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## Significance of venous thromboembolism in women with uterine carcinosarcoma

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### HIGHLIGHTS

- Venous thromboembolism (VTE) was examined in uterine carcinosarcoma (UCS).
- Approximately 8% of women with UCS developed VTE.
- Patient factors for VTE: older age, large body habitus, and non-Asian
- Tumor factors for VTE: residual disease, large tumor, and stage IV disease
- VTE was associated with decreased survival in UCS.

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## ABSTRACT

**Objective.** To identify risk factors for venous thromboembolism (VTE) and to examine the association of VTE and survival in women with uterine carcinosarcoma.

**Methods.** This multicenter retrospective study examined 906 women who underwent primary surgical treatment for stage I–IV uterine carcinosarcoma. Time-dependent analyses were performed for cumulative incidence of VTE after surgery on multivariate models.

**Results.** There were 72 (7.9%) women who developed VTE after surgery with 1-, 2-, and 5-year cumulative incidences being 5.1%, 7.3%, and 10.2%, respectively. On multivariate analysis, older age (hazard ratio [HR] per year 1.03,  $P = 0.012$ ), non-Asian race (HR 6.28,  $P < 0.001$ ), large body habitus (HR per  $\text{kg}/\text{m}^2$  1.04,  $P = 0.014$ ), residual disease at surgery (HR 3.04,  $P = 0.003$ ), tumor size  $\geq 5$  cm (HR 2.73,  $P = 0.003$ ), and stage IV disease (HR 2.12,  $P = 0.025$ ) were independently associated with increased risk of developing VTE. A risk pattern analysis identified that obese Non-Asian women with large tumors (13.7% of population) had the highest incidence of VTE (2-year cumulative rate, 26.1%) whereas Asian women with no residual disease (47.1% of population) had the lowest (2-year cumulative rate, 1.6%) ( $P < 0.001$ ). Presence of carcinoma/sarcoma in metastatic sites was significantly associated with increased risk of VTE compared to carcinoma alone (2-year rates, 31.2% versus 8.4%,  $P = 0.049$ ). VTE was independently associated with decreased progression-free survival on multivariate models (5-year rates, 24.9% versus 47.2%, HR 1.46, 95%CI 1.05–2.04,  $P = 0.026$ ).

**Conclusion.** Our study suggests that VTE represents a surrogate marker of aggressive tumor behavior and diminished patient condition in uterine carcinosarcoma; obese Non-Asian women with large tumors carry a disproportionately high risk of VTE, suggesting that long-term prophylaxis may benefit this population.

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## 1. Introduction

Uterine carcinosarcoma is a rare high-grade endometrial cancer and represents the phenomena of epithelial-to-mesenchymal transition (EMT) with the sarcoma component being dedifferentiated from the carcinoma component [1]. Uterine carcinosarcoma is typically a disease of the elderly, a population that often has multiple medical comorbidities and physical deconditioning [1]. Moreover, women with uterine carcinosarcoma frequently present with advanced-stage disease [2]; all of these are known to be risk factors for developing venous thromboembolism (VTE) [3–5].

VTE is a common clinical problem in women with gynecologic malignancies, including ovarian (VTE incidence, 6.4–23.2%), cervical (12.3%), and endometrial (8.1%) cancers [6–9]. Across these three cancer types, VTE is recognized as a manifestation of aggressive tumor characteristics such as advanced or metastatic disease (VTE incidence, 23.5–44.8%), thrombocytosis (22.3–25.0%), high-risk histology (ovarian clear cell carcinoma 11.9–43.1%; and uterine serous/clear cell carcinomas 28.6–29.2%), as well as poor patient condition including hypoalbuminemia (19.3–53.2%) [6–9]. Additionally, women who develop VTE have worse survival outcomes as demonstrated in published studies [6–9].

Because uterine carcinosarcoma has similar clinical and molecular characteristics to other high-risk endometrial cancer types [10,11], and is associated with risk factors for developing VTE, it is likely that women with uterine carcinosarcoma carry a high risk of developing VTE. To date there has been no prior study examining the significance of VTE solely in the uterine carcinosarcoma population. Therefore, identifying a subgroup of women with an increased risk of VTE may alter the management of uterine carcinosarcoma.

The objective of this study was (i) to examine incidence and risk factors for VTE and (ii) to examine the association of VTE and survival in women with uterine carcinosarcoma.

## 2. Patients and methods

## 2.1. Study eligibility

This is a secondary analysis of a formerly organized surgical database for uterine carcinosarcoma [2,12–15]. Previously, we conducted a large-scale multicenter retrospective review of women with stage I–IV uterine carcinosarcoma who underwent primary hysterectomy-based

surgical treatment between 1993 and 2013. We obtained Institutional Review Board approval at each participating institution. There were 26 institutions from the United States and Japan that participated in this study (906 cases). By utilizing this surgical database, we queried the cases of women who developed VTE after the initial surgery for uterine carcinosarcoma.

## 2.2. Clinical information

From the database, we obtained the following information for the analysis: patient baseline characteristics, pathology results, initial treatment information, and survival outcomes. For patient characteristics, patient age (continuous), country (USA versus Japan), race (White, Black, Hispanic, and Asian), body mass index (BMI, continuous), gravidity (null versus multi), and preoperative CA-125 level (continuous) were evaluated.

Histopathologic results included carcinoma component (low-grade versus high-grade), sarcoma component (homologous versus heterologous), tumor size from the uterine specimen ( $\geq 5$  versus  $< 5$  cm) [16], presence of sarcoma dominance (yes versus no), depth of myometrial tumor invasion (inner-half versus outer-half), lympho-vascular space invasion (LVSI, present versus absent), pelvic and para-aortic lymph node status (metastasis, non-metastasis, and not examined), and cancer stage (I, II, III, and IV). In addition, histology subtypes of the carcinoma component were examined as classified previously [2].

Treatment information abstracted included: residual disease at the end of primary hysterectomy-based surgery (yes versus no), use of postoperative chemotherapy (yes versus no), and use of postoperative radiotherapy (yes versus no). For survival outcomes, progression-free survival (PFS) and cause-specific survival (CSS) were recorded.

## 2.3. Evaluation of VTE

Information regarding VTE, itemized in the universal data record form at the time of data collection, was examined for the time interval between the hysterectomy-based surgery and the last follow-up date. Type of VTE was grouped into deep venous thrombosis (DVT) or pulmonary embolism (PE). Across the study sites, the diagnosis of VTE was made by radiographic imaging modalities including computed tomography, pulmonary angiogram, ventilation perfusion lung scan, or Doppler study. This database does not contain information regarding prophylactic anti-coagulation.

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