Thrombosis Research 177 (2019) 117–121

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Implanted vascular access device related deep vein thrombosis in oncology patients: A prospective cohort study

Adam Suleman[a], Virginia Jarvis[b], Adnan Hadziomerovic[b,c], Marc Carrier[a,b,d], Sheryl McDiarmid[b,e,*]

[a] The University of Ottawa, 451 Smyth Rd., Ottawa, Ontario K1H8M5, Canada
[b] The Ottawa Hospital Research Institute, 725 Parkdale Ave, Ottawa, Ontario K1Y 4E9, Canada
[c] Department of Medical Imaging, University of Ottawa, 501 Smyth Rd., Ottawa, Ontario K1H8L6, Canada
[d] Department of Medicine, University of Ottawa, Box 201a, 501 Smyth Rd., Ottawa, Ontario K1H8L6, Canada
[e] The Ottawa Hospital, Box 710, 501 Smyth Rd., Ottawa, Ontario K1H 8L6, Canada

ARTICLE INFO

Keywords:
Neoplasm
Venous thrombosis
Implanted vascular access devices

ABSTRACT

Background: Implanted vascular access devices (IVADs) have significantly improved the management of cancer patients. These patients are at an increased risk of venous thromboembolism and IVADs are a known risk factor. We sought to assess the incidence of IVAD-related upper extremity deep vein thrombosis (IVAD-related UEDVT) associated with BioFlo® IVADs (Angiodynamics, Inc.).

Methods: A total of 394 cancer patients were enrolled over 12 months. The primary outcome was the incidence of IVAD-related UEDVT confirmed by diagnostic imaging. IVAD-related UEDVT was defined as symptomatic ipsilateral upper extremity (axillary vein or proximal) deep vein thrombosis and symptomatic pulmonary embolism (PE). Patients were followed until initiation of therapeutic anticoagulation, catheter removal, death, or up to 12 months.

Results: 389 patients were included in the analysis. The median age of the cohort was 58.2 years; 68% (n = 273) were females. Sixty-six percent had gastrointestional cancer (including pancreatic cancer) and 68% had metastases. Eighty four percent of IVADs were right sided insertions. Ninety eight percent of catheter tip placements were distal superior vena cava (n = 237), cavo-atrial junction (n = 67) or atrium (n = 90). Overall, 5 patients had symptomatic IVAD-related UEDVT (1.29%, 95% CI 0.2 to 2.4%).

Conclusion: IVAD-related UEDVT is an infrequent complication in cancer patients with BioFlo® IVADs.

1. Introduction

Venous thromboembolism (VTE) is the second highest cause of mortality in cancer patients [1]. Although the risk of deep vein thrombosis (DVT) is a known complication in cancer patients that has been well-described [2–6], the mechanisms are incompletely understood. The use of implanted vascular access devices (IVADs) has been instrumental in improving quality of life and satisfaction in patients requiring chemotherapy [7]. Previous literature has estimated the risk of an IVAD-related upper extremity deep vein thrombosis (UEDVT) in the oncology population to range from 4% to 10% [8–10]. The occurrence of IVAD-related UEDVT is multifactorial, related to both modifiable factors such as catheter size, insertion side, and tip placement and non-modifiable factors, such as the diagnosis of cancer [11].

Prevention of an IVAD-related UEDVT in the oncology population is crucial. Some IVADs are constructed with catheter tubing composed of a novel anti-thrombogenic polymer which has been shown in in-vitro to reduce thrombus accumulation [12]. We sought to assess the incidence of IVAD-related UEDVT associated with BioFlo® IVADs (Angiodynamics, Inc.) constructed with this material.

2. Methods

2.1. Setting

We conducted a prospective cohort study of consecutive cancer patients receiving an IVAD for the administration of chemotherapy between August 2015 and September 2017 at The Ottawa Hospital. The

* Corresponding author at: The Ottawa Hospital Research Institute, 725 Parkdale Ave, Ottawa, Ontario K1Y 4E9, Canada.
E-mail addresses: asule095@uottawa.ca (A. Suleman), gjarvis@toh.ca (V. Jarvis), ahadziomerovic@toh.ca (A. Hadziomerovic), mcarrier@toh.ca (M. Carrier), smcdiarmid@toh.ca (S. McDiarmid).

https://doi.org/10.1016/j.thromres.2019.02.033
Received 29 December 2018; Received in revised form 17 February 2019; Accepted 28 February 2019
Available online 06 March 2019

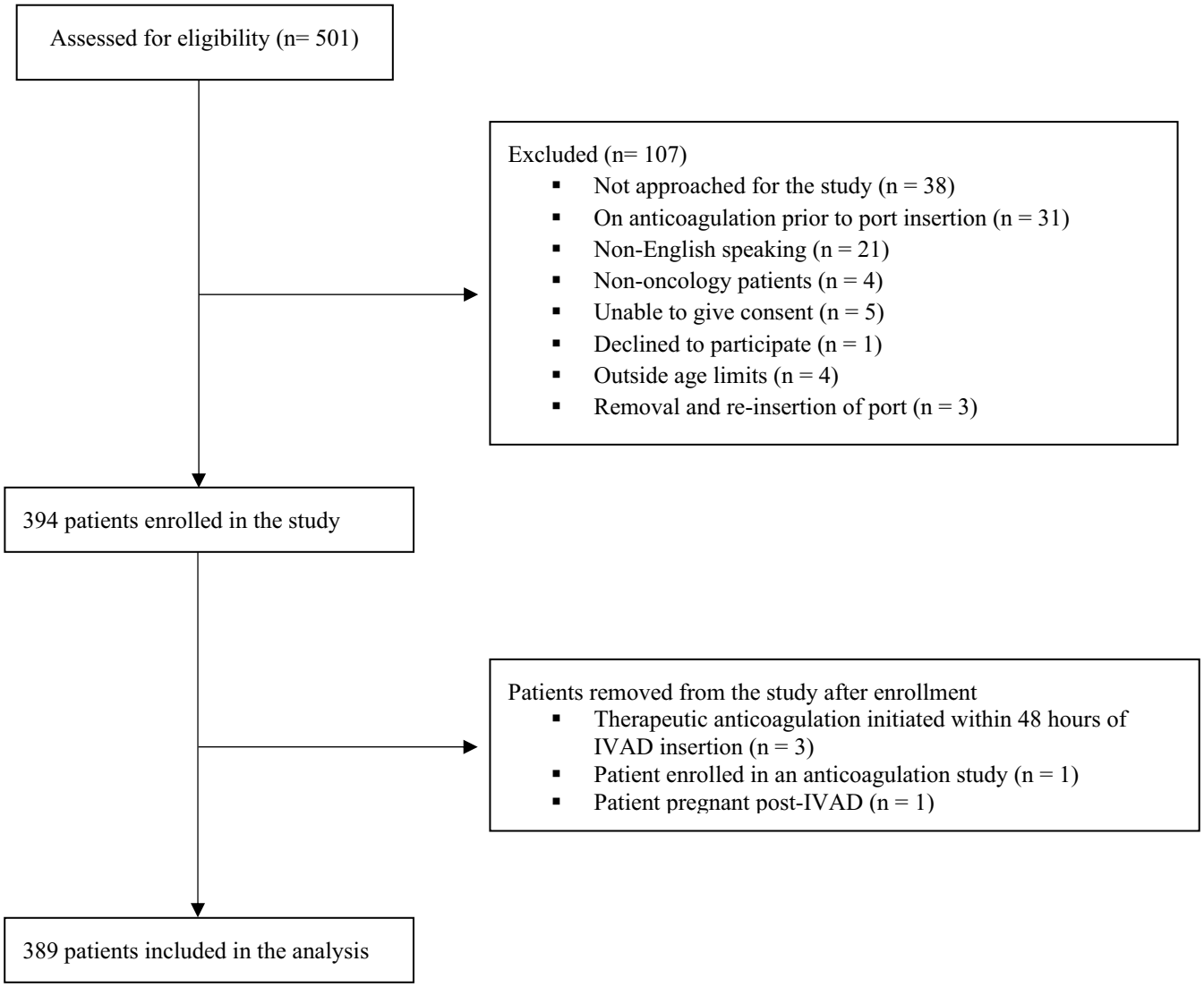

Fig. 1. Reasons for exclusion from the study.

vascular access program is led by an Advanced Practice Nurse (APN), who is accountable for oversight of the insertion, care and maintenance of all non-dialysis central venous catheters in both inpatient and outpatient populations. As per institutional policies, the IVAD was flushed with 0.9% normal saline and locked with 500 units Hepalean® (5 ml of Heparin Sodium 100 U.S.P. units/mL) post each treatment or monthly if the device was not used. All post IVAD insertion complications are managed by the vascular access team as per routine practices.

This study was approved by The Ottawa Hospital Research Ethics Board.

2.2. Inclusion and exclusion criteria

Patients were eligible for inclusion in the study if they had a diagnosis of active cancer requiring treatment, were 18 years and older, and had a life expectancy of > 3 months. Informed consent was obtained from all patients enrolled in the study. Patients were excluded from the study if they had or anticipated the presence of dialysis grafts or ipsilateral intraluminal devices, had a central veno-occlusive disease or were pregnant or lactating. Patients were also excluded if they required therapeutic doses of anticoagulation, or had thrombocytopenia (platelet count $< 50 \times 10^9$ per liter) or coagulopathy (INR $>$ 1.5).

2.3. Device insertion procedure

The IVADs were placed by interventional radiologists in accordance with the institution's standard protocol using conscious sedation and local anesthesia. The internal jugular vein was accessed just cephalad to the clavicle using ultrasonography combined with a micro-puncture approach [13]. The side of IVAD insertion was preferably right unless the patient had a diagnosis of right-sided breast cancer and was scheduled for breast radiation to the affected side during the expected dwell time of the IVAD. Following placement, fluoroscopic imaging was performed to confirm catheter tip position. Pre, intra and post procedure care was provided by registered nurses affiliated with the vascular access program. All patients received an 8 French BioFlo PORT (Angiodynamics, Inc., Latham, NY).

2.4. Measures

Baseline patient characteristic, laboratory values, IVADs' characteristics and comorbidities were collected on all included patients. Patients were contacted every 3 months for one year by a registered nurse, who assessed IVAD status, any associated complications and their overall satisfaction with the device. The vascular access program also routinely captures data on all insertions, removals, complications

and interventions into a clinical database [14].

The primary outcome of this study was symptomatic IVAD-related UEDVT defined as a symptomatic VTE in any deep vein throughout the course of the catheter, or symptomatic pulmonary embolism (PE) associated with the IVAD-related UEDVT [15]. These include the axillary, brachiocephalic, jugular and subclavian veins on the ipsilateral side of the IVAD insertion. Thrombosis within the superior vena cava (SVC) was also considered to be associated with the IVAD when there was evidence that thrombosis had formed along the catheter pathway or was present at the tip of the catheter and adherent to the wall of the SVC. An ultrasound was not routinely performed in a patient with a PE if no symptoms of UEDVT were present.

Secondary outcomes included IVAD-associated bacteremia and any other symptomatic VTE outside of the catheter pathway that required therapeutic anticoagulation. All outcome events were adjudicated (MC).

Baseline patients and catheter characteristics are summarized by reporting mean and standard deviation or median and quartiles where appropriate for continuous variables and frequency and percentages for categorical variables. Number and proportions of patients developed different adverse events are reported, along with 95% confidence intervals (95% CI).

All statistics are performed using SAS software, version 9.3 (SAS Institute).

3. Results

Out of the 501 IVADs implanted, 394 were enrolled into the study. Reasons for exclusion from the study are included in Fig. 1. Five patients were removed from the study within 48 h of IVAD insertion; 3 patients were started on therapeutic anticoagulation for asymptomatic VTE (2 portal vein thromboses and 1 mesenteric vein thrombosis) detected on staging CTs which had not been reported at the time of IVAD insertion; one patient was inadvertently enrolled in a blinded anticoagulation study, and another was found to be pregnant. A total of 389 patients were included in the analysis. The baseline characteristics of the study population are described in Table 1. A majority of patients were female (68%) and the median age was 59 years. Thirty seven percent of patients had a diagnosis of breast cancer, 29% colorectal cancer and overall 68% had metastatic disease at the time of IVAD implantation. All patients were followed until death, until therapeutic anti-coagulation was initiated for any reason, or for a total follow-up period of 12 months. No patients were lost to follow-up.

IVADs were primarily inserted on the right side (84%) and the catheter tips were most often placed in the distal superior vena cava (17%), cavoatrial junction (59%), or atrium (23%), with 1% in the mid-superior vena cava. There were 106,158 catheter dwell days in the study with a median catheter dwell-time of 273 days (range 4–365 days).

Five out of three hundred and eighty-nine patients (1.29%, 95% CI 0.2 to 2.4%) had an IVAD-related UEDVT over a 12-month follow-up period. Two patients amongst the 144 patients with breast cancer and 3 patients amongst the 111 patients with a diagnosis of colorectal cancer developed an UEDVT. None of the 34 patients with gastric/esophageal or pancreatic cancer had an UEDVT. None of the 63 patients who had the IVAD inserted on the left side had an UEDVT. Three of the 5 patients with UEDVT had metastatic disease.

All adverse effects from the one-year study period are described in Table 2. Four patients had bloodstream infections, however none were attributed to the device. Twenty-three patients (5.91%, 95% CI 3.6 to 8.3%) had PE over the 12-month follow-up period. Twelve patients had incidental findings of PE on CT, and eleven patients were symptomatic and diagnosed by CT pulmonary angiography. Of the patients presenting with PE, two had a confirmed leg DVT and no patients had UEDVT. Therapeutic anticoagulation (TA) was initiated on 26 additional patients for reasons listed in Table 3. Of the patients who

Table 1
Baseline patient demographics and catheter characteristics of 389 patients with port insertions.

	N = 389	Percentage (%)
Number of patients		
Gender		
Female	266	68.3
Age		
Median, range	59 (20–84)	
Diagnosis		
Breast	144	37.0
Colorectal	111	28.5
Pancreatic	30	7.7
Hem/malignancy	21	5.4
Liver/gallbladder	19	4.9
Other	17	4.4
Esophageal/gastric	14	3.6
Lung	12	3.1
Sarcoma	11	2.8
Gynecological	10	2.6
Metastatic disease		
Yes	266	68.3
No	123	31.7
Number of catheters		
Tip placement		
Atrium	90	23.1
Cavoatrial junction	229	58.9
Distal SVC	68	17.5
Mid SVC	2	0.5
Insertion side		
Right	326	83.8
Left	63	16.2
Dwell time (days)		
Total	106,158	
Median	273	
Range	4–365	

Table 2
Adverse events of 389 patients with port insertions.

Adverse event	N out of 389	Percentage (%)
CRDVT	5	1.29
Filling defect on tip of IVAD	1	0.26
Brachiocephalic	3	0.77
Internal jugular	1	0.26
Pulmonary embolism from any cause	23	5.91
Colorectal	12	3.08
Breast	3	0.77
Hem/malignancy	2	0.51
Other	2	0.51
Esophageal/gastric	1	0.26
Gynecological	1	0.26
Liver/gallbladder	1	0.26
Pancreatic	1	0.26
Catheter-related bloodstream infection	0	0
100-day all-cause mortality rate	30	7.7
365-day all-cause mortality rate	85	22

Table 3
Reasons for therapeutic anticoagulation initiation during the 12-month follow-up period.

Reason for therapeutic anticoagulation	N out of 26	Percentage (%)
Leg DVT	13	50.0
Portal vein thrombosis	4	15.5
Mesenteric vein thrombosis	2	7.7
Atrial fibrillation	3	11.5
Renal vein thrombosis	1	3.8
Contralateral UEDVT	2	7.7
Post liver resection	1	3.8

Table 4
Reasons for IVAD removal during the 12-month follow-up period.

Reason for IVAD removal	N out of 51	Percentage (%)
Completed treatment	36	70.6
Tunnel infection without bacteremia	2	3.9
Patient request	2	3.9
IVAD malposition	6	11.7
Erosion through skin	3	5.9
Wound dehiscence	1	2.0
Removal as part of a sarcoma surgical resection	1	2.0

developed a PE or an IVAD-related UEDVT, a majority had a diagnosis of colorectal cancer (52.2%). A total of 85 patients (22%) died during the study period, of which 30 (7.7%) died within the first 100 days. No deaths were attributable to a PE. Fifty-one patients (13%) had their IVADs removed during the study for reasons listed in Table 4.

4. Discussion

The rate of IVAD-related UEDVT is low at 1.29% (95% CI 0.2%–2.4%) in our study. Our reported rate of IVAD-related UEDVT seems lower than previously reported rates [8,10,16]. In a recent study including 600 cancer patients, 5.5% had IVAD-related DVT [16]. Similarly, we reported a higher rate of IVAD-related UEDVT (4.5%, 95% CI, 2.5 to 6.3%) with a different IVAD. In both studies, the majority of patients were diagnosed with breast cancer or colorectal cancer [10,16]. A recently published prospective cohort study examining the rate of IVAD related VTE in 3032 patients across France found a rate of 3.8% [15]. This rate is higher than what was found in this study, and their population included patients who were on prophylactic and therapeutic anticoagulation, which may have decreased the rate of IVAD-related UEDVT.

The definition of a IVAD-related UEDVT varies significantly in the literature, with some definitions including all PE as having a potential association with the IVAD, and others only defining them as symptomatic UEDVTs on the ipsilateral side of the IVAD [8,17,18]. Given that cancer patients are at higher risk of incident VTE complications [19–21], it is challenging to determine if the VTE is related to the IVAD or not. For the purposes of this study, we have not considered PE as a IVAD-related VTE unless there was a concurrent finding of VTE on the ipsilateral side of IVAD insertion. This is consistent with recommendations from the International Society on Thrombosis and Haemostasis [22].

Our study used novel IVADs with an anti-thrombogenic polymer. Catheter material has previously been shown to influence the risk of thrombosis, with newer catheter materials having fewer thrombotic complications [23,24]. Therefore, our lower reported rate of IVAD-related UEDVT might be related to the use of a device with an anti-thrombogenic polymer instead of the classic silicone catheter [10]. Furthermore, we hypothesize that having a specialized team of RNs and interventional radiologists inserting novel IVADs under standard protocols may also contribute to the lower rate of VTE complications.

Guidelines mention that IVADs should be inserted on the right side, in the jugular vein, and that the distal extremity should be located at the junction of the superior vena cava and right atrium to reduce the risk of IVAD-related UEDVT [25]. These guidelines are largely based on a right-sided insertion having a higher morbidity risk [26]. Previous studies have reported a seven fold increase of thrombosis when the catheter tip was located in the upper half of the superior vena cava and a 5 fold increase when the catheter was placed on the left side [26]. However, in specific populations such as the breast cancer population, the side of IVAD-insertion cannot always be optimal. A recent randomized study found that the side of implantation was not a predictive factor for IVAD-related UEDVT in patients with solid tumours [27]. Our study shows similar results, with no association between side of IVAD insertion and rate of IVAD-related UEDVT.

Our study has many strengths. All patients were followed prospectively for 12 months post IVAD insertion. The cohort in this study included high-risk cancers, such as gastric and pancreatic cancers. Patients receiving anticoagulation therapy for any reason were excluded from the study. Our study is also the first of its kind to report the incidence of IVAD-related UEDVT with a specific IVAD with an anti-thrombogenic polymer in cancer population. Despite the many strengths of this study, there were some limitations. The study was a single arm observational study and did not include a control group, limiting direct comparisons between devices. It is therefore difficult to determine whether the low risk of IVAD-related DVTs is attributable to the safety of the procedure and IVAD itself, or to the highly trained specialized team inserting the IVAD. This study did not censor patients who required prophylactic anticoagulation during an admission to hospital while their IVAD was in situ, and it is therefore difficult to determine whether prophylaxis may have contributed to the low rate of IVAD-related UEDVT in this population. This study did not have equal representation of all types of malignancies, and it may be difficult to extrapolate these findings broadly, such as to patient with hematological, gynecological and lung cancers.

5. Conclusion

IVAD-related UEDVT is an infrequent complication in cancer patients with BioFlo® IVADs. The low rate to IVAD-related DVT is likely due to appropriate patient selection through the use of established device selection protocols implemented by a vascular access nurses; a highly skilled team of interventional radiologist assisted by ultrasound guidance for insertion of IVADs with proper tip placement and the use of novel catheter materials resistant to thrombus accumulation.

Acknowledgments

We would like to acknowledge Elham Sabri for her assistance with the statistical analyses used for the data analysis.

This study was funded by AngioDynamics administered through The Ottawa Hospital Research Institute. AngioDynamics was not involved in the study design, implementation, or data analysis.

References

[1] A.A. Khorana, Venous thromboembolism and prognosis in cancer, Thromb. Res. 125 (2010) 490–493, https://doi.org/10.1016/j.thromres.2009.12.023.
[2] S. Eichinger, Cancer associated thrombosis: risk factors and outcomes, Thromb. Res. 140 (Suppl. 1) (2016) S12–S17, https://doi.org/10.1016/S0049-3848(16)30092-5.
[3] A.A. Khorana, M. Carrier, D.A. Garcia, A.Y.Y. Lee, Guidance for the prevention and treatment of cancer-associated venous thromboembolism, J. Thromb. Thrombolysis 41 (2016) 81–91, https://doi.org/10.1007/s11239-015-1313-4.
[4] Khorana AA, Otten H-M, Zwicker JI, Connolly GC, Bancel DF, Pabinger I, et al. Prevention of venous thromboembolism in cancer outpatients: guidance from the SSC of the ISTH. J Thromb Haemost JTH 2014;12:1928–31. doi:https://doi.org/10.1111/jth.12725.
[5] M.M.J. Beckers, H.J.T. Ruven, C.A. Seldenrijk, M.H. Prins, D.H. Biesma, Risk of thrombosis and infections of central venous catheters and totally implanted access ports in patients treated for cancer, Thromb. Res. 125 (2010) 318–321, https://doi.org/10.1016/j.thromres.2009.06.008.
[6] Narducci F, Jean-Laurent M, Boulanger L, El Bédoui S, Mallet Y, Houpeau JL, et al. Totally implantable venous access port systems and risk factors for complications: a one-year prospective study in a cancer centre. Eur J Surg Oncol EJSO 2011;37:913–8. doi:https://doi.org/10.1016/j.ejso.2011.06.016.
[7] S.N. Nagel, U.K.M. Teichgräber, S. Kausche, A. Lehmann, Satisfaction and quality of life: a survey-based assessment in patients with a totally implantable venous port system, Eur. J. Cancer Care (Engl) 21 (2010) 197–204, https://doi.org/10.1111/j.1365-2354.2011.01275.x.
[8] Yukisawa S, Fujiwara Y, Yamamoto Y, Ueno T, Matsueda K, Kohno A, et al. Upper-extremity deep vein thrombosis related to central venous port systems implanted in cancer patients. Br. J. Radiol. 2010;83:850–3. doi:https://doi.org/10.1259/bjr/41019720.
[9] L.E. Flinterman, F.J.M. Van Der Meer, F.R. Rosendaal, C.J.M. Doggen, Current perspective of venous thrombosis in the upper extremity, J Thromb Haemost JTH 6

(2008) 1262–1266, https://doi.org/10.1111/j.1538-7836.2008.03017.x.
[10] S. Piran, V. Ngo, S. McDiarmid, G.L. Gal, W. Petrcich, M. Carrier, Incidence and risk factors of symptomatic venous thromboembolism related to implanted ports in cancer patients, Thromb. Res. 133 (2014) 30–33, https://doi.org/10.1016/j.thromres.2013.10.026.
[11] J.W. Blom, C.J.M. Doggen, S. Osanto, F.R. Rosendaal, Old and new risk factors for upper extremity deep venous thrombosis, J Thromb Haemost JTH 3 (2005) 2471–2478, https://doi.org/10.1111/j.1538-7836.2005.01625.x.
[12] BioFlo Ports with Endexo Technology. AngioDynamics n.d. http://www.angiodynamics.com/products/19/BioFlo-Ports-with-Endexo-Technology/ (accessed February 4, 2019).
[13] The use of micropuncture technique for vascular or body cavity access|MedReviews n.d. http://medreviews.com/journal/reviews-in-cardiovascular-medicine/vol/15/no/3/use-micropuncture-technique-vascular-or-body-cavity-access (accessed November 15, 2018).
[14] S. McDiarmid, Data: the real D in decision making, Vasc Access 6 (2012) 21–25.
[15] Decousus H, Bourmaud A, Fournel P, Bertoletti L, Labruyère C, Presles E, et al. Cancer-associated thrombosis in patients with implanted ports: a prospective multicenter French cohort study (ONCOCIP). Blood 2018:blood-2018-03-837153. doi:https://doi.org/10.1182/blood-2018-03-837153.
[16] Dridi M, Mejri N, Labidi S, Afrit M, Benna HE, Miled KB, et al. Implantable port thrombosis in cancer patients: a monocentric experience. Cancer Biol Med 2016;13:384–8. doi:10.20892/j.issn.2095-3941.2016.0057.
[17] Chaudhury A, Balakrishnan A, Thai C, Holmstrom B, Nanjappa S, Ma Z, et al. Validation of the Khorana score in a large cohort of cancer patients with venous thromboembolism. Blood 2016;128:879–879.
[18] A. Delluc, G. Le Gal, D. Scarvelis, M. Carrier, Outcome of central venous catheter associated upper extremity deep vein thrombosis in cancer patients, Thromb. Res. 135 (2015) 298–302, https://doi.org/10.1016/j.thromres.2014.11.020.
[19] A.T. Cohen, A. Katholing, S. Rietbrock, L. Bamber, C. Martinez, Epidemiology of first and recurrent venous thromboembolism in patients with active cancer, Thromb. Haemost. 117 (2017) 57–65, https://doi.org/10.1160/TH15-08-0686.
[20] J.F. Timp, S.K. Braekkan, H.H. Versteeg, S.C. Cannegieter, Epidemiology of cancer-associated venous thrombosis, Blood 122 (2013) 1712–1723, https://doi.org/10.1182/blood-2013-04-460121.
[21] S. Noble, J. Pasi, Epidemiology and pathophysiology of cancer-associated thrombosis, Br. J. Cancer 102 (2010) S2–S9, https://doi.org/10.1038/sj.bjc.6605599.
[22] J.I. Zwicker, G. Connolly, M. Carrier, P.W. Kamphuisen, A.Y.Y. Lee, Catheter-associated deep vein thrombosis of the upper extremity in cancer patients: guidance from the SSC of the ISTH, J. Thromb. Haemost. 12 (2008) 796–800.
[23] M. Gallieni, M. Pittiruti, R. Biffi, Vascular access in oncology patients, CA Cancer J. Clin. 58 (2008) 323–346, https://doi.org/10.3322/CA.2008.0015.
[24] Wildgruber M, Lueg C, Borgmeyer S, Karimov I, Braun U, Kiechle M, et al. Polyurethane versus silicone catheters for central venous port devices implanted at the forearm. Eur J Cancer Oxf Engl 1990 2016;59:113–24. doi:https://doi.org/10.1016/j.ejca.2016.02.011.
[25] Debourdeau P, Farge D, Beckers M, Baglin C, Bauersachs RM, Brenner B, et al. International clinical practice guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters in patients with cancer. J Thromb Haemost JTH 2013;11:71–80. doi:https://doi.org/10.1111/jth.12071.
[26] Verso M, Agnelli G, Kamphuisen PW, Ageno W, Bazzan M, Lazzaro A, et al. Risk factors for upper limb deep vein thrombosis associated with the use of central vein catheter in cancer patients. Intern. Emerg. Med. 2008;3:117–22. doi:https://doi.org/10.1007/s11739-008-0125-3.
[27] W.-Y. Lin, C.-P. Lin, C.-H. Hsu, Y.-H. Lee, Y.-T. Lin, M.-C. Hsu, et al., Right or left? Side selection for a totally implantable vascular access device: a randomised observational study, Br. J. Cancer 117 (2017) 932–937, https://doi.org/10.1038/bjc.2017.264.