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Full Length Article

Cancer prognosis in patients with venous thromboembolism (VTE) and patients with clinical and laboratory biomarkers predictive of VTE risk

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ABSTRACT

Venous thromboembolism (VTE) is a well-documented complication of cancer and its treatment. While VTE contributes significant morbidity and some thrombotic mortality to cancer patients, a growing body of clinical and experimental data supports the finding that VTE is an important prognostic marker for cancer progression and mortality. This would suggest that hemostatic activation is an expression of an aggressive tumor phenotype. A number of clinical and laboratory biomarkers have been shown to be predictive of an increased risk of cancer-associated VTE. In addition, it is now becoming apparent that these same biomarkers are also predictive of cancer mortality. The application of this information to reduce cancer-associated VTE and improve cancer survival await the results of ongoing prophylaxis antithrombotic studies.

1. Cancer prognosis in patients with venous thromboembolism

In 1938 Edith Sproul reported the finding of venous and arterial thrombosis FOR 4258 consecutive necropsies performed at the Presbyterian Hospital in New York [1]. Cancer cases accounted for 598 (14%) of the autopsy cases. Of the total autopsies, thrombosis was noted in 617 (14.4%) cases. Proportionally, cancer accounted for the greatest proportion of cases with thrombosis, with thrombosis found in 125 cases (21%). While the majority of cancer cases had advance and metastatic disease, the incidence of thrombosis varied widely among tumor types. The incidence of autopsy noted thrombosis ranged from 14.8% in lung cancer to a high of 56.2% in cases with carcinoma of the body and tail of the pancreas. Other cancers with significant findings of thrombosis included of cancers of the stomach (21.8%), kidney (25.9%), uterus (22.2%) and ovary (23.5%). While it could not be determined whether the venous thromboembolism detected in the autopsy cases were directly responsible for the subjects demise, in 13 of the non-pancreatic cancer cases pulmonary emboli were noted. However, it was observed that venous thrombosis was observed in the malignancies with the poorest prognosis. A more recent report on 4739 cancer autopsies, of which 2900 cases were adenocarcinomas, did find evidence of pulmonary embolus (PE) in a quarter of the cases [2]. The authors estimated that the PE was directly related to death in approximately 10% of the cases.

The observation regarding the high incidence of thrombosis in patients dying of pancreatic cancer was again confirmed in an autopsy study of 157 cases of carcinoma of the pancreas [3]. In this review of the autopsy records from the Philadelphia General Hospital, venous and arterial thromboembolism was detected in 48 (30.8%) cases of pancreatic carcinoma. Twenty-three cases had multiple thromboembolisms. In addition, eight cases had significant pulmonary embolus detected at autopsy which may have been responsible for the patient's demise.

After the report of Thompson and Rodgers [3] it was well accepted that thromboembolic complications were common in pancreatic cancer, but less frequent in other cancers. While thromboembolic events may add additional morbidity to the management of the cancer patient, it was believed that such thromboembolic events are less likely to impact the survival of the cancer patient. This opinion was subsequently challenged by the report of Sorensen and colleagues using linked data from the Danish National Registry of Patients, the Danish Cancer registry and the Danish Mortality files [4]. Patients with cancer who had an episode of deep vein thromboembolism (VTE) when compared to control cancer patients without VTE were more likely to have metastasis 44% vs. 35.1% (ratio 1.26; 95% CI; 1.13–1.40). The patients with cancer and VTE also had a significantly poorer 1 year survival of 12% compared with 36% in the cancer controls ($P < 0.001$). Patients in whom cancer was diagnosed within one year of their VTE also had a greater risk of metastatic disease (1.23; 95% CI: 1.08–1.40) and a shorter survival (38% versus 47%; $P < 0.001$) [3]. This analysis of clinical registry data would appear to support that the occurrence of a VTE suggests more advance disease with distant metastasis.

Levitan and colleagues [5] analyzed the Medicare Claims Data to assess the rate of thromboembolic event in different malignancies,

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probability of readmission for recurrent VTE and survival of cancer patients with and without a VTE. The rate of symptomatic VTE ranged widely with patient having ovarian, brain and pancreas cancer having rates greater than 10%. The VTE rate for colon, leukemia, renal, gastric and lymphoma were greater ranged from 7.7% to 98%. Patients with malignancy and VTE had a significantly greater mortality at 183 days after initial hospitalization when compared to cancer patients without a history of VTE (94% versus 42%; $P = 0.0001$) [4]. Without information of the respective stage of malignancy for each cancer type with and without a history of VTE, it can only be assumed based upon previous autopsy and registry data that the survival difference reflected more advanced stage of the cancer patients with VTE.

The first reports to suggest that the prognostic impact of venous thromboembolism on cancer survival is independent of stage comes from two reports on VTE incidence and outcome for patients with colorectal and breast cancer using merged data from the California Cancer registry and the California Patient Discharge Data Set [6,7]. The reports evaluated event and outcome data for 68,142 colorectal patients and 108,255 breast cancer patients. The 2 year incidence of symptomatic VTE in colorectal and breast cancer was 3.1% and 1.2% respectively. The highest incidence of VTE occurred in the first 6 months. Despite the low 2 year incidence of symptomatic VTE in both malignancies, the occurrence of a thromboembolic event had a significant impact on 1 or 2 year survival for patients with localized and regionally advanced disease. For patients with colorectal cancer the risk-adjusted predictor of death at 1 year for patients with VTE compared to matched staged patients without VTE was for localized disease (HR, 1.8; 95% CI: 1,4–2.3) or regional-stage disease (HR, 1.5; 95% CI: 1.3–1.8) [6]. However, this was not observed with patients with metastatic disease (HR, 1.0; 95% CI 1.0–1.2). For breast cancer patients the risk adjusted predictor of death at 2 years was (HR, 2.3; 95% CI: 2.1–2.6) with the effect being most significant with localized (HR, 5.2; 95% CI: 3.6–7.1) or regional stage disease (HR, 3.5; 95% CI: 2.5–4.8) [7]. However, unlike colorectal cancer patients with metastasis; for breast cancer patients with metastatic disease; the development of VTE continued to impact survival (HR, 1.9; 95% CI: 1.5–2.4). The authors' interpretation of their findings is that the development of a cancer–associated VTE is an expression of a biologically more active malignancy. However, the potential weakness of these two reports is that linked-registry derived data may not accurately reflect the patients' stage at the time of the VTE event.

The historical reported incidence of VTE in cancer patients undergoing active treatment of their malignancy has been challenged in recent years by the frequent reported detection of unsuspected or more commonly termed, incidental VTE found during multi-detector computerized tomography (MDCT) of the chest, abdomen and pelvis employed for malignancy staging or restaging [8–11]. Incidental pulmonary embolism (iPE) has in several reports been shown to have the same risk of recurrence and prognosis as pulmonary emboli detected by dedicated CT scans performed for the evaluation of symptomatic events [9–11].

O'Connell and colleagues [12] performed a case controlled study of incidental PE in cancer patients with newly diagnosed incidental PE detected on cancer staging studies. The patients with the incidental PE (n = 70) were compared to a patient cohort (n = 137), without a history of VTE, but matched for gender, age, cancer type, stage as determined by their most recent MDCT and year of cancer diagnosis. There was also no significant difference between the iPE patients and their matched controls in regards to hematologic data including hemoglobin, white blood cell count and platelet count. The patients with iPE patients were statistically more likely to have had a prior history of VTE and a major surgical event within 2 months of detection of the incidental thrombosis. A careful retrospective chart review clearly found that the iPE patients were more symptomatic than the matched controls with greater complaints of fatigue, shortness of breath and cough. The hazard ratio (HR) for death among the iPE patients as compared with matched controls was 1.5 (95% CI: 1.01–2.27); median overall survival 8 vs. 12 months; $P = 0.048$). The impact of iPE on overall survival was more pronounced among the 53 patients with proximal clots (HR, 1.70; 95% CI: 1.06–2.74; median overall survival 7 vs. 12 months). The more proximal the iPE, the more significant was the impact on survival ($P_{Trend} = 0.019$). When iPE patient survival, compared to controls, was calculated from the time of diagnosis of their malignancy the HR was 1.63 (95% CI: 1.08–2.48, $P = 0.019$). Patients with proximal PE were more than twice as likely to die by 6 months (HR, 2.28; 95% CI: 1.20–4.33). Seventeen of the 70 patients with iPE had isolated subsegmental clots (ISSPE). There was no statistical difference in survival between the matched control patients and the ISSPE patients (HR, 1.04; 95% CI: 0.44–2.39, $P = 0.92$). The results of this carefully designed case control study would add greater support to the hypothesis that the development of thrombosis in cancer patients is strongly linked to the aggressive biology of the associated malignancy.

Surgery is a well-recognized risk factor for VTE [13]. Patients undergoing cancer surgery may have a higher risk with major surgery. In a review of 20,762 cancer patients who underwent major cancer surgery the 30-day symptomatic VTE rate was 3.5% [14]. However, the VTE event rate was highly dependent on the type of malignancy and surgical procedure. The event rate ranged from 13.2% (95% CI: 8.8–18.9%) for an esophageal resection to 1.8% (95% CI: 1.5–2.1%) for a prostatectomy. Surgical procedures including radical cystectomy, pancreatectomy, pancreatic duodenectomy and gastrectomy all had a symptomatic VTE event rates greater than 5%.

The long-term impact of cancer surgery associate thrombotic event on patient prognosis was evaluated in a retrospective case control study from Memorial Sloan-Kettering Cancer Center (MSKCC) [15]. The authors reviewed the records of 23,541 patients who underwent a surgical procedure at MSKCC. Four hundred and seventy-four (2%) of these patients had a VTE within 30 days of the procedure. The VTE patients had a significantly worse 5-year survival compared to the patients without VTE (43.8% vs. 61.2%; $P < 0.0001$). Two hundred and five patients, stages 0–3, and a history of VTE were matched by age, gender, cancer type, stage and surgical procedure to 2050 controls. The matched VTE patients had a significantly worse overall 5-year survival (54.7% vs. 66.3%; $P < 0.0001$) and disease-specific survival (67.8 vs. 79.5%; $P = 0.0007$) when compared to their controls. The disease-specific survival difference was also observed in the patients with earlier stage disease (stage 0–2) when compared to their matched controls (82.9% vs. 87.3%; $P = 0.01$). This case control study confirms that the negative prognosis associated with cancer-related VTE is even reflected in the post-surgical thrombotic events.

2. Do clinical and/or laboratory biomarkers predictive of an increased risk of cancer–associated VTE effect cancer prognosis independent of a VTE?

A number of prospective and retrospective studies have reported a number of clinical and laboratory biomarkers that are predictive of an increased risk of VTE in patients with and without cancer [16–27]. Additional studies have shown that patients who have a combination of these clinical and laboratory markers can have an even greater risk of developing a VTE [28]. Among the better characterized clinical and laboratory biomarkers are elevated leucocyte [16,17] and platelet count [16,18], elevated soluble P-selectin (sPsl) [19], elevated D-dimer, [21–23] elevated Prothrombin Fragment 1 + 2 [20], elevated Tissue factor activity and antigen [23–26], and elevated Factor VIII [27]. Additional markers less well characterized include mean platelet volume (MPV) [28] and C-reactive protein (CRP) [29,30]. However, the most validated prediction model for the risk of developing VTE during cancer treatment was reported by Khorana and colleagues [16]. The score incorporates specific tumor type, platelet and leukocyte count, hemoglobin (or use of erythropoietic agents) and BMI, with each clinical characteristic each given a specific value and the cumulative score