Central Venous Catheter Thrombosis in Cancer: A Multi-Centre Retrospective Study Investigating Risk Factors and Contemporary Trends in Management

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ABSTRACT

OBJECTIVES: Central venous access is needed to facilitate chemotherapy for many cancer patients. Central venous catheter-related thrombosis (CVCT) is a major complication that can cause significant morbidity and mortality. We sought to explore the rate of CVCT in a general cancer population in Australia and to identify factors associated with increased risk of thrombosis.

DESIGN: This is a multi-centre retrospective cohort study.

SETTING AND PARTICIPANTS: We analysed key patient, treatment, and cancer-related factors for 317 patients with cancer and central venous catheters inserted for systemic therapy.

MAIN OUTCOME MEASURES: Symptomatic CVCT confirmed with imaging and management of patients with CVCT.

RESULTS: A total of 402 cases of central line insertion were analysed. Central venous catheter-related thrombosis occurred in 24 patients (6.0%). Having a peripherally inserted central catheter (PICC; HR = 3.78, 95% CI = 1.28-11.19, P = .02) compared with an implantable port and a body mass index of $\geqslant$25.0 kg/m^2 (HR = 3.60, 95% CI = 1.31-9.85, P = .01) were independently associated with increased risk of thrombosis. Central venous catheter-related thrombosis was managed mostly with removal of the catheter (19 of 24 cases) and anticoagulation, including direct-acting oral anticoagulants in 5 patients.

CONCLUSIONS: This work explored rates of CVCT in a general cancer population, observing increased rates in those with PICCs or increased body mass index.

KEYWORDS: Adverse event management, breast cancer, pancreatic cancer, colorectal cancer, gastric cancer, acute lymphocytic leukaemia (ALL), acute myeloid leukaemia (AML)

Introduction

Obtaining reliable central venous access remains a necessity for many patients with malignancy and is a major decision in management. A range of central venous access devices (CVADs) exist, including implantable ports and peripherally inserted central catheters (PICCs). Having an active malignancy is one of the strongest risk factors for venous thrombosis, conferring a seven-fold increased risk compared with those without a malignancy.[1] The presence of a foreign intravascular device further compounds this risk, and consequently, central venous catheter-related thrombosis (CVCT) is a relatively common complication in patients with malignancy, occurring asymptomatically in 14% to 18% of patients and causing symptoms in approximately 5%.[2] Vein thrombosis in cancer patients often confers a poor prognosis, increasing the risk of mortality.[3] (Timp, Braekkan and Versteeg, 2013) Furthermore, those with cancer have a higher risk of death from venous thrombosis compared with those without cancer.[5] In addition, CVCT

confers significant morbidity by causing catheter malfunction and disrupting tightly planned treatment schedules, and by increasing cost as new access devices are required.[6] Patients may also suffer chronic pain secondary to post thrombotic syndrome of the upper extremity following CVCT.[7] Furthermore, the presence of thrombosis on a catheter provides a fertile microenvironment for bacteria to grow, increasing rates of bacterial colonisation and catheter related sepsis. Pulmonary embolism, right heart thromboembolism, superior vena cava syndrome, and paradoxical embolism to the systemic circulation are other uncommon, yet potentially life-threatening complications. Finally, treatment of thrombosis can increase the risk of bleeding and be burdensome, as the historically preferred treatment regimen of low molecular weight heparin (LMWH) requires once or twice daily injections.

Vein thrombosis is a multifactorial disease, influenced by a range of diverse risk factors.[8] Patients who have a history of

previous thrombosis, current systemic or catheter-related infection, particularly one which causes disseminated intravascular coagulation, and inherited or acquired thrombophilic disorders, such as protein C and S deficiency or heparin-induced thrombocytopaenia, are at higher risk. Having a PICC, larger or multi-lumen catheter, catheter tip located proximal to the superior vena cava as opposed to in the lower third of the superior vena cava, and catheter located in the femoral or cephalic veins has been associated with CVCT. Some therapies are also prothrombotic, including medications such as asparaginase, steroids, immunomodulatory agents, and fluoropyrimides, as well as thoracic radiotherapy, and previous CVAD insertion. Finally, certain cancers, such as brain, haematological, gastric, and pancreatic malignancies, pose a high risk of thrombosis, as does the presence of metastatic disease.

The management of thrombosis in malignancy is changing rapidly due to recent studies of direct-acting oral anticoagulants (DOACs) in malignancy. However, it is not known how Australian clinicians are managing CVCT in cancer patients. In addition, a range of clinical tools exist to predict risk of thrombosis in cancer patients without central venous access; however, no similar tool exists for patients with CVADs. Developing such a tool is desirable as it may assist clinicians in decisions regarding central line insertion or guide further trials into prophylaxis against CVCT. Therefore, the aims of this retrospective study were to investigate the rates of CVCT in patients with cancer, to identify factors predicting thrombosis and to provide real-world data regarding how central line thrombosis is managed.

Methods

Electronic medical records of all haematology and oncology patients with a CVAD in the Illawarra Shoalhaven Local Health District were identified and searched from June 2018 to March 2019 by one researcher (LH). Data from 2 separate electronic medical record systems were searched manually, and all available records in the system were accessed to cross-check the information (e.g. imaging, nursing notes, documentation regarding insertion of catheter). Three centres were included in this study, all of which are defined as inner regional centres according to the Australian Statistical Geography Standard.[9] These centres were the Milton-Ulladulla, Shoalhaven, and Illawarra Cancer Care Centres. All patients with a CVAD used for systemic anti-cancer treatments were included. Those using the CVAD primarily for other purposes such as antibiotics or vasopressors were excluded from this study. Data collected included the nature of insertion and characteristics of CVAD, cancer history, demographic, clinical and laboratory variables, and rates and management of complications. Data regarding medication use was not able to be used in analysis due to the extreme heterogeneity of medications used in this diverse population. Catheter insertion was performed using imaging guidance, either ultrasound (typically if inserted by clinical nurse consultants) or fluoroscopic (typically if inserted by radiologists, or vascular or general

surgeons). In our district, most implantable ports are locked with heparin, while most PICCs are not. Catheter-related thrombosis was defined as thrombosis associated with the vein(s) that the catheter was located in.[10] Ethical approval was granted by the Joint University of Wollongong and Illawarra Shoalhaven Local Health District Health and Medical Human Research Ethics Committee (approval number: 2019/ETH08696). Informed consent was not required for this retrospective low-risk study in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The primary outcome was time to symptomatic, catheter-associated thrombosis, confirmed on imaging. Screening for asymptomatic thrombosis was not performed due to pragmatic reasons in this retrospective study as this is not performed routinely clinically. Time until event or censorship was defined as the time from insertion of the line until either thrombosis, line removal, date of last follow-up, or censor date of March 1, 2019. Unadjusted and multivariable Cox proportional hazards regression analyses were used to estimate the association between key variables and thrombosis, and to calculate corresponding hazard ratios (HRs) and 95% confidence intervals (CIs). A two-sided P-value of .05 was used to determine significance. Variables were included in the multivariate model if $P < .10$ in univariate analyses. Patient groups were compared using the chi-square test for categorical data, and the independent samples t-test for continuous data. Cancer types were classified into 3 categories according to risk of thrombosis, with categories based on prior research: very high risk (stomach, pancreas, haematological, brain, cancer of unknown primary, mesothelioma), high risk (lung, gynaecologic, genitourinary excluding prostate), and low risk (breast, colorectal, prostate, bone, head and neck, melanoma, cutaneous, testicular).[11-13] Haematological cancers were categorised with solid tumours as very high risk based on previous research indicating a similar risk of thrombosis.[12] Body mass index (BMI) was dichotomised using a cut-off of 25 kg/m². Prior to performing multivariate analysis, independent variables were assessed for multicollinearity. The generalised R^2, representing the proportion of total variability of the outcome that is explained by the model, was calculated.[14] All data analysis was performed using SPSS Version 25.0 (IBM Corporation, Chicago, IL).

Results

Patient cohort

Patient characteristics are summarised in Table 1. In total, 402 distinct central line encounters were analysed, corresponding to 317 patients and 166 972 catheter days; 258 patients (81.4%) had one catheter inserted, and the remaining 59 patients had more than one catheter inserted. The median duration of follow-up was 534 days (range = 353-878 days). The median line duration was significantly shorter for those with PICC lines compared with implantable ports, 70 days (32-120 days) compared with 425 days (256-814 days) ($P < .001$). The mean age of

Table 1. Baseline characteristics.

	NO THROMBOSIS (N = 378)	THROMBOSIS (N = 24)	χ2	*P*-VALUE
Age, mean (SD)	61.9 (12.7)	62.7 (11.3)		.76
Female sex, n (%)	196 (48.8)	14 (3.5)	0.38	.54
Prior DVT/PE	51 (13.5)	3 (12.5)	0.02	.89
Sepsis or DIC	105 (27.9)	8 (33.3)	0.33	.57
Cancer thrombosis risk	Very high: 139 (36.8) High: 26 (6.9) Moderate: 213 (56.3)	Very high: 12 (50.0) High: 2 (8.3) Moderate: 10 (41.7)	2.00	.37
Metastatic disease,[a] n (%)	124 (40.3)	3 (18.8)	2.95	.09
Platelet count (×10⁹/L)	<150: 58 (15.8) 150-449: 269 (73.1) ≥450: 41 (11.1)	<150: 2 (8.3) 150-449: 19 (79.2) ≥450: 3 (12.5)	0.96	.62
Smoker	59 (16.3)	2 (8.3)	1.08	.30
Catheter type, n (%)	PICC: 149 (39.5) Port: 228 (60.5)	PICC: 16 (66.7) Port: 8 (33.3)	6.87	.009*
Catheter site, n (%)	Left side: 92 (24.7)	Left side: 11 (45.8)	5.26	.02*
BMI (kg/m²)	<25: 166 (44.0) ≥25: 211 (56.0)	<25: 5 (20.8) ≥25: 19 (79.2)	4.97	.026*
Antithrombotics, n (%)	80 (21.3)	1 (4.2)	4.09	.04*

Abbreviations: BMI, body mass index; DIC, disseminated intravascular coagulation; DVT, deep venous thrombosis; PE, pulmonary embolism; PICC, peripherally inserted central catheter; SD, standard deviation.
[a]Solid tumours with stage IV disease exclude patients with haematological malignancy.
*$P < .05$.

the cohort was 62 years, and 209 cases were female (52%). The date of line insertion ranged from 1996 to 2019. The most common cancer types included were colorectal adenocarcinoma (137 cases, 34%), breast carcinoma (75 cases, 19%), diffuse large B cell lymphoma (22 cases, 5%), and pancreatic adenocarcinoma (21 cases, 5%); 179 cases with solid tumours had distant metastatic disease (44.5%) and 78 cases (19%) had a haematological malignancy. More patients had implantable ports compared with PICCs (236 cases, 58.7% vs 165 cases, 41.0%, respectively). Most PICCs inserted were single lumen (101, 61.2%). Catheters were inserted by surgeons (187, 46.5%), clinical nurse consultants (119 cases, 29.6%), or radiologists (83 cases, 20.6%).

Six cases with implantable ports received therapeutic enoxaparin for 7 days postoperatively, while no cases with PICCs received therapeutic anticoagulation at the time of the procedure (unless otherwise clinically indicated). Regarding regular antithrombotic therapy, 23 cases (5.7%) received single agent antiplatelet therapy, 9 cases (2.2%) received dual-antiplatelet therapy, 27 cases (6.7%) received enoxaparin, 13 received rivaroxaban (3.2%), 9 received warfarin (2.2%), and 4 received dabigatran (1.0%); 54 cases had a previous history of deep venous thrombosis or pulmonary embolism (13.4%), 1 patient was documented as heterozygous for the Factor V Leiden mutation, and another patient had essential thrombocythaemia; 113 cases of sepsis or disseminated intravascular coagulation occurred while a central line was in situ (28.1%), and this was

significantly more frequent in those with haematological malignancies compared with those without a haematological malignancy (57.1% vs 21.4%, respectively, $P < .01$).

Factors associated with increased risk of thrombosis

CVCT occurred in 24 cases (6.0%), corresponding to a rate of thrombosis of 8 of 236 with implantable ports (3.4%, 0.67 per 100 000 catheter days) and 16 of 165 with PICCs (9.7%, 0.90 per 1000 catheter days), or an overall rate of 0.14 per 1000 catheter days. Rates of thrombosis were highest closest to time of line insertion, with approximately one third of cases occurring in the first month after insertion, and the median time until thrombosis being 46 days (range = 21-81 days). There was no significant difference in time until onset of thrombosis between catheter types (median = 58.5, range = 21.9-91.6 days for implantable ports vs 42.5, 13-77.8 days for PICCs; $P = .35$).

Factors associated with CVCT on univariate analysis included PICCs, left-sided position, very high cancer thrombotic risk, and BMI of 25.0 kg/m² or greater (Table 2).

Overall, 6 variables were included in the multivariate model (see Table 2). The model was able to predict the development of thrombosis, $\chi^2(7) = 28.03$, $P < .001$, and explained 46.9% of the variability of thrombosis occurring. After adjustment, variables that were independently associated with an

Table 2. Univariate and Multivariate Analysis of Factors Associated with Thrombosis.

VARIABLE		UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
		HR (95% CI)	*P*-VALUE	HR (95% CI)	*P*-VALUE
Catheter type	Port	1.00	Ref.	1.00	Ref.
	PICC	5.11 (2.11-12.37)	<.001*	3.78 (1.28-11.19)	.02*
Catheter site	Left side	2.73 (1.22-6.10)	.01*	1.74 (0.76-3.98)	.19
Lumen number	One	1.00	Ref.	1.00	Ref.
	≥Two	2.53 (0.93-6.87)	.07	1.16 (0.37-3.66)	.80
Cancer thrombotic risk	Moderate	1.00	Ref.	1.00	Ref.
	High	1.96 (0.43-8.99)	.39	1.06 (0.21-5.27)	.95
	Very high	2.53 (1.08-5.93)	.032*	1.33 (0.46-3.86)	.61
BMI (kg/m^2)	<25	1.00	Ref.	1.00	Ref.
	≥25	2.71 (1.01-7.27)	.048*	3.60 (1.31-9.85)	.01*
Antithrombotics	Yes	0.15 (0.02-1.14)	.07	0.20 (0.03-1.50)	.12

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; PICC, peripherally inserted central catheter; Ref., reference. Analyses performed using Cox proportional hazards regression model.
*$P < .05$.

increased likelihood of thrombosis were the presence of a PICC (HR = 3.78, 95% CI = 1.28-11.19, P=.02) and a BMI of 25.0 kg/m^2 or greater (HR = 3.60, 95% CI = 1.31-9.85, P=.01). Catheter site, lumen number, use of antithrombotics, and the cancer thrombotic risk were not significantly associated with thrombosis after adjustment.

There was no significant association between age (HR = 1.15, P=.73), sex (HR = 1.20, P=.66), PICC size (HR = 0.53, P=.42), rates of sepsis or disseminated intravascular coagulation (HR = 1.41, P=.43), previous deep venous thrombosis or pulmonary embolism (HR = 0.84, P=.77), platelet count prior to line insertion (platelets = 150-450 × 10^9/L, HR = 1.59, P=.54; platelets ≥ 450 × 10^9/L, HR = 1.61, P=.60), metastatic or haematological disease (HR = 0.88, P=.75), or rates of current smoking (HR = 0.49, P=.33) and thrombosis.

The catheter was removed in 19 cases, while the line remained in situ until completion of therapy for 5 patients; 15 cases were treated with enoxaparin, while 4 received rivaroxaban and 1 case apixaban. The only patient who had documented recurrent thrombosis was a gentleman in whom anticoagulation was not pursued due to recent upper gastrointestinal haemorrhage.

Discussion

Venous thrombosis is a common and burdensome complication of central venous access. In Australia, inner regional areas have the highest incidence rate of all cancers combined,[15] however cancer outcomes worsen as distance from the city increases.[16] As such, it is important that the current management of cancer patients in regional areas is better studied, to identify areas to improve. This is the first study exploring the nature of CVCT in regional Australian cancer patients. In this study, the key finding was that thrombosis was quite frequent, occurring in 3.4% of patients with implantable ports and 9.7% of PICCs.

Rates of CVCT reported vary substantially depending on the population studied, ranging from 5% to 18%.[2,17] In a large metropolitan Australian study of 3130 cancer patients, Ellis et al[18] found that CVCT occurred in 3.6% of all central catheters, and 4.9% for those with a PICC. Our rates of thrombosis were slightly higher, likely reflecting our higher risk population: 29.6% of our patients had very high risk cancers, as opposed to 4.1% in the study by Ellis et al.

This research aimed to identify predictors of CVCT. Patient-related factors known to increase thrombosis include increased BMI, smoking, increased age, history of thrombophilia, and previous venous thromboembolism (VTE).[9,19] Treatment-related factors include drugs (e.g. fluoropyrimidines, immunomodulatory agents, asparaginase, etc.),[20] and the type and characteristics of the catheter.[8] Cancer-related factors include the extent and type of malignancy.[12] Our multivariate model explained a moderate degree (46.9%) of the variability of thrombosis, suggesting that other unmeasured variables and/or random variation may also influence risk of thrombosis. While this may not be high enough to use a clinical risk prediction tool, it highlights variables that may be useful for inclusion in future similar studies. Being overweight or obese, compared with normal weight or underweight, was associated with a more than three times greater likelihood of thrombosis, confirming the work of others.[19,21] Being overweight or obese is known to be a prothrombotic condition, characterised by increased expression of prothrombotic molecules such as tissue factor and plasminogen activator inhibitor-1, systemic inflammation, and increased platelet activation.[22] In addition, PICCs conferred a more than four-fold risk of thrombosis compared with implantable ports, highlighting the importance of considering which type of catheter to recommend in patients at high risk of thrombosis. For example, in a high-risk patient such as one with metastatic pancreatic adenocarcinoma whom is about

to commence on a fluoropyrimidine-based regimen, a implantable port may be preferable to a PICC. The greater rate of thrombosis with PICCs compared with implantable ports may be a consequence of their longer catheter length, greater endothelial trauma, and slower flow.

Other factors were associated with thrombosis on univariate analysis. Left-sided catheters were associated with increased risk compared with right-sided catheters, however not after adjustment. This has been reported in some but not all other research, and if true, may reflect the effects of a longer catheter, or greater endothelial disruption and flow disturbance.[23,24] Furthermore, antiplatelet or anticoagulant therapy was associated with lower risk of thrombosis, but this effect did not persist after adjustment. It is interesting that metastatic or haematological malignancy was not associated with thrombosis, as these factors are known to be strongly thrombogenic. It is possible that those with non-metastatic disease were exposed to additional risk factors (e.g. post-operative state), or that an effect may have been masked by the subsequent development of metastatic disease in those who were initially diagnosed with localised disease. In addition, those with cancers of a very high thrombotic risk, as defined by previous models,[11-13] had an increased risk of thrombosis on univariate but not multivariate analysis. As most patients with haematological malignancies, defined as being very high risk of thrombosis, receive PICCs rather than implantable ports in our institution, this may explain why significance was lost on multivariate analysis.

Significant research has been conducted attempting to identify patients with CVADs and cancer who may benefit from prophylactic anticoagulation. Almost 1 in 10 patients with PICCs suffered thrombosis, a number sufficiently frequent to consider chemoprophylaxis. Approximately one third of cases occurred within the first month of insertion. Others studies of PICCs have observed thrombosis occurring mostly within the first 1 to 3 weeks of insertion, presumably reflecting greater endothelial damage around insertion.[19,25,26] A recent meta-analysis found that prophylactic LMWH may be considered to reduce CVCT.[27] Furthermore, 2 recent phase-3 randomised controlled trials have investigated the use of DOACs for chemoprophylaxis in cancer. Carrier et al[28] found that apixaban reduced the risk of thrombosis, while Khorana et al[29] did not find any benefit of rivaroxaban. However, neither of these studies included patients with CVCT. Both trials used a model to identify a high-risk population, and as the rate of thrombosis in our cohort of patients with PICCs (9.7%) is comparable with the rate of thrombosis in the placebo group in both of these studies (10.2% in the AVERT trial and 8.8% in the CASSINI trial), those with PICCs may represent another high-risk group where trials of chemoprophylaxis using DOACs around time of catheter insertion may be of benefit. Finally, in 2019, Lv et al[30] conducted a non-randomised prospective trial comparing the use of rivaroxaban or LMWH for prophylaxis against no anticoagulation on rates of PICC associated thrombosis in patients with stomach, lung, oesophageal, breast, colorectal, or ovarian cancer. They observed lower rates of upper extremity venous thrombosis in patients on rivaroxaban or LMWH compared with controls. However, important clinical variables such as completion rates of chemotherapy were imbalanced between the control and the intervention groups, and not adjusted for, suggesting that these results may be confounded by another factor.

International guidelines for managing CVCT in cancer patients have been recently updated.[31] Current guidelines recommend against routine catheter removal, unless they are in a suboptimal position, non-functional, no longer required, or clinically infected. However, we observed that most patients were treated with catheter removal (79%) and anticoagulation (91.7%), likely reflecting concerns about the risk of infection, line dysfunction, lack of need for the catheter, or troublesome symptoms.

The landscape for treating thrombosis in cancer patients is evolving due to recent trials of DOACs; however, patients with CVCT have generally been excluded from these trials.[32] In our limited sample, 5 patients were treated successfully with DOACs; however, all also had their catheter removed. Laube et al[33] conducted a retrospective cohort study of 82 patients with cancer who received rivaroxaban for port-related thrombosis. Port removal was required in 3 patients (3.7%), and major bleeding occurred in 2 patients (2.4%). Nevertheless, DOACs may represent a potential management option, although more research is required to better assess safety and efficacy.

Limitations of this study include the inherent biases of confounding associated with retrospective design. Analysis was restricted to patients with symptomatic CVCT for practical reasons; however, there may have been additional asymptomatic cases of thrombosis in the upper extremities or elsewhere which were not detected as routine imaging was not undertaken. Data may be incomplete if documentation was missing in the electronic medical record, for example, if the patient had a procedure conducted externally; however, as the majority of patients are followed closely in the Cancer Care Centres and external documentation is scanned into the medical records, this is likely to represent only a small proportion of patients. Furthermore, we included patients already receiving antiplatelet or anticoagulation therapy, which may mean that the incidence of thrombosis in this cohort is lower than in other populations not receiving antithrombotic therapy. Data regarding whether devices were locked with heparin or not was not available for each patient, so could not be studied in this article. In addition, as only a limited number developed thrombosis, power was limited, and recommendations for management cannot be made from this work and should be considered hypothesis generating only. Finally, there may be other variables which may influence risk of thrombosis, such as lumen size, or chemotherapy regimen, which were not able to be investigated in this study due to the heterogeneity of the population.

In conclusion, this large multi-centre retrospective cohort study investigated factors associated with CVCT in cancer

patients, observing that PICCs and increased BMI were independent risk factors. Contemporary trends in managing CVCT were explored. This research identified that future randomised clinical trials of DOACs for prophylaxis or treatment of CVCT in cancer patients would be of use.

Author Contributions

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