number of patients	14	118	
Median duration of chemotherapy		4.7	83.6	< 0.001
response (months)	Range	0.9 - 31	0 - 218	
	Number of patients	14	117	
Duration of response	> 1 year	8 (57.1%)	97 (85.1%)	0.01
to chemotherapy	≤ 1 year	6 (42.9%)	17 (14.9%)	
	Number of patients	14	114	
Progression / relapse	Yes	16 (100%)	45 (37.2%)	<0.001
	No	0 (0%)	76 (62.8%)	
	Number of patients	16	121	
Disease status	With disease	16 (100%)	52 (43%)	<0.001
	Without disease	0 (0%)	69 (57%)	
	Number of patients	16	121	
Survival status	Alive	0 (0%)	81 (63.3%)	<0.001
	Dead	16 (100%)	47 (36.7%)	
	Number of patients	16	128	
Median disease free	0	70.8	< 0.001	
survival (months)	Range	0	0 - 222.8	
	Number of patients	16	127	
Median overall survival (months)		16.5	88	< 0.001

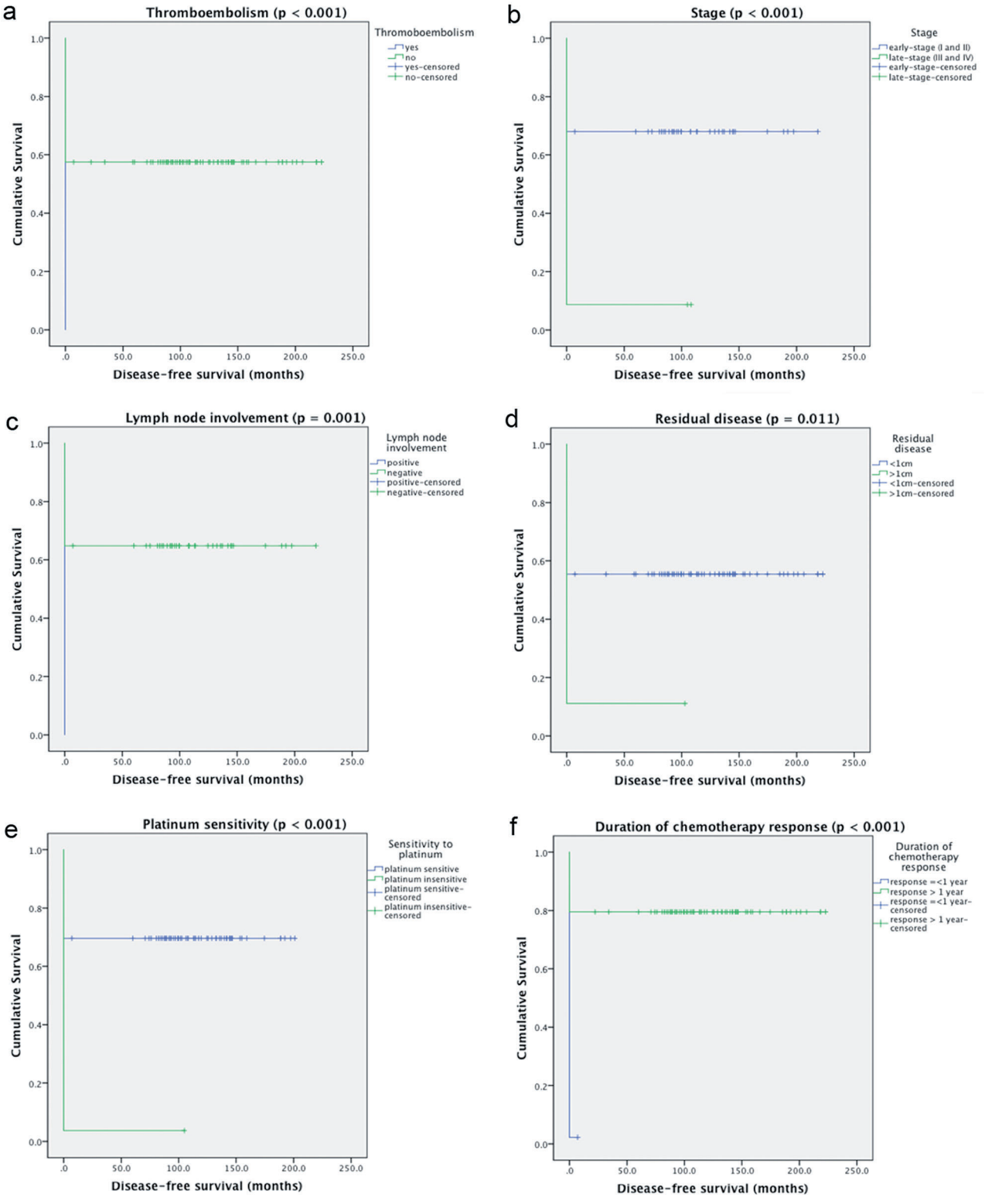

Figure 1. — Disease-free survival according to different parameters: (a) thromboembolism, (b) stage, (c) lymph node involvement, (d) residual disease, (e) platinum sensitivity, and (f) chemosensitivity.

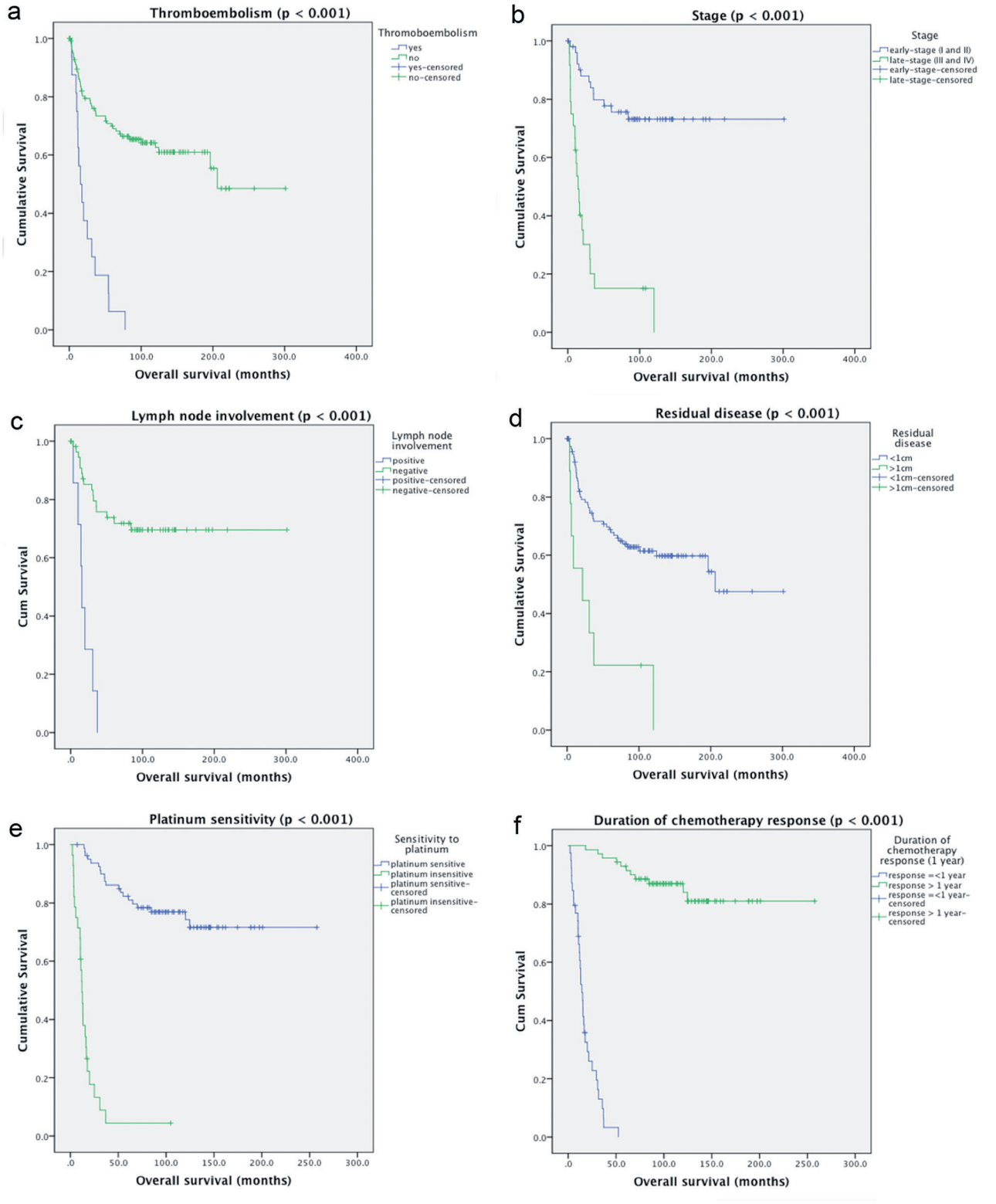

Figure 2. — Overall survival according to different parameters: (a) thromboembolism, (b) stage, (c) lymph node involvement, (d) residual disease, (e) platinum sensitivity, and (f) chemosensitivity.

CI 0.1–0.9; $p = 0.03$), and the duration of chemotherapy response for more than one year (HR 75.8, 95% CI 15.5–370.3; $p < 0.001$) were independent prognosticators for OS.

Discussion

The survival of patients with early-stage CCC is similar to patients with serous carcinoma, but the reverse was observed in advanced diseases [10]. Tumor stage is an important prognostic parameter in CCC as shown in the present study [25, 26]. Some studies showed a survival benefit of performing lymphadenectomy [25, 26], but some authors and the present group did not find it significant [27]. Although the incidence of lymph node metastasis is only < 5% in CCC, the mortality is three times higher in those with lymph node metastasis than those without [26], and because of its low proliferation activity, CCC is generally considered to be resistant to platinum-based chemotherapy compared with the serous counterpart [12]. The present patients had a relatively high response rate to chemotherapy. The exact reason was not known, but a response rate up to 70% had also been reported [15]. The use of adjuvant platinum-based chemotherapy in the present patients had no effect on either the DFS or OS.

It had been suggested that cancer patients with VTE, in general, had poor prognosis especially if the VTE occurred within the first year of diagnosis [28, 29]. For patients with EOC, whether those with VTE have poorer survival remains controversial. While some did not show a significant prognostic value of VTE [30, 31], others found that those with VTE were associated with a worse survival [7, 8].

The prognostic implication of VTE specifically in CCC is equally conflicting. Some investigators found that VTE does not have any impact on the prognosis [14, 15]. Nevertheless, Recio *et al.* demonstrated a worse outcome for those with VTE (mean survival 14.2 months; five-year survival rate 0%) compared with those without (mean survival 33.8 months; five-year survival rate 38%) ($p = 0.009$) [13]. Matsurra *et al.* also observed that those with DVT had a higher risk of death than the control (HR 2.97, 95% CI 1.31–6.75; $p = 0.01$) [9]. Furthermore, in the study by Diaz *et al.*, patients who developed VTE during the primary treatment had a significantly shorter median progression-free survival (11 *vs*. 76 months; $p = 0.01$) and OS (19 *vs*. 90 months; $p = 0.001$) than those without VTE, and VTE remained as an independent predictor of death (HR 3.6; $p = 0.005$) on multivariate analysis after controlling for tumor stage [17]

The present authors postulate three hypotheses on the detrimental survival effect of VTE in this cohort. First, the mortality might be due to VTE and its complications like PE and bleeding. However, this was not likely in the present patients because anti-coagulant was initiated immediately after VTE was diagnosed, and no DVT or treatment complications were found except for one patient with documented PE. The second possibility is VTE may be a surrogate marker for advanced or recurrent disease and the latter per se is inherently associated with poor prognosis. Nevertheless, some authors like Diaz *et al.* demonstrated that VTE had no significant impact on survival in recurrent CCC and so the poor outcomes in patients with VTE cannot be totally attributable to its association with the disease status and tumor volume [17]. Another plausible explanation, which may be the most likely, is the interaction between the coagulatory pathway, the inflammatory cascade, and tumor metastasis [4]. On one hand, activated oncogenes like K-ras, EGFR and MET, as well as inactivated tumor suppressor genes like p53 and pTEN, may promote the expression of tissue factor (TF) and release procoagulants such as cancer procoagulant (CP), TF-bearing microparticles and other fibrinolysis inhibitors, resulting in a prothrombotic state [32]. On the other hand, VTE itself also modifies the tumor biology and microenvironment. For example, TF can increase the local generation of coagulation proteases including factor VIIa and form a complex with it, leading to the cleavage of protease activate receptors (PAR) inside the tumor cells [32, 33]. This then upregulates the expression of angiogenic factors including VEGF and causes neovascularization and tumor growth [5, 32, 34]. It has been shown that the levels of TF and TF-bearing microparticles, a potent form of TF, were raised in cancer patients with VTE including CCC and these could potentially be a predictor for cancer-related death [2, 3, 35].

VTE can occur anytime during the disease course. One retrospective study showed that 30% of VTE in ovarian cancer patients was identified within three months of major pelvic or abdominal cancer surgery [7]. Saadeh *et al.* showed that one-third of VTE occurred before treatment, one-third within 28 days after surgery, and another one-third during chemotherapy [8]. Duska *et al.* also found that among their 18 patients who developed VTE despite appropriate thromboprophylaxis, 50% had VTE at the postoperative period [16]. The present study showed that the overall incidence of VTE was low in ovarian cancer patients even without routine medical thromboprophylaxis including those in perioperative period, and among the CCC patients, only 1/144 (0.69%) developed postoperative VTE. It is unclear why the incidence of VTE is lower in Asians than the western population. On the other hand, torrential bleeding had been observed in some Asian patients after receiving anti-coagulant in the immediate postoperative period and exploratory laparotomy was required (data not published). These results challenge the routine perioperative thromboprophyaxis as suggested by most authorities [18-20].

Some suggested survival benefit of using low molecular weight heparin (LMWH) in advanced cancer patients [36-38]. A recent meta-analysis from 11 randomized controlled studies demonstrated that the one-year mortality was similar in patients with and without LMWH [39]. The data in

EOC were scarce. A multi-center phase II randomized open-label study on 77 newly diagnosed EOC patients who received chemotherapy together with either placebo or one of the three regimens of dalteparin (50, 100 or 150 IU/kg daily) for the first three cycles, showed that ≥ 85% of the dalterparin group had at least 50% decrease of CA 125 level [40]. However, the response was not assessed with the RECIST criteria, and due to poor subject recruitment, the study was terminated prematurely, and the anti-tumor effect of dalteparin and patients' survival performance could not be evaluated because of a lack of the non-LMWH controls. Until now, it is not recommended to employ anticoagulant to improve the survival of ambulatory cancer patients without VTE outside clinical trial settings [18].

There are several limitations of this study. The practice and extent of lymphadenectomy and debulking, the use of platinum-based chemotherapy and other second-line chemotherapy, as well as the diagnostic accuracy of VTE evolved over time and therefore, not all patients received identical regimen of chemotherapy. As imaging was not routinely performed, it is conceivable that some sub-clinical VTE would not have been detected. Nevertheless, the present study does provide a long-term follow-up data for patients with ovarian CCC and demonstrated the adverse effect of VTE on survival.

In conclusion, VTE is rare in EOC patients even without routine medical thromboprophylaxis. Ovarian cancer, even in CCC, and cancer operation should not be the sole indications for medical thromboprophyalxis. A risk stratification system should be developed for its prescription and periodic review on its safety is needed. Medical thromboprophyalxis should be given in patients with other risk factors like long operation time, obesity, immobility, and Caucasians. For low-risk patients, thromboprophylaxis may not be necessary and extra precaution is mandatory if the physicians think the benefit of thromboprophylaxis outweighs the risk of bleeding. Advanced stage, duration of response of chemotherapy for < 1 year, and the presence of VTE are associated with poor survival outcomes in CCC. The negative survival impact of VTE may be related to the interaction between the coagulation cascade, inflammatory pathway, and tumor biology. More studies are needed to verify the findings of the current study and unravel the underlying biochemical basis of CCC.

References

[1] Trousseau A.: "Phlegmasia alba dolens. Clinique Medicale del'Hotel-Dieu de Paris, 3". London: New Sydenham Society, 1865.

[2] Uno K., Homma S., Satoh T., Nakanishi K., Abe D., Matsumoto K., *et al.*: "Tissue factor expression as a possible determinant of thromboembolism in ovarian cancer". *Br. J. Cancer*, 2007, *96*, 290.

[3] Abu Saadeh F., Norris L., O'Toole S., Mohamed B.M., Langhe R., O'Leary J., *et al.*: "Tumour expresion of tissue factor and tissue factor pathway inhibitor in ovarian cancer- relationship with venous thrombosis risk". *Thromb. Res.*, 2013, *132*, 627.

[4] Wang X., Wang E., Kavanagh J.J., Freedman R.S.: "Ovarian cancer, the coagulation pathway, and inflammation". *J. Transl. Med.*, 2005, *3*, 25.

[5] Fernandez P.M., Rickles FR: "Tumor angiogenesis and blood coagulation". *In*: Lugassy G.F.A., Kakkar A.K., Rickles F.R., (eds). *Thrombosis and Cancer*. London, United Kingdom: Martin Dunitz, 2004, 69.

[6] Tateo S., Mereu L., Salamano S., Klersy C., Barone M., Spyropoulos A.C., *et al.*: "Ovarian cancer and venous thromboembolic risk". *Gynecol. Oncol.*, 2005, *99*, 119.

[7] Rodriguez A.O., Wun T., Chew H., Zhou H., Harvey D., White R.H.: "Venous thromboembolism in ovarian cancer". *Gynecol. Oncol.*, 2007, *105*, 784.

[8] Saadeh F.A., Norris L., O'Toole S., Gleeson N.: "Venous thromboembolism in ovarian cancer: incidence, risk factors and impact on survival". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2013, *170*, 214.

[9] Matsuura Y., Robertson G., Marsden D.E., Kim S.N., Gebski V., Hacker N.F.: "Thromboembolic complications in patients with clear cell carcinoma of the ovary". *Gynecol. Oncol.*, 2007, *104*, 406.

[10] Anglesio M.S., Carey M.S., Kobel M., Mackay H., Huntsman D.G., Vancouver Ovarian Clear Cell Symposium S.: "Clear cell carcinoma of the ovary: a report from the first Ovarian Clear Cell Symposium, June 24th, 2010". *Gynecol. Oncol.*, 2011, *121*, 407.

[11] Sugiyama T., Kamura T., Kigawa J., Terakawa N., Kikuchi Y., Kita T., *et al.*: "Clinical characteristics of clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy". *Cancer*, 2000, *88*, 2584.

[12] Itamochi H., Kigawa J., Terakawa N.: "Mechanisms of chemoresistance and poor prognosis in ovarian clear cell carcinoma". *Cancer Sci.*, 2008, *99*, 653.

[13] Recio F.O., Piver M.S., Hempling R.E., Driscoll D.L.: "Lack of improved survival plus increase in thromboembolic complications in patients with clear cell carcinoma of the ovary treated with platinum versus nonplatinum-based chemotherapy". *Cancer*, 1996, 78, 2157.

[14] Goff B.A., Sainz de la Cuesta R., Muntz H.G., Fleischhacker D., Ek M., Rice L.W., *et al.*: "Clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy in stage III disease". *Gynecol. Oncol.*, 1996, *60*, 412.

[15] Pather S., Quinn M.A.: "Clear-cell cancer of the ovary-is it chemosensitive?" *Int. J. Gynecol. Cancer*, 2005, *15*, 432.

[16] Duska L.R., Garrett L., Henretta M., Ferriss J.S., Lee L., Horowitz N.: "When 'never-events' occur despite adherence to clinical guidelines: the case of venous thromboembolism in clear cell cancer of the ovary compared with other epithelial histologic subtypes". *Gynecol. Oncol.*, 2010, *116*, 374.

[17] Diaz E.S., Walts A.E., Karlan B.Y., Walsh C.S.: "Venous thromboembolism during primary treatment of ovarian clear cell carcinoma is associated with decreased survival". *Gynecol. Oncol.*, 2013, *131*, 541.

[18] Lyman G.H., Khorana A.A., Kuderer N.M., Lee A.Y., Arcelus J.I., Balaban E.P., *et al.*: "Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update". *J. Clin. Oncol.*, 2013, *31*, 2189.

[19] Gould M.K., Garcia D.A., Wren S.M., Karanicolas P.J., Arcelus J.I., Heit J.A., *et al.*: "Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines". *Chest*, 2012, *141*, e227S.

[20] National Collaborating Centre for Acute and Chronic Conditions: "Venous thromboembolism: reducing the risk: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. NICE clinical guideline". London: National Institute for Health and Clinical Excellence, 2010, 1.

[21] Teoh D., Berchuck A., Alvarez Secord A., Lee P.S., Lowery W.J., Sfakianos G.P., *et al.*: "Cost comparison of strategies for the management of venous thromboembolic event risk following laparotomy for ovarian cancer". *Gynecol. Oncol.*, 2011, *122*, 467.

[22] Uppal S., Hernandez E., Dutta M., Dandolu V., Rose S., Hartenbach E.: "Prolonged postoperative venous thrombo-embolism prophylaxis is cost-effective in advanced ovarian cancer patients". *Gynecol. Oncol.*, 2012, *127*, 631.

[23] Weida D., Patrick L.Y., Andrew Y.W.: "Is it safe to perform operation for colorectal malignancy in Chinese patients without DVT prophylaxis? An 8-year experience from a regional hospital in Hong Kong". *Chin. Med. J. (Engl.)*, 2010, *123*, 1973.

[24] Cheuk B.L., Cheung G.C., Cheng S.W.: "Epidemiology of venous thromboembolism in a Chinese population". *Br. J. Surg.*, 2004, *91*, 424.

[25] Magazzino F., Katsaros D., Ottaiano A., Gadducci A., Pisano C., Sorio R., *et al.*: "Surgical and medical treatment of clear cell ovarian cancer: results from the multicenter Italian Trials in Ovarian Cancer (MITO) 9 retrospective study". *Int. J. Gynecol. Cancer*, 2011, *21*, 1063.

[26] Mahdi H., Moslemi-Kebria M., Levinson K.L., Gojayev A., Lockhart D., Ali-Fehmi R., *et al.*: "Prevalence and prognostic impact of lymphadenectomy and lymph node metastasis in clinically early-stage ovarian clear cell carcinoma". *Int. J. Gynecol Cancer*, 2013, *23*, 1226.

[27] Suzuki S., Kajiyama H., Shibata K., Ino K., Nawa A., Sakakibara K., *et al.*: "Is there any association between retroperitoneal lymphadenectomy and survival benefit in ovarian clear cell carcinoma patients?" *Ann. Oncol.*, 2008, *19*, 1284.

[28] Sorensen H.T., Mellemkjaer L., Olsen J.H., Baron J.A.: "Prognosis of cancers associated with venous thromboembolism". *N. Engl. J. Med.*, 2000, *343*, 1846.

[29] Chew H.K., Wun T., Harvey D., Zhou H., White R.H.: "Incidence of venous thromboembolism and its effect on survival among patients with common cancers". *Arch. Intern. Med.*, 2006, *166*, 458.

[30] Black D., Iasonos A., Ahmed H., Chi D.S., Barakat R.R., Abu-Rustum N.R.: "Effect of perioperative venous thromboembolism on survival in ovarian, primary peritoneal, and fallopian tube cancer". *Gynecol. Oncol.*, 2007, *107*, 66.

[31] Fotopoulou C., duBois A., Karavas A.N., Trappe R., Aminossadati B., Schmalfeldt B., *et al.*: "Incidence of venous thromboembolism in patients with ovarian cancer undergoing platinum/paclitaxel-containing first-line chemotherapy: an exploratory analysis by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group". *J. Clin. Oncol.*, 2008, *26*, 2683.

[32] Rak J., Yu J.L., Luyendyk J., Mackman N.: "Oncogenes, trousseau syndrome, and cancer-related changes in the coagulome of mice and humans". *Cancer Res.*, 2006, *66*, 10643.

[33] Liu Y., Jiang P., Capkova K., Xue D., Ye L., Sinha S.C., *et al.*: "Tissue factor-activated coagulation cascade in the tumor microenvironment is critical for tumor progression and an effective target for therapy". *Cancer Res.*, 2011, *71*, 6492.

[34] Kasthuri R.S., Taubman M.B., Mackman N.: "Role of tissue factor in cancer". *J. Clin. Oncol.*, 2009, *27*, 4834.

[35] Han L.Y., Landen C.N., Jr., Kamat A.A., Lopez A., Bender D.P., Mueller P., *et al.*: "Preoperative serum tissue factor levels are an independent prognostic factor in patients with ovarian carcinoma". *J. Clin. Oncol.*, 2006, *24*, 755.

[36] Kakkar A.K., Levine M.N., Kadziola Z., Lemoine N.R., Low V., Patel H.K., *et al.*: "Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: the fragmin advanced malignancy outcome study (FAMOUS)". *J. Clin. Oncol.*, 2004, *22*, 1944.

[37] Klerk C.P., Smorenburg S.M., Otten H.M., Lensing A.W., Prins M.H., Piovella F., *et al.*: "The effect of low molecular weight heparin on survival in patients with advanced malignancy". *J. Clin. Oncol.*, 2005, *23*, 2130.

[38] Akl E.A., Gunukula S., Barba M., Yosuico V.E., van Doormaal F.F., Kuipers S., *et al.*: "Parenteral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation". *Cochrane Database Syst. Rev.*, 2011, CD006652.

[39] Che D.H., Cao J.Y., Shang L.H., Man Y.C., Yu Y.: "The efficacy and safety of low-molecular-weight heparin use for cancer treatment: a meta-analysis". *Eur. J. Intern. Med.*, 2013, *24*, 433.

[40] Elit L.M., Lee A.Y., Parpia S., Swystun L.L., Liaw P.C., Hoskins P., *et al.*: "Dalteparin low molecular weight heparin (LMWH) in ovarian cancer: a phase II randomized study". *Thromb. Res.*, 2012, *130*, 894.

Corresponding Author:
KA YU TSE, M.D.
Department of Obstetrics and Gynaecology
Queen Mary Hospital
102, Pokfulum Road (Hong Kong)
e-mail: tseky@hku.hk