

## Impact of venous thromboembolism on survival in patients with malignancy

An association between venous thromboembolism (VTE) and cancer is well recognised (Lee, 2004). Recent population-based studies have provided some insights into the incidence and timing of VTE events in patients with common cancers (White *et al*, 2007), and we have recently described increased relative risks of VTE in common and rare cancer types (Rose *et al*, 2007). There is evidence that patients with cancer who develop VTE have shortened survival (Sorensen *et al*, 2000; Alcalay *et al*, 2006; Chew *et al*, 2006, 2007) but the impact of VTE on survival in patients with specific cancers remains to be fully defined. This study aimed to compare outcome in VTE patients with specific cancer types with VTE-free patients and assess if VTE affected overall survival.

Patients were enrolled at two University teaching hospitals (Walsgrave Hospital, Warwickshire and Derriford Hospital, Plymouth) into prospectively maintained databases of patients. Patients with VTE participated in the VEnous thromboembolism RegIsTY (VERITY), which prospectively enrolls patients attending deep vein thrombosis (DVT) outpatient clinics. Details of the VERITY registry have been published previously (O'Shaughnessy *et al*, 2004). Data are collected by trained hospital staff in a standardised electronic case report form and submitted to the electronic database. Patient data are anonymised and identified in the database only by a VERITY number. Demographic characteristics, medical history, presenting symptoms, diagnosis, treatment practices including location of treatment, and follow-up data are collected. All patients underwent a Doppler ultrasound examination to confirm the diagnosis and determine the extent of DVT. Additional investigations were undertaken if appropriate according to local clinical algorithms. All patients with VTE received standard treatment with low molecular weight heparin and warfarin. Patients without VTE were enrolled in a separate, prospective database of consecutive patients maintained at Walsgrave Hospital. This database included all patients suspected of having a DVT but for whom the diagnosis was excluded after Doppler ultrasound examination. The presence of known malignancy (defined by ongoing treatment for cancer or metastatic disease) and type of malignancy detected at the time of thrombosis or subsequently during follow-up was documented in the database. The outcome parameter used in this analysis was death.

Statistical analysis was carried out using the Statistical Package for the Social Sciences (spss) version 13.0 (SPSS Inc., Chicago, Ill, USA) for Windows and GraphPad InStat<sup>®</sup> version

3.06 (GraphPad Software, San Diego, CA, USA) for Windows software. Overall survival was estimated by the Kaplan–Meier method. The log-rank test was used to compare survival between groups across the whole follow-up period. The alpha level for statistical significance was set at 0.05.

Between February 2001 and December 2006, 902 patients with confirmed VTE were included in this analysis, 699 consecutive patients at Walsgrave Hospital (described previously, Paneesha *et al*, 2006) and 203 patients at Derriford Hospital. Between February 2001 and December 2005, 2263 consecutive patient episodes from 2016 patients without VTE were recorded. For patients with VTE, median age at presentation was 66 years (range 16–96 years) and 51.3% were male; for VTE-free patients, median age was 69 years (18–105 years) and 67.1% were male. Cancer was present in 42% of patients with confirmed VTE (379/902) and in 11% of non-VTE cases (222/2016). Cancer type was specified in 73.1% of cancer cases; 19.7% had bowel cancer, 19.6% had breast, 16.9% had prostate, 10.5% had lung and 7.6% had gynaecological cancer.

Median follow-up was 21 months (range 0–74 months) in patients with VTE and 22.2 months (0–65 months) in those negative for VTE. Mean overall survival in non-VTE patients without malignancy was 56 months compared with 54 months in VTE patients with malignancy. Survival was analysed between cancer patients with and without VTE according to cancer type. Median survival in patients with and without VTE was 30 vs. 31 months for prostate cancer, 17 vs. 50 for gynaecological cancer and 8 vs. 3.5 for lung cancer. For patients with unspecified cancer type, median survival was 9 vs. 30 months. For breast and bowel cancer, the numbers were large enough to allow calculation of Kaplan–Meier estimates of survival, which are shown in Fig 1. For patients with breast or bowel cancer, the log-rank test revealed a significant difference between the survival rates over time with VTE patients having shorter survival ( $P = 0.016$  and  $P = 0.05$ , respectively). For bowel cancer patients, for whom the statistical significance was marginal, median survival time was 8 months vs. 36 months in those with and without VTE.

This analysis suggests that common cancers, specifically breast and bowel, are associated with adverse outcome in the presence of objectively confirmed VTE. A previous study of cancer survival based on the California Cancer Registry and the California Patient Discharge dataset reported reduced survival at 2 years for breast cancer (Chew *et al*, 2007) and colorectal cancer (Alcalay *et al*, 2006) patients. In those

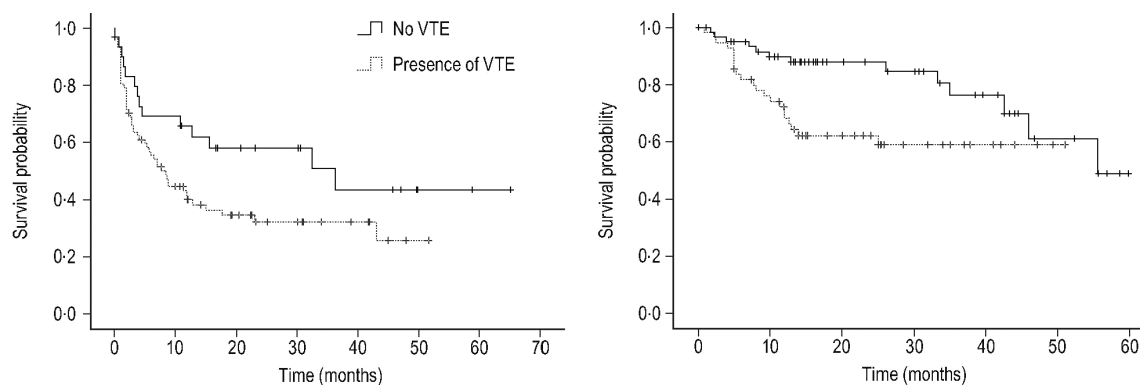


Fig 1. Kaplan–Meier survival curves showing impact of cancer (bowel or breast) on overall survival in patients with and without VTE. Left panel: Overall survival in patients with bowel cancer. Right panel: Overall survival in patients with breast cancer.

analyses, the authors were able to assess the impact of metastatic disease and showed that local or regional disease correlated with adverse survival in colorectal cancer, but with metastatic disease in breast cancer. A weakness of our study was that no record was made of metastatic disease. In addition, no histological description, tumour grade or stage was recorded. Our retrospective study was also limited by conducting the analysis in two separate groups, unmatched for age and sex. Nonetheless, this analysis, and our previous study, which confirmed the adverse impact on survival of elevated D-dimer in patients with VTE and malignancy (Paneesha *et al*, 2006), again confirms that VTE can impact cancer survival. Taken with our previous analysis that showed high relative risks of VTE in certain rare cancer types, such as pancreatic and endocrine cancer (Rose *et al*, 2007), further larger studies are required to define the impact of VTE on cancer outcome and the potential role of antithrombotic prophylaxis on survival. We have now initiated a more detailed prospective study of consecutive patients with and without VTE (Prospective Follow-Up Survey in VERITY Hospitals) to further assess the impact of several parameters including cancer type, presence of metastatic disease and quantitative D-dimer on major adverse outcomes of thrombosis recurrence, bleeding and death.

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### Conflict of interest

Aidan McManus has received consultancy fees from Sanofi-Aventis.

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