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Risk Factors for Chemotherapy-Associated Venous Thromboses in Gynaecological Oncology Patients

Risikofaktoren für Chemotherapie-assoziierte venöse Thrombosen bei gynäkoonkologischen Patientinnen

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ABSTRACT

Introduction Venous thromboses and their consequences are among the main causes of death in patients with tumour diseases. The objective of this study is the analysis of risk factors and the evaluation of the applicability of two risk scores in a purely gynaecological oncology patient collective. The identification of patients at high risk for the occurrence of venous thromboses could enable the implementation of targeted medication-based thrombosis prophylaxis which has a significant benefit and, simultaneously, a low risk.

Materials and Methods A retrospective case-control study on 152 patients who were undergoing oncological treatment in the Department of Gynaecology of the Mainz University Medical Centre between 2006 and 2013 investigated the data from 104 patients with breast, 26 with ovarian and 22 with cervical cancer. A control was assigned to 76 subjects in the case group who suffered a venous thrombosis during chemotherapy and this control coincided in the points of tumour location, age, lymph node involvement, metastasis and time of initial diagnosis. The group differences were analysed using the χ^2 test, t test, Mann-Whitney-U test and a logistic regression analysis.

Results There were clear group differences in the lack of inpatient thrombosis prophylaxis ($p = 0.014$), elevated leukocyte counts ($p = 0.018$) prior to the start of chemotherapy and port systems ($p = 0.032$). Surgical interventions were confirmed to be an independent risk factor ($p \leq 0.001$). The Khorana and Protecht scores did not emerge from the analysis as independent predictors for a thrombosis. More patients died in the case group than in the control group ($p = 0.028$; OR: 8.1; CI: 1.254–52.162).

Conclusion In this patient collective, surgeries represent an independent risk factor for venous thromboses. In addition, a correlation was seen between inpatient thrombosis prophylaxis, leukocytosis as well as port systems and an increased risk of thrombosis. Neither the Khorana nor the Protecht score were independent risk factors for venous thromboses. Significantly more thrombosis patients died during the observation period.

ZUSAMMENFASSUNG

Einleitung Venöse Thrombosen und deren Folgen zählen zu den Haupttodesursachen bei Patienten mit Tumorerkrankungen. Ziel dieser Studie ist die Analyse von Risikofaktoren sowie die Evaluation der Anwendbarkeit zweier Risikoscores an einem rein gynäkoonkologischen Patientinnenkollektiv. Mit der Identifikation von Hochrisikopatientinnen für das Auftreten von venösen Thrombosen könnte die Durchführung einer

gezielten medikamentösen Thromboseprophylaxe mit hohem Nutzen bei gleichzeitig geringem Risiko ermöglicht werden.

Material und Methoden In einer retrospektiven Fallkontrollstudie an 152 Patientinnen, die sich zwischen 2006 und 2013 in onkologischer Behandlung an der Frauenklinik der Universitätsmedizin Mainz befanden, wurden die Daten von 104 Patientinnen mit Mamma-, 26 mit Ovarial- und 22 mit Zervixkarzinom untersucht. 76 Probandinnen der Fallgruppe, die während der Chemotherapie eine venöse Thrombose erlitten haben, wurde eine Kontrolle zugeordnet, die in den Punkten Tumorlokalisation, Alter, Lymphknotenbefall, Metastasierung und Zeitpunkt der Erstdiagnose übereinstimmt. Mittels χ^2-Test, t-Test, Mann-Whitney-U-Test und einer logistischen Regressionsanalyse wurden die Gruppenunterschiede analysiert.

Ergebnisse Für eine fehlende stationäre Thromboseprophylaxe (p = 0,014), erhöhte Leukozytenzahlen (p = 0,018) vor Beginn der Chemotherapie und Portsysteme (p = 0,032) zeigten sich deutliche Gruppenunterschiede. Operative Eingriffe wurden als unabhängiger Risikofaktor bestätigt (p ≤ 0,001). Khorana- und Protecht-Score gingen nicht als unabhängige Prädiktoren für eine Thrombose aus der Analyse hervor. In der Fallgruppe sind mehr Patientinnen verstorben als in der Kontrollgruppe (p = 0,028; OR: 8,1; KI: 1,254–52,162).

Fazit Operationen stellen in diesem Patientenkollektiv einen unabhängigen Risikofaktor für venöse Thrombosen dar. Daneben zeigte sich ein Zusammenhang zwischen einer stationären Thromboseprophylaxe, Leukozytose sowie Portsystemen und einem erhöhten Thromboserisiko. Weder Khorana- noch Protecht-Score waren unabhängige Risikofaktoren für venöse Thrombosen. Deutlich mehr Thrombosepatientinnen sind im Beobachtungszeitraum verstorben.

Introduction

Venous thromboses (VT) and their consequences are among the main causes of death in patients with tumour diseases [1]. About 20 % of all newly diagnosed VT are associated with a tumour disease [2]. For several years already, research has focused on understanding the connection between malignant diseases and the increased incidence of VT. The increased expression of procoagulatory proteins as well as illness- and treatment-associated external factors appear to impart a reciprocal effect on the blood clotting system [3]. The presence of a malignant disease itself as well as the associated therapies influence the risk of thrombosis. On cytostatic treatment, a two- to six-fold increase in risk of VT is reported [4, 5]. The understanding of this correlation is essential for the prevention and targeted therapy of thrombotic events and may be decisive for the patient's survival as a result. The preferably early identification of patients at high risk in an outpatient or hospitalised situation is of major importance for targeted medication-based thrombosis prophylaxis. Apart from multiple myeloma, administering outpatient thrombosis prophylaxis is currently not recommended in guidelines [6 – 10]. Scores which comprise various blood parameters, among other things, can be used as the basis classifying tumour patients into risk groups. In addition to the Khorana risk score published by Khorana et al. in 2008 [11], the Protecht score (Prophylaxis-of-thromboembolism-during-chemotherapy) was presented by Verso and colleagues in 2012 [12]. For the Khorana score, points are assigned based on leukocyte, platelet and haemoglobin values and body mass index (BMI) prior to the start of chemotherapy as well as tumour location, and these points can be used to assess the risk of thrombosis. For the Protecht score, points are additionally assigned if therapy containing platinum and/or gemcitabine is used (▶ **Table 1**).

Both scores were able to be validated in patient groups with tumours of various entities to assess the risk of thrombosis. However, in clinical practice to date, these scores have been used only very little on a routine basis for risk assessment. In addition, thrombosis prophylaxis in an outpatient setting has not been recommended to date [9].

▶ **Table 1** Parameters of the Khorana and Protecht risk scores.

Patient characteristics	Point value
Tumour location:	
▪ Very high risk (stomach, pancreas)	2
▪ High risk (bladder, testes, lungs, lymphomas, gynaecological malignancies)	1
▪ Platelet counts prior to start of chemotherapy ≥ 350 × 10^9/l	1
▪ Haemoglobin values prior to start of chemotherapy < 10 g/dl or use of erythrocyte growth factors	1
▪ White blood cell counts prior to start of chemotherapy > 11 × 10^9/l	1
▪ Body mass index ≥ 35 kg/m^2	1
Protecht score	**additional**
▪ Chemotherapy containing platinum or gemcitabine	1
▪ Chemotherapy containing platinum or gemcitabine	2

The objective of our study was the analysis and pretherapeutic determination of additional risk factors for the development of VT on chemotherapy as well as the use of the Khorana and Protecht risk scores in a purely gynaecological patient collective. The identification of patients at high risk could enable the implementation of targeted medication-based thrombosis prophylaxis – even in an outpatient setting – with a significant benefit and, simultaneously, a low risk.

Material and Methods

We conducted a retrospective case control study with patients who received treatment for carcinoma of the breast, ovary or cervix from January 2005 to December 2013 at the Department and

Outpatient Unit for Obstetrics and Women's Health of the University Medical Centre of the Johannes Gutenberg University, Mainz.

Study Collective

The collective with VT (VT case group) was composed of patients who suffered a venous thrombosis within the scope of chemotherapy. All locations of VT except for thromboses in the port system were included. Patients who had a thrombosis prior to cytostatic treatment were not included in the study. Since thrombosis was diagnosed during chemotherapy in only 3 patients with endometrial carcinoma, this tumour entity was not included in the analysis. To conduct an explorative data analysis, a control patient who also underwent cytostatic therapy and who was not affected by a thrombosis was assigned to each patient from the VT case group. Matching between the two groups is performed based on the following points (▶ **Table 2**): tumour type; age of the patient at the time of the VT; presence of metastases or – if no metastases were present – lymph node involvement and presence of a recurrence at the time of the thrombosis according to TNM classification; year of initial diagnosis or if the chemotherapy in the case of a thrombosis took place due to recurrence/metastasis, year of the recurrence/metastasis which led to repeat chemotherapy.

The patients were identified based on the ICD-10 diagnostic codes. All other relevant information could be found in the patient files. The thrombosis was diagnosed using radiological imaging by means of Doppler ultrasound, CT or MRI.

The controls were selected based on tumour board protocols. The clinical-pathological tumour data of the sample such as tumour size, lymph node involvement, presence of metastases or a recurrence can be found in ▶ **Table 2**. Patients who were not in treatment during chemotherapy but rather due to vascular occlusion were not included in the case group. In the cases, the laboratory values were documented before the start of the line of chemotherapy during which the thrombosis occurred (from the last blood count before the start of therapy, generally on the day or morning before the first chemotherapy). In the case of the controls, the laboratory values before the start of chemotherapy which is to be equated with the line of therapy of the corresponding case were considered.

Statistical Methods

The patient-related data were collected and statistical calculations performed using the statistics and analysis software SPSS (Statistical Package for the Social Sciences, Version 22, IBM Deutschland GmbH, 71139 Ehningen).

The analysis was conducted using descriptive statistics to determine the standard deviation, the mean and median.

In order to identify differences between the two groups with regard to possible risk factors for VTs, the χ^2 test was performed for the categorical variables. In the case of variables with an overly low frequency, the results from the – in this case – more accurate exact Fisher test were alternatively used. The continuous and normally distributed variables were evaluated for group differences by means of the unrelated, two-sided t tests as well as the Levene test in advance which checks the equality of the variances, and the corresponding p values and 95% confidence interval (CI) were determined. In contrast to this, the variables with skewed distribution were analysed with the unrelated Mann-Whitney-U test.

▶ **Table 2** Clinical-pathological tumour data of the sample.

Clinical-pathological tumour data	VT case group (n = 76)	Control group (n = 76)
Tumour size		
▪ T1	20	30
▪ T2	28	27
▪ T3	12	14
▪ T4	6	0
▪ missing	10	5
Lymph node involvement		
▪ yes	59	54
▪ no	17	22
Metastasis		
▪ M0	44	44
▪ M1	32	32
Recurrence		
▪ yes	22	22
▪ no	54	54

The binary-logistic regression of independent variables, which yields the odds ratio (OR) as well as the associated p values and 95% CI for the parameters considered as results, took place for the multivariate data analysis. Since the Bonferroni correction for multiple testing was not performed, the results of the statistical investigations should be assessed in a purely explorative way. The significance level was set at 5%.

Results

Description of the sample

▶ **Table 3** shows the absolute and percentage distribution of the VT patients and corresponding controls in relation to the variables documented. Each group has 52 patients with breast cancer, 13 patients with cervical cancer and 11 patients with ovarian cancer and thus all in all, the data from 152 patients were analysed.

Obesity was present in 14.5% of cases and in 10.5% of controls, with a BMI of 35 kg/m^2 or more (median of the cases: 27.4 kg/m^2; median of the controls: 25.7 kg/m^2). The ECOG performance status before the start of therapy revealed values of 0 to 3 in the VT case group and the majority (81.6%) had a status of 0. In the control group, values of 0 to 1 were reached. Here as well, the majority (97.4%) of patients had a value of 0. In the patient files, nicotine consumption was noted in about one-fifth of the patients from the VT case group (21.1%) and 18.4% from the control group.

▶ **Table 3** Personal and treatment-related characteristics of the sample.

Characteristics of the sample	VT case group (n = 76) Number (%)	Control group (n = 76) Number (%)	p value
Tumour location			
Breast	52 (68.4)	52 (68.4)	
Cervix	13 (17.1)	13 (17.1)	
Ovary	11 (14.5)	11 (14.5)	
Age during observation period			
< 65 years	56 (73.7)	56 (73.7)	
≥ 65 years	20 (26.3)	20 (26.3)	
BMI			0.462[1]
< 35 kg/m^2	65 (85.5)	68 (89.5)	
≥ 35 kg/m^2	11 (14.5)	8 (10.5)	
ECOG performance status prior to therapy			
▪ 0	62 (81.6)	74 (97.4)	
▪ 1	9 (11.8)	2 (2.6)	
▪ 2	4 (5.3)	0	
▪ 3	1 (1.3)	0	
▪ 4	0	0	
Nicotine abuse	16 (21.1)	14 (18.4)	0.684[1]
Laboratory values			
Platelet count ≥ 350 × 10^9/L	26 (34.7)	16 (21.1)	0.062[1]
White blood cell count > 11 × 10^9/L	7 (9.3)	5 (6.6)	0.532[1]
Haemoglobin level < 100 g/L	3 (4)	7 (9.2)	0.226[1]
Secondary diagnoses (yes/no)	40 (52.6)	36 (47.4)	0.516[1]
Arterial hypertension	30 (39.5)	33 (43.4)	
Diabetes mellitus type 2	9 (11.8)	6 (7.9)	
Hypercholesterolaemia	6 (7.9)	5 (6.6)	
Coronary heart disease	4 (5.3)	1 (1.3)	
Varicosis	2 (2.6)	1 (1.3)	
Arterial occlusive disease	2 (2.6)	0	
Dilated cardiomyopathy	0	2 (2.6)	
Factor V Leiden	2 (2.6)	0	
Von Willebrand syndrome	1 (1.3)	0	
Thrombocythemia	1 (1.3)	0	
Surgeries			
In the 6 months prior to thrombosis (cases) or in the 4 weeks before and during chemotherapy (controls)	62 (81.6)	32 (42.1)	< 0.001[1]
Number of surgeries			
▪ 0	14 (18.4)	44 (57.9)	
▪ 1	28 (36.8)	29 (38.2)	
▪ 2	23 (30.3)	3 (3.9)	
▪ 3	10 (13.2)	0	
▪ 4	1 (1.3)	0	
Presence of a port system	51 (67.1)	38 (50)	0.032[1]
Cytostatic chemotherapy			
Neoadjuvant	4 (5.3)	4 (5.3)	
Adjuvant	40 (52.6)	40 (52.6)	
Palliative	32 (42.1)	32 (42.1)	

Continued next page

▶ **Table 3** Personal and treatment-related characteristics of the sample. *(Continued)*

Characteristics of the sample	VT case group (n = 76) Number (%)	Control group (n = 76) Number (%)	p value
Radiation			
At the same time as chemotherapy	4 (5.3)	5 (6.6)	
Administration of packed red cells	16 (21.1)	15 (19.7)	0.840[1]
Erythropoietin administration	15 (19.7)	20 (26.3)	0.226[1]
G-CSF application	20 (26.3)	18 (23.7)	0.708[1]
Hospitalisation			
In the 3 weeks prior to thrombosis (cases) or during chemotherapy (controls)	39 (51.3)	38 (50)	0.871[1]
Inpatient thrombosis prophylaxis	29 (74.4)	36 (94.7)	0.014[1]
Died	29 (38.2)	14 (18.4)	

[1] χ^2 test

Laboratory values

Laboratory values of the VT patients were documented before the start of the line of chemotherapy during which the VT occurred. In the case of the controls, the laboratory values before the start of chemotherapy which is to be equated with the line of therapy of the corresponding case were considered. At this point in time, 34.7% of the VT patients and 21.1% of the controls had platelet counts of 350×10^9/l or higher (median of the cases: 306×10^9/l; median of the controls: 292×10^9/l). Elevated white blood cell counts over 11×10^9/l were seen in 9.3% of cases and 6.6% of controls (median of the cases: 7.8×10^9/l; median of the controls: 6.9×10^9/l). An Hb below a level of 100 g/l was recorded in 4% of the VT cases and 9.2% of the controls (mean of the cases: 122.3 g/l, standard deviation of the cases: 14.0 g/l; mean of the controls: 125.1 g/l, standard deviation of the controls: 16.6 g/l). There were no laboratory values for one patient from the case group.

Secondary diagnoses

The most common secondary diagnosis in both groups was arterial hypertension, followed by type 2 diabetes mellitus and hypercholesterolaemia. Four patients from the VT case group and one patient from the control group had coronary heart disease as a previous illness. Varicose veins were previously known in only two patients from the case group and one patient from the control group. The rarer secondary diagnoses included peripheral arterial occlusive disease and dilated cardiomyopathy. One patient from the VT case group was the only patient with factor V Leiden and Von Willebrand syndrome as well as thrombocythemia.

Death and surgery

During the observation period, 38.2% (n = 29) of the patients in the VT case group died. Among the controls, 18.4% (n = 14) were no longer alive. More than three-quarters of the VT cases underwent surgery in the corresponding time period, whereas fewer than half of the controls underwent a surgical intervention. The number of surgeries among the VT cases ranged from 0 to 4 and, by contrast, among the controls, it ranged from 0 to 2. About 45% of the VT patients underwent 2 or more surgeries. Among the controls, this figure was only about 4%.

Oncological and supportive therapy

Most chemotherapy was administered adjuvantly in the VT cases (n = 38; 50%) as well as in the controls (n = 40; 52.6%). Chemotherapy was performed palliatively in 42.1% of the cases (n = 32) and controls (n = 32) in each case. Four patients in the VT group and also in the control group received neoadjuvant therapy. Four patients from the VT case group and 5 patients from the control group with carcinoma of the cervix received radiation of the tumour area at the same time as chemotherapy. A port system was present in 67.1% of the VT cases at the time of the thrombosis; a catheter system of this type had been implanted in 50% of the controls. Within the scope of cytostatic therapy and the adverse effects often associated with it, 21.1% of the VT cases and 19.7% of the controls required the administration of packed red cells. Erythropoietin was administered in 19.7% of the VT cases and 26.3% of the controls. Granulocyte colony-stimulating factors (G-CSF) were administered to about one-quarter of all patients. In addition, about half of the patients required an inpatient stay of ≥ 1 night. The inpatient hospitalisation in the 3 weeks prior to VT was considered. The reasons for the inpatient admission were varied, for example, due to infection, febrile neutropenia, for packed red cell transfusion in the case of anaemia, for radiochemotherapy (if anaesthesia required or in the case of low-dose radiochemotherapy for several days in a row), for cyclophosphamide administration as part of dose-dense ETC therapy, for a deterioration in the overall condition, subileus symptoms. The timing and frequency of the inpatient admissions also varies accordingly. There was no breakdown of why the patient was hospitalised.

Of the hospitalised patients, about three-quarters of the VT case group and nearly all patients in the control group received inpatient antithrombotic prophylaxis.

Risk scores

The point value of the Khorana score can be calculated from the parameters recorded (▶ **Table 4**). Outpatient prophylactic anticoagulation is recommended starting at a point value of ≥ 3. The score achieves values from 0 to 2 in over 90 % of the patients from the VT case group and approximately 90 % of the control patients. The highest possible point value of 5 is not reached by any patient. If the variables of the Protecht score are included, this yields values of 3 or more in about 21 % of the VT cases and in about 17 % of the controls. A point value of 6 or 7 cannot be assigned to any patient.

Analysis of the risk factors for chemotherapy-associated thrombosis

The p values of the χ^2 test are listed in ▶ **Table 3**.

The statistical data analysis demonstrated significant group differences in the χ^2 test for the presence of a port system (p value: 0.032) and for the administration of inpatient thrombosis prophylaxis (p value: 0.014). With a p value of 0.532 in the case of leukocytosis, there is indeed no relevant group difference. However, the Mann-Whitney-U test which is not listed in the table and which assesses the continuous variable "white blood cell counts" yields a significant p value of 0.018 (mean rank 84.5 VT case group; 67.6 control group). The most significant group difference was seen with regard to surgeries performed. For this variable, there were significant differences in the χ^2 test (p value: < 0.001) as well as in the t test with regard to the number of surgeries (p value < 0.001; 95 % confidence interval − 1.22 to − 0.7). Moreover, surgical interventions can be classified in the multivariate analysis as an independent risk factor (binary logistic regression analysis: p value 0.001, OR: 32.8). The results from the binary-logistic regression are shown in ▶ **Table 5**. There were no statistical significances for all other variables investigated, such as BMI, nicotine abuse, thrombocythemia, anaemia, secondary diagnoses, hospitalisation and radiation. In addition, no significant group differences could be determined in the Khorana and Protecht score.

▶ **Table 4** Distribution of the point values in the Khorana and Protecht risk scores.

Risk scores	VT case group (n = 76) Number (%)	Control group (n = 76) Number (%)	p values
Khorana score			0.415[1]
▪ 0	19 (25)	28 (36.8)	
▪ 1	35 (46.1)	29 (38.2)	
▪ 2	16 (21.1)	10 (13.2)	
▪ 3	5 (6.5)	7 (9.2)	
▪ 4	1 (1.3)	2 (2.6)	
▪ 5	0	0	
Protecht score			0.536[1]
▪ 0	17 (22.4)	27 (35.5)	
▪ 1	28 (36.8)	27 (35.5)	
▪ 2	15 (19.7)	9 (11.8)	
▪ 3	13 (17.1)	6 (7.9)	
▪ 4	2 (2.6)	4 (5.3)	
▪ 5	1 (1.3)	3 (3.9)	
▪ 6	0	0	
▪ 7	0	0	

[1] χ^2 test

▶ **Table 5** Influence of the variables on the appearance of a VT – results from the multivariate, binary-logistic regression analysis.

Variables	p value	OR	95 % CI	
			from	to
BMI ≥ 35 kg/m²	0.267	3.433	0.390	30.261
Laboratory values (continuous variables)				
Platelet count	0.704	1.001	0.994	1.009
White blood cell count	0.429	1.148	0.816	1.614
Haemoglobin	0.082	0.637	0.384	1.058
Secondary diagnoses (yes/no)	0.421	0.556	0.133	2.324
Nicotine abuse (yes/no)	0.102	5.948	0.703	50.366
Surgeries (yes/no)	0.001	32.750	4.233	253.400
Presence of a port system (yes/no)	0.152	0.306	0.060	1.546
Administration of packed red cells (yes/no)	0.898	1.099	0.258	4.676
GCSF administration (yes/no)	0.947	0.940	0.152	5.826
Inpatient thrombosis prophylaxis (yes/no)	0.220	0.228	0.021	2.426
Risk scores				
Points in the Khorana score	0.334	0.368	0.049	2.791
Points in the Protecht score	0.874	0.905	0.263	3.112

Discussion

From the retrospective case-control study on 152 patients who underwent oncological treatment between 2005 and 2013 at the Department of Gynaecology of the Mainz University Medical Centre, the link of the risk of thrombosis with the use of inpatient thrombosis prophylaxis, leukocytosis and the presence of a port system was significant. Performing surgical interventions turned out to be an independent risk factor for the development of venous thromboses.

For other variables investigated, no statistical difference between the two groups could be identified, no more than as for the values in the Khorana and Protecht score.

Hospitalisation as a risk factor

The risk of a venous thrombosis increases due to the malignant disease itself and also due to the associated cytostatic treatment [4, 5]. In this investigation – in contrast to other studies [13, 14] – no clear influence of hospitalisation during chemotherapy on the development of a VT could be demonstrated. However, the results of this study suggest that patients who did not receive any prophylaxis during the inpatient admission suffered a VT within 3 weeks far more frequently. Both groups involve a large number of hospitalisations during the observation period (VT case group: 39; control group: 38 hospitalisations). This group difference may have influenced the overall result of the investigation. This investigation included patients from 2005 to 2013. At this time, inpatient anticoagulation was at the discretion of the attending physician and also postoperatively, anticoagulation was only individually prescribed.

According to the recommendations of the American Society of Clinical Oncology and the AWMF, all oncology patients have received inpatient prophylactic anticoagulation for about the past 3 years in our facility, whereas the use of compression stockings is considered to be of secondary importance. If there are signs of bleeding or platelets < 30 000/mm^3, no anticoagulation is administered as a rule. In addition, mobilisation on the ward is an essential component of the inpatient prophylaxis.

Postoperatively patients with breast cancer received postoperative prophylaxis for 7 days on an outpatient basis using low-molecular-weight heparin. In the case of more major intraabdominal interventions, anticoagulation was also prescribed postoperatively after discharge for 4 weeks. It should be noted that this internal guideline has been rigorously implemented for only about 3 years with awareness of the topic and in accordance with the international recommendations [9, 15].

An important point to be investigated for a prospective, multicentre follow-up study would be the reason for the hospitalisation which could also give indications of an increased risk of thrombosis.

Leukocytosis as a risk factor

In our investigation, no significant link between leukocytosis > 11 × 10^9/L and the development of a VT could be found. Nevertheless, the Mann-Whitney-U test shows that significantly higher white blood cell values prior to the start of chemotherapy were present in the VT case group. There does not appear to be a link between elevated white blood cell counts and a VT in patients without a malignancy. In a study on 20 000 healthy subjects, neither elevated white blood cell counts nor other inflammatory markers could be associated with VT [16].

Similarly as in our investigation, Connolly et al. found the highest white blood cell counts prior to cytostatic therapy in patients who subsequently developed a VT. Likewise mortality was the highest in this group, at 20 % [17]. In another current study, the presence of leukocytosis of > 11 × 10^9/L was shown to be an independent risk factor [18]. The processes and interactions between white blood cells and platelets which cause thrombosis are still unclear. Connolly et al. suspected that leukocytosis reflects either a more aggressive malignant process and comorbidities such as inflammatory diseases, or is directly responsible for disease progression and the carcinoma-associated thrombosis [17]. It is also described that the tissue factor as well as the VEGF are increased many times over in the white blood cells of tumour patients [19, 20]. In patients with pancreatic cancer, a link between elevated white blood cell levels and tissue factor plasma activity was able to be demonstrated [21]. As a result, the authors suspect direct involvement of the white blood cells in the thrombus formation [17]. Another explanation is P-selectin, a protein expressed on the surface of activated platelets which is involved in the interaction between white blood cells and platelets and is considered to be a biomarker for the elevated risk of tumour-associated thrombosis [22]. In addition, white blood cells secrete cytotoxic mediators, such as tumour necrosis factor α, interleukin-1 and interferons which contribute to the body's own defences and the destruction of tumour cells [23]. The products secreted by the white blood cells may, however, also create an optimal environment for tumour growth, thrombus formation, metastasis and chemotherapy resistance [24, 25].

In our investigation, significantly higher white blood cell counts were seen before the start of therapy in patients with thrombosis. However, in the binary-logistic regression analysis, this trend was put into perspective with the inclusion of several potential risk factors.

Port catheter as a risk factor

In previous investigations of other research groups, it was able to be shown that there is an increased risk of thrombosis if central venous catheters or port systems are present. In the study of De Cicco et al., thromboses occurred in 66 % of study participants [26], whereas Cortelezzi and colleges were able to establish a rate of 12 % [27]. It should be borne in mind that in both studies, no purely gynaecological patient collective, rather a mixed or haemato-oncological patient collective was investigated and patients with central venous catheters (CVCs) were included. Since in the case of ports and also CVCs, an endothelial lesion as well as an intravenous foreign body is present through which there is also a risk of infection during piercing of the port or in the case of an indwelling tube, the studies were used despite the methodological differences.

In another multicentre, prospective study on 3032 patients, the risk factors for the occurrence of a catheter-associated (at the upper extremity in the area surrounding the port) thrombosis differ from those for the occurrence of a non-catheter-associated

thrombosis [18]: An independent risk factor for the port-associated VTs was the implantation of the port in the cephalic vein. In the case of the non-port-associated VTs, the presence of anaemia (Hb value < 10 g/dl) as well as leukocytosis (> 11×10^9/L), among others, turned out to be independent risk factors [18]. In our study, a strikingly strong correlation between the presence of a port and the occurrence of vascular occlusion was shown in the χ^2 test, whereby the exact location of the VT (e.g. leg veins or arm veins) was not taken into account in the investigation. In further prospective investigations on gynaecological tumour patients, the exact location of the VT should be taken into account in the statistical analysis.

Surgery as a risk factor

Along with the implanted central port catheters, surgery also leads to localised endothelial lesions and is classified in many places as an independent risk factor [28–30]. According to a meta-analysis by Prandoni et al. [31], there is a postoperative VT in 20% of patients without a neoplasm [4], whereas the risk increases to 37% in the case of tumour patients [31]. In their study on 625 patients, the research group working with Heit was able to declare surgical procedures with subsequent hospitalisation as the greatest risk factor, with a probability of thrombosis nearly 22 times as high [4].

The present study was able to prove a strong correlation between surgery and the thrombotic event. There were significant differences between the patients who suffered a VT and patients without a VT with regard to performing surgery in general as well as for the number of surgeries. According to the logistic regression analysis, the likelihood of suffering a VT greatly increases following prior surgery in this collective of tumour patients. However, to interpret these results, it should be borne in mind that, in both patient groups, the observation periods had to be adapted to ensure comparability. In the case of patients who suffered a VT, the surgeries in the 6 months prior to the VT were documented. In the case of the patients who did not suffer any vascular occlusion, the surgeries were documented in the 4 weeks before and during the corresponding chemotherapy. Since the cytostatic therapy generally extends over several months, the observation period should nearly coincide for both groups. Nonetheless, there could also have been group differences based on the retrospective design. The OR calculated at 32.75 provides only limited information due to the small number of cases (152). It should further be noted that the type of surgery (laparotomy, laparoscopy, mastectomy, port implantation, etc.) can have different effects on the VT risk. However in this study, no subgroup analysis was performed with regard to the “surgeries” variable. With a p value of 0.001, the impact of surgeries on the occurrence of a VT is very pronounced overall in the present investigation. It is clear that surgeries of any type should be classified as a relevant risk factor, even in a purely gynaecological patient group.

Further potential risk factors

The other variables investigated (▶ **Table 3**) do not give any indications of an increased risk of thrombosis, although a correlation is known from previous studies. Elevated platelet counts [32], obesity [4, 33–35], nicotine abuse [36] and the administration of granulocyte growth factors [37](34) have already been described as being the cause of venous vascular occlusions. The results are not clear with regard to the presence of anaemia [37, 38]. In addition, no correlation between elevated values in the Khorana and Protecht score and thrombosis can be seen in the present study.

The reasons for the differing results may lie in the relatively small patient collective as well as the retrospective study design. In addition, this study is the only investigation to date which analyses a purely female sample with breast, ovarian or cervical cancer. Surgeries in the past 6 months were the only independent risk factor for the occurrence of VTs in patients on cytostatic therapy. The resultant statistically relevant group difference can be interpreted as an interfering factor which can distort the evaluation of the other potential risk factors.

The data from multiple other studies show that the mortality in tumour patients greatly increases after the occurrence of thromboses [1, 39, 40]. Accordingly, an objective of medical intervention should be the prevention of thrombosis – both in a direct way through medication-based antithrombotic measures as well as indirectly through a possible decrease in tumour progression [41–44].

One new, promising approach is the TiC-Onko score which includes clinical markers such as BMI, family predisposition and tumour location as well as genetic markers in order to analyse the risk of thrombosis [45]. This score should be evaluated in further investigations on gynaecological oncology collectives.

Recommendation for VT prophylaxis

According to the current S3 guideline, prophylactic anticoagulation in the inpatient setting should be urgently recommended postoperatively and also during hospitalisation on chemotherapy after ruling out contraindications. Patients with major intraabdominal oncological interventions should receive prolonged VT prophylaxis for 4 weeks. A general recommendation for purely prophylactic anticoagulation of outpatients on chemotherapy is currently not expressed within the scope of gynaecological oncology tumour diseases [15].

Conclusion

In gynaecological oncology patients, there is a clear link between a VT during chemotherapy and a lack of inpatient thrombosis prophylaxis, the presence of a port system and leukocytosis. The influence of previous surgeries on the risk of thrombosis in patients with chemotherapy is clear in this purely gynaecological collective. To validate risk models, prospective studies on gynaecological oncology patients on chemotherapy which include the type of surgeries performed as well as the VT location in the risk assessment should be initiated.

To minimise patient mortality as a result of a venous thrombosis, additional investigations must prospectively examine the benefit of prophylactic anticoagulation in the outpatient setting in patients at risk.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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