Risk factors of thrombosis in cancer : the role of microparticles

Tesselaar, M.E.T.

2 Risk factors for catheter-related thrombosis in cancer patients

Margot Tesselaar, Jan Ouwerkerk, Marianne Nooy,
Frits Rosendaal and Susanne Osanto

European Journal of Cancer, 40: 2253-2259; October 2004

Abstract

We investigated the risk factors for venous thrombosis in cancer patients with implantable ports undergoing chemotherapy. One hundred and seventy one ports were placed in a central ("chest ports") and 84 in a peripheral vein ("arm ports"), 181 received prophylactic nadroparin and 10 coumarin. Clinically overt thrombosis was confirmed by ultrasound or angiography. Catheter-related thrombosis incidence without anticoagulants was 28% in arm and 33% in chest ports, but with anticoagulants this was 32% in arm and only 1% in chest ports (odds ratio (OR) 34.8 95% confidence interval (CI) 7.3–165). Left-sided placement compared with right-sided and catheter tip position in the superior *vena cava* compared with right atrium were associated with a 3.5 respectively 2.6-fold increased risk. Thrombosis was associated with elevated homocysteine levels (OR = 3.8, 95% CI 1.3–11.3), but not with factor V Leiden or prothrombin 20210A gene mutations, or high concentration of factor VIII, IX or XI. Prophylaxis with anticoagulants is recommended for chest, but not for arm ports. Determination of plasma homocysteine levels may identify patients at an increased risk for thrombosis.

Chapter 2

Introduction

The use of centrally or peripherally inserted venous catheters with implantable ports has become common in cancer patients receiving chemotherapy. Catheters are implanted for the long-term administration of chemotherapy courses with sclerosing agents, in patients with toxic chemotherapy regimens and anticipated haematological toxicity requiring frequent blood sampling and, more recently, in patients who require continuous administration of drug infusions. Many different types of implantable devices consisting of a small-volume subcutaneous injection (s.c.) port (commonly called ports) have been introduced with different types of catheters and devices. Port-associated complications such as infections, thrombosis or even pulmonary embolism, are the cause of significant morbidity and occasionally mortality and remain a significant problem in current daily practice.

Catheter-related thrombosis is probably frequently under-diagnosed as most patients with catheter-related thrombosis are asymptomatic or have non-specific symptoms. The reported incidence of catheter-related venous thrombosis varies considerably, in part due to the method of detecting thrombi, with incidences of greater than 60% being reported (1;2). De Cicco and colleagues (1) reported a very high incidence of 66%, but only 6% of patients with catheter-related thrombosis, screened by venography, were symptomatic. Lokich and colleagues (3) reported an incidence of 42%, of which 28.3% were symptomatic. Van Roode and colleagues (4) showed that in patients with haematological malignancies, 26 of 105 patients (25%) developed subclinical thrombosis, of whom nine became clinically manifest. Clinical presentation of catheter-related thrombosis may include arm or head swelling, erythema, pain and congestion of collateral veins, whereas catheter malfunctioning may be the first clinical manifestation of an otherwise asymptomatic catheter-related thrombosis. Thrombosis may lead to prompt catheter removal and anticoagulant treatment.

A hypercoagulable state associated with malignancy, co-morbidity of cancer patients, the use of certain anti-cancer drugs and the presence of a foreign body may contribute to the higher venous thrombosis incidence observed in cancer patients (5). Thrombogenicity of different central venous catheters has been reported to vary depending on the catheter material and size of the catheter used. Polyethylene catheters are associated with a higher incidence than silastic catheters (6;7), whereas there is no difference in the incidence of venous thrombosis following the use of silastic or hydromer-coated polyurethane catheters (6;7).

While several factors may contribute to the development of venous thrombosis, few of these factors have been examined in well-controlled studies (8;9). We therefore investigated various risk factors and the incidence of catheter-related thrombosis in a cohort of cancer patients undergoing chemotherapy and determined the risk of catheter-related thrombosis associated with anticoagulant treatment and prothrombotic risk factors.

Patients and methods

Patients

Between April 1994 and January 2003, 243 consecutive cancer patients in the Leiden University Medical Centre Department of Clinical Oncology received a central venous catheter for either repeated administration of chemotherapy with sclerosing agents known to irritate the veins resulting in frequent phlebitis or for continuously infused chemotherapy. Patients were treated with various combination chemotherapy regimens, most of which contained cisplatin, doxorubicin or both cisplatin and (epi)-doxorubicin. Of these patients, 132 were men and 111 were women, with a mean age of 44 years (range 14–78 years). The most frequently treated types of cancer were bone tumours, *i.e.*, osteosarcoma or Ewing's sarcoma (124 [51%] patients) and distal oesophagus or stomach cancer (54 [22%] patients) (Table 1). One hundred and thirty-nine (57%) patients had distant metastases at the time of insertion of the catheter.

Implantable ports

All catheters implanted were composed of two parts, namely a single lumen radio-opaque catheter connected to an injection reservoir, the port, containing a silicone diaphragm. For the chest ports, we used the Port-A-Cath (Sims Deltec, St-Paul, MN) and for the arm ports, either a Port-a-Cath (Smiths Medical Deltec) or a Vital port (Cook Pacemaker Corporation, Leechburg, PA). The injection port reservoir of the chest ports was made of Titanium and the catheter of polyurethane, with an outer diameter of 2.6 mm and an inner diameter of 1.6 mm. Arm ports also had a Titanium reservoir and the material of the catheter was made of polyurethane in the Deltec and of silastic in the Vital Cook catheters. The outer diameter of the Deltec catheter was 1.9 mm; the internal diameter was 1.0 mm. The outer diameter of the Vital Cook catheter was 1.7 mm; the inner diameter was 0.9 mm.

All catheters were introduced into the veins by experienced interventional radiologists in the angiography interventional radiology suite. Under local anaesthesia, the catheter was tunnelled and a surgeon made the connection between the reservoir and catheter during the same session. After placement, correct positioning of the tip of the catheter was confirmed by chest X-ray and shown to be localised in either the *vena cava* superior or the right atrium. In general, ports were not immediately removed after cessation of chemotherapy in order to be able to use the ports for second- or third-line chemotherapy, if needed. Experienced nurses flushed all ports every 4–6 weeks with 5 ml of a heparin-sodium solution 100 IE/ml and at the end of each cycle of chemotherapy infusions to maintain patency. In patients in whom the port was replaced, the time period of insertion of both catheters was analysed. Chest ports were placed in the subclavian vein, but preferably in the jugular vein. Arm ports were placed in an arm vein.

Table 1

	Patients with thrombosis *n* (%)	**Patients without thrombosis *n* (%)**	**OR (95% CI)**
Gender			
Female	19 (57.6)	92 (43.8)	1
Male	14 (42.4)	118 (56.2)	0.6 (0.3-1.2)
Median age in years (range)	42 (16-67)	44 (14-78)	
Type of tumour			
osteo-or Ewing's sarcoma	19 (57.6)	105 (50.0)	1.4 (0.7-2.9)
oesophagus/stomach	7 (21.2)	47 (22.4)	2.1 (0.9-5.3)
ovarian	5 (15.2)	9 (4.3)	5.6 (1.5-20.4)
mamma	0 (0.0)	12 (5.7)	
miscellaneous	2 (6.1)	37 (17.6)	0.9 (0.4-1.7)
Metastatic disease	15 (45.5)	124 (59.0)	1.8 (0.7-4.2)
Chemotherapeutic agents			
anthracyclines	26 (78.8)	171 (81.4)	0.7 (0.2-3.0)
cisplatin	28 (84.8)	156 (74.3)	0.5 (0.2-1.4)
taxane	5 (15.2)	13 (6.2)	0.3 (0.1-1.8)
5-FU civ	8 (24.2)	72 (34.3)	1.6 (0.4-3.5)
Platelet count (*10^9 cells/L)			
≤ 400	4 (12.1)	28 (13.3)	1
> 400	29 (87.9)	182 (86.7)	1.1 (0.4-3.5)

Thrombosis and prophylaxis

The diagnosis of symptomatic thrombosis (*n* = 28), suspected by either symptoms such as arm swelling, pain or bluish discoloration, or suspected because of device malfunctioning (*n* = 5) was confirmed by duplex ultrasonography or phlebography of the upper extremity venous system, while the investigator was unaware of any antithrombotic medication.

Before 1998 (*n* = 66), no prophylaxis with anticoagulants was given, but two patients already received anticoagulant treatment with coumarins for various unrelated reasons, e.g., myocardial infarction, recent surgery, and remained on coumarin treatment. Since 1998, all patients (*n* = 177) received thrombosis prophylaxis with low molecular weight heparin (LMWH) (nadroparin 2850 IE s.c. daily), except for the three patients who had already received coumarin treatment for other reasons did not receive additional prophylaxis with LMWH. Five patients received a second catheter due to catheter-related thrombosis and received coumarin.

Blood sampling

Since 1999, citrated (room temperature) and acidic citrated blood (on melting ice) samples were obtained from 101 patients, after informed consent was obtained. For factor VIII, IX, XI, G1691A (FV) mutation and G20210A (FII) mutation analysis, blood was collected in tubes containing 0.106 mol/l trisodium citrate. Plasma was prepared by immediate centrifugation for 10 min at 3200 rotations per minute (rpm) and stored at −70°C. DNA was extracted from white cells and the G1691A mutation and G20210A mutation determined by the polymerase chain reaction (PCR). The fibrinogen concentration was determined according to Clauss (10). Factor VIII: C (11), factor IX: C and factor XI: C levels were measured by a one-stage clotting assay. Elevated levels of factor VIII were defined as >200 IU/dl and of factor IX and factor XI as >150 IU/dl. For homocysteine concentration assays, blood was collected in Stabilyte tubes containing 0.5 mol/l trisodium citrate and plasma was prepared by immediate centrifugation and stored at −70°C. Total homocysteine concentration was determined with the high performance liquid chromatography (HPLC) sodium borohydride / monobromobimane method ($NaBH_4$/mBrB method used $NaBH_4$ for reduction and mBrB derivation) (12). Elevated levels of homocysteine were defined based on the distribution of plasma levels in cohorts with different age and gender. For women, elevated levels of homocysteine were defined as greater than 13.4 mmol/l for those aged 19–59 years, greater than 16.4 mmol/l for those aged 60–70 years and greater than 17.4 mmol/l for patients over 70 years of age. For men, this was defined as greater than

15.2 mmol/l for 19–59 year old, greater than 18.3 mmol/l for those aged 60–70 years and greater than 19.1 mmol/l for patients over 70 years of age.

Statistical analysis

We compared catheters in patients who experienced catheter-related thrombosis with catheters in patients who did not experience such events.

We investigated putative risk factors by calculating exposure odd ratios (ORs) as an estimate of the relative risk (RR). The ORs show how much higher the risk of disease, *e.g.*, thrombosis, is in the presence of a risk factor than in its absence. An OR ratio of 1 indicates the absence of an association.

Results

Of 243 patients who received 255 devices, in 171 (67%) a catheter was placed in a central vein, *i.e.*, jugular internal or subclavian vein ("chest ports") and in 84 (33%) instances in a peripheral vein, i.e., cubital or basilical vein ("arm ports"). The mean time *in situ* for the chest ports was 207 days (median 178 days; range 9–1092 days) and for arm ports 352 days (median 321 days; range 7–1795 days).

Thirty-three (14%) of the 243 cancer patients developed a catheter-related thrombosis during chemotherapy; 28 (85%) were associated with patient symptoms and five detected because of device malfunctioning. The mean time until detection of thrombosis was 22 days (median 51 days; range 6–309 days), and eighty-five percent occurred within 2 months. In four of the 28 (14%) thromboses that occurred within 2 months, the port was still functioning.

Except for ovarian cancer, there was no association between tumour type, presence or absence of metastatic disease, platelet count, number of chemotherapeutic cycles or type of chemotherapy and thrombosis incidence (Table 1). Both arm and chest posts were implanted on the right (n = 152) and left (n = 103) side; the risk of venous thrombosis was 3.5-fold higher for left-sided placement compared with right-sided placement (OR = 3.5, 95% CI 1.6–7.5) (Table 2).

Table 2. Risk of thrombosis in relation to site of placement of catheter

	Venous thrombosis		OR (95% CI)
	Left-sided placement	Right-sided placement	
All catheters (*n* = 255)	22/103	11/152	3.5 (1.6–7.5)
Chest ports (*n* = 171)	4/38	4/133	3.8 (0.9–15.9)
Arm ports (*n* = 84)	18/65	7/19	1.5 (0.5–4.5)

The position of the tip of the catheter (atrium versus *cava superior* vein) was associated with the risk of venous thrombosis: the risk was almost 3-fold higher when the catheter tip was located in the *superior vena cava* compared with the atrium (OR = 2.7, 95% CI 1.1–6.6). We did not find an association with the type of catheter, or the manufacturer. In 8 (5%) of 171 chest ports and 25 (30%) of 84 arm ports, venous thrombosis occurred, *i.e.*, the risk of venous thrombosis was 8-fold higher for arm ports than for chest ports (OR = 8.1 95% CI 3.5–19.1, Table 3).

Table 3. Risk of thrombosis in relation to the type of catheter and use of anticoagulants

	Venous thrombosis		OR (95% CI)
	Arm ports	Chest ports	
All catheters (*n* = 255)	25/84	8/171	8.1 (3.5–19.1)
Without anticoagulants (*n* = 64)	13/46	6/18	0.8 (0.2–2.5)
With anticoagulants[a] (*n* = 191)	12/38	2/153	34.8 (7.3–165)

[a] Nadroparin (*n* = 181) or coumarin (*n* = 10).

In 64 patients who did not receive anticoagulants, the risk to develop venous thrombosis was similar in patients with arm ports and patients with chest ports; in 13 (28%) of the 46 arm ports, and 6 (33%) of the 18 chest ports, venous thrombosis occurred. In patients who received anticoagulants (in 95% of the catheters nadroparin s.c. was given) catheter-related venous thrombosis occurred more often in those with arm ports (12 [32%] of 38 ports) than in those with chest ports (2 [1%] of 153 ports), OR = 34.8 95% CI 7.3–165 (Table 3). None of the 10 patients on coumarin therapy developed venous thrombosis.

From 101 patients in whom prothrombotic factors were determined, eighteen (18%) had developed venous thrombosis. The prevalence of factor V Leiden and prothrombin 20210A did not differ between the group of patients with venous thrombosis and the group

of patients without evidence of catheter-related thrombosis, nor did we find an association between elevated levels of FVIII, FIX and FXI and the development of thrombosis (Table 4). However, elevated plasma homocysteine levels were more frequently found in the group of patients with venous thrombosis (median 12.7 mmol/l; range 5.4–31.8), i.e., 8 (44.4%) of 18 patients with venous thrombosis, compared with 14 (16.9%) of 83 patients without venous thrombosis (median 12.3 mmol/l; range 8.3–20.1). Elevated plasma homocysteine concentration was associated with a 3.8-fold increased risk of development of thrombosis (OR = 3.8 95% CI 1.3–11.3, Table 4), there was no linear correlation between the actual plasma homocysteine level and thrombosis.

Table 4. Number of patients with factor V Leiden or factor II 20210A gene mutations, elevated plasma levels of clotting factors or homocysteine

	Patients with thrombosis (*n* = 18) *n* (%)	**Patients without thrombosis (*n* = 83) *n* (%)**	**OR (95% CI)**
Factor V Leiden/ factor II 20210A mutation	1 (5.6)	7 (8.4)	0.6 (0.1–5.5)
↑ FVIII	3 (16.7)	6 (7.2)	2.2 (0.5–9.6)
↑ FIX	4 (22.2)	25 (30.1)	0.9 (0.3–3.2)
↑ FXI	2 (11.1)	5 (6)	2.0 (0.4–11.0)
↑ Homocysteine	8 (44.4)	14 (16.9)	3.8 (1.3–11.3)

Discussion

We found an incidence of 14% of catheter-related thrombosis in cancer patients receiving anthracycline- and cisplatin-containing combination chemotherapy via implantable central or peripheral venous ports. Most cases of venous thrombosis occurred within 2 months after insertion of the catheter. The administration of anticoagulants, mainly prophylaxis with s.c. administered nadroparin, was associated with a markedly reduced incidence of thrombosis for chest, but not for arm ports. We identified arm ports, left-sided placement, catheter tip location in the *superior cava* vein and elevated levels of homocysteine as important risk factors for the development of thrombosis.

Platelet counts, the presence of stage IV metastatic disease, individual cytotoxic drug and the cumulative dose of the cytotoxic drugs administered, were not associated with the development of catheter-related thrombosis. Ovarian carcinoma seemed to be an additional risk factor for the development of catheter-related thrombosis, probably reflecting the intrinsically high risk of developing thrombosis in patients with ovarian carcinoma (13), compared with other tumour types.

Most studies on peripherally inserted catheters, although performed in patients with diseases other than cancer, showed a much lower incidence of thrombosis of up to 5% (14) and (15). In agreement with our findings, Kuriakose and colleauges (16) also observed a higher incidence in peripheral ports of 11% compared with 3% in chest ports in patients with mainly cancer or myeloproliferative disorders undergoing chemotherapy.

Left-sided placement as well as location of the catheter tip in the *superior vena cava* instead of the right atrium was found to be associated with a more than 3-fold respectively 2.6-fold increase in risk for the development of thrombosis. The high incidence of thrombosis, despite the prophylactic use of anticoagulants, found in patients with arm ports compared with chest ports may have resulted from arm movements, kinking of the catheter, mechanical displacement of the catheter, or a nod in the catheter at the level of the armpit. Such factors may have contributed to changes in blood flow or injury of the vascular endothelium and release of clotting activators, especially in cancer patients with peripherally inserted arm ports.

Conflicting data exist in the literature with regard to the association between gene abnormalities and the risk of catheter-related thrombosis in cancer patients. We found no association between the risk for thrombosis and known risk factors for venous thrombosis, nor with elevated levels of factor VIII, IX or XI. This is consistent with our previous data (17) and data from Ramacciotti and colleagues (18), who also did not find an association between gene polymorphisms tested, i.e., Factor V Leiden, factor II G20210A, factor XIII val 34leu and Methylene tetrahydrofolate reductase (MTHFR) C677T, and the risk of venous thrombosis in cancer patients. In agreement with these findings, Riordan and colleagues (19) found a low prevalence of factor V Leiden gene mutation in 28 cancer patients with catheter-related venous thrombosis. In contrast, other groups did find an association between factor V Leiden and prothrombin gene mutations and thrombosis in paediatric (20) and in adult patients with haematological malignancies (21). One explanation could be that gene mutations only carry a low additional risk that does not have a substantial impact on thrombosis incidence when other factors already result in a high incidence of venous thrombosis.

Elevated plasma homocysteine levels have been identified as a risk factor for venous thrombosis. Damage of the endothelial cells by homocysteine has been proposed as a cause of homocysteine-associated venous thrombosis, but the exact mechanism is unknown (22). Elevated levels of homocysteine, as observed in our cancer patients, may thus play a causative role in the development of catheter-related thrombosis, in particular during the administration of endothelial cell-damaging chemotherapy. In cancer patients, plasma homocysteine levels may originate from proliferating cancer cells (23). The role of elevated homocysteine levels, MTHFR polymorphism, possibly associated with cancer dietary deficiency, and the protective effect of dietary supplementation in cancer patients (24) and (25) clearly deserves further investigation in larger cohorts of patients. Reduced dietary folate intake in cancer patients, may well contribute to increased homocysteine levels and the development of venous thrombosis in these patients.

The high incidence of thrombosis and the associated complications rate compel further investigation into the exact role of elevated homocysteine levels.

Prophylaxis with anticoagulants is a controversial issue at present and policies differ in different countries. The question of whether prophylaxis with either LMWH or coumarin could protect against catheter-related venous thrombosis in cancer patients, either solid tumour or haematological patients, has been addressed in five randomised studies, of which three have appeared as full papers (2,26-29). Monreal and colleagues (2) and Bern and colleagues (26) both performed a randomised placebo-controlled study in solid tumour patients. Both studies demonstrated that prophylaxis, with LMWH and warfarin, respectively, could protect against catheter-related venous thrombosis. In both studies, a venography was performed as the end-point in each patient after 90 days of insertion of the catheter. On the basis of these two studies, the American College of Chest Physicians recommended prophylaxis with LMWH or low-dose warfarin in cancer patients with central venous catheters (30). More recently, Heaton and colleagues (27) randomly assigned 88 patients with haematological malignancies to low-dose warfarin or no treatment. The end-point of this study was clinically suspected venous thrombosis, confirmed by venography. No significant difference in venous thrombosis incidence was found between the warfarin and control groups. More recently, two randomised studies have been performed (28,29). One in mostly haematological malignancy patients (28) with or without the use of warfarin, and the other (29) in mostly solid tumour patients, employing LMWH. In both studies, no major differences were observed, but the studies have not yet been reported as peer-reviewed papers.

In conclusion, this is the first report identifying elevated plasma homocysteine levels as a major risk factor for catheter-related thrombosis. As our study was based on small numbers, further investigation of homocysteine levels in a larger group of cancer patients is warranted to unravel the relationship between factors influencing plasma homocysteine levels in cancer patients undergoing chemotherapy and the occurrence of venous thrombosis. Based on the high incidence of thrombosis in our patient group, despite the use of prophylactic anticoagulants, we strongly advise against the use of arm ports in cancer patients undergoing anthracycline- and/or cisplatin-based combination chemotherapy. In contrast, the use of a chest port to facilitate administration of such chemotherapy is associated with a low risk of thrombosis, provided that thrombotic prophylaxis is given. Our data underscore the findings of Monreal and colleagues (2) and Bern and colleagues (26), with respect to the need for thrombosis prophylaxis in cancer patients with central venous catheters. Conflicting data in the literature with regard to this question may be explained by the absence of stratification for identified prothrombotic risk factors (*e.g.*, elevated levels of homocysteine, arm ports and side of catheter placement) resulting in such factors not being well balanced between the two randomised groups of patients.

Acknowledgements

We thank T.C. Visser, LUMC Leiden for performing the gene mutation analyses and determination of plasma clotting factors and D. Oppenraaij-Emmerzaal, A. de Graaf and Dr. H.J. Blom, UMC Nijmegen for determination of homocysteine levels.

References

1. M. De Cicco, M. Matovic, L. Balestreri, G. Panarello, D. Fantin and S. Morassut et al., Central venous thrombosis: an early and frequent complication in cancer patients bearing long-term silastic catheter. A prospective study, Thromb. Res. 86 (1997). 101–113.
2. M. Monreal, A. Alastrue, M. Rull, X. Mira, J. Muxart and R. Rosell et al., Upper extremity deep venous thrombosis in cancer patients with venous access devices – prophylaxis with a low molecular weight heparin (fragmin), Thromb. Haemostasis 75 (1996). 251–253.
3. J.J. Lokich and B. Becker, Subclavian vein thrombosis in patients treated with infusion chemotherapy for advanced malignancy, Cancer 52 (1983). 1586–1589.
4. C.J. van Rooden, F.R. Rosendaal, R.M.Y. Barge, J.A. van Oostayen, F.J.M. van der Meer and A.E. Meinders et al., Central venous catheter related thrombosis in haematology patients and prediction of risk by screening with Doppler-ultrasound, Brit. J. Haematol. 123 (2003). 507–512.
5. A.Y. Lee and M.N. Levine, The thrombophilic state induced by therapeutic agents in the cancer patient, Semin. Thromb. Hemost. 25 (1999). 137–145.
6. M. Borow and J.G. Crowley, Prevention of thrombosis of central venous catheters, J. Cardiovasc. Surg. (Torino) 27 (1986). 571–574.
7. T. Pottecher, M. Forrler, P. Picardat, D. Krause, J.P. Bellocq and J.C. Otteni, Thrombogenicity of central venous catheters: prospective study of polyethylene, silicone and polyurethane catheters with phlebography or post-mortem examination, Eur. J. Anaesthesiol. 1 (1984). 361–365.
8. V. Puel, M. Caudry, P. Le Metayer, J.C. Baste, D. Midy and C. Marsault et al., Superior vena cava thrombosis related to catheter malposition in cancer chemotherapy given through implanted ports, Cancer 72 (1993). 2248–2252.
9. K.R. Simpson, D.M. Hovsepian and D. Picus, Interventional radiologic placement of chest wall ports: results and complications in 161 consecutive placements, J. Vasc. Interv. Radiol. 8 (1997). 189–195.
10. A. Clauss, Gerinnungsphysiologische Schnellmethode zur Bestimmung des Fibrinogens, Acta. Haemat. 17 (1957). 237–246.
11. T. Koster, A.D. Blann, E. Briet, J.P. Vandenbroucke and F.R. Rosendaal, Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis, Lancet 345 (1995). 152–155.
12. T. Fiskerstrand, H. Refsum, G. Kvalheim and P.M. Ueland, Homocysteine and other thiols in plasma and urine: automated determination and sample stability, Clin. Chem. 39 (1993). 263–271.
13. J.A. Baron, G. Gridley, E. Weiderpass, O. Nyren and M. Linet, Venous thromboembolism and cancer, Lancet 351 (1998). 1077–1080.
14. R.D. Lyon, K.A. Griggs, A.M. Johnson and J.R. Olsen, Long-term follow-up of upper extremity implanted venous access devices in oncology patients, J. Vasc. Interv. Radiol. 10 (1999). 463–471.
15. M.J. Foley, Radiologic placement of long-term central venous peripheral access system ports (PAS Port): results in 150 patients, J. Vasc. Interv. Radiol. 6 (1995). 255–262.
16. P. Kuriakose, G. Colon-Otero and R. Paz-Fumagalli, Risk of deep venous thrombosis associated with chest versus arm central venous subcutaneous port catheters: a 5-year single-institution retrospective study, J. Vasc. Interv. Radiol. 13 (2002). 179–184.
17. N.I. Weijl, M.F. Rutten, A.H. Zwinderman, H.J. Keizer, M.A. Nooij and F.R. Rosendaal et al., Thromboembolic events during chemotherapy for germ cell cancer: a cohort study and review of the literature, J. Clin. Oncol. 18 (2000). 2169–2178.
18. E. Ramacciotti, N. Wolosker, P. Puech-Leao, E.A. Zeratti, P.R. Gusson and A. del Giglio et al., Prevalence of factor V Leiden, FII G20210A, FXIII Va134Leu and MTHFR C677T polymorphisms in cancer patients with and without venous thrombosis, Thromb. Res. 109 (2003). 171–174.

19. M. Riordan and P.L. Weiden, Factor V Leiden mutation does not account for central venous catheter-related thrombosis, Am. J. Hematol. 58 (1998). 150–152.

20. C. Wermes, M.V. Prondzinski, R. Lichtinghagen, M. Barthels, K. Welte and K.W. Sykora, Clinical relevance of genetic risk factors for thrombosis in paediatric oncology patients with central venous catheters, Eur. J. Pediatr. 158 (1999). S143–S146.

21. R. Fijnheer, B. Paijmans, L.F. Verdonck, H.K. Nieuwenhuis, M. Roest and A.W. Dekker, Factor V Leiden in central venous catheter-associated thrombosis, Brit. J. Haematol. 118 (2002). 267–270.

22. M. den Heijer and M.B.A.J. Keijzer, Hyperhomocysteinemia as a risk factor for venous thrombosis, Clin. Chem. Lab. Med. 39 (2001). 710–713.

23. L.L. Wu and J.T. Wu, Hyperhomocysteinemia is a risk factor for cancer and a new potential tumor marker, Clin. Chim. Acta 322 (2002). 21–28.

24. I.G. Campbell, S.W. Baxter, D.M. Eccles and D.Y.H. Choong, Methylenetetrahydrofolate reductase polymorphism and susceptibility to breast cancer, Breast Cancer Res. 4 (2002).

25. X.P. Miao, D.Y. Xing, W. Tan, J. Qi, W.F. Lu and D.X. Lin, Susceptibility to gastric cardia adenocarcinoma and genetic polymorphisms in methylenetetrahydrofolate reductase in an at-risk chinese population, Cancer Epidem. Biomar. Prev. 11 (2002). 1454–1458.

26. M.M. Bern, J.J. Lokich, S.R. Wallach, A. Bothe Jr., P.N. Benotti and C.F. Arkin et al., Very low doses of warfarin can prevent thrombosis in central venous catheters. A randomized prospective trial, Ann. Intern. Med. 112 (1990). 423–428.

27. D.C. Heaton, D.Y. Han and A. Inder, Minidose (1 mg) warfarin as prophylaxis for central vein catheter thrombosis, Int. Med. J. 32 (2002). 84–88

28. S. Coubon, M. Goodyear, M. Burnell, S. Dolan, P. Wasi and D. Macleod et al., A randomized double-blind placebo controlled study of low dose warfarin for the prevention of symptomatic central venous catheter-associated thrombosis in patients with cancer, Blood 100 (2003) (Suppl.). 703a.

29. P. Reichardt, A. Kretzschmar, M. Biakhov, D. Irwin, C. Slabber and L. Miller et al., A Phase III double blind, placebo-controlled study evaluating the efficacy and safety of daily low-molecular-weight heparin (dalteparin sodium, fragmin) in preventing catheter-related complications in cancer patients with central venous catheters, Proc. Am. Soc. Clin. Oncol. (2003).

30. W.H. Geerts, J.A. Heit, G.P. Clagett, G.F. Pineo, C.W. Colwell and F.A. Anderson et al., Prevention of venous thromboembolism, Chest 119 (2001). 132S–175S.