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The impact of hereditary thrombophilia on the incidence of postoperative venous thromboembolism in colorectal cancer patients: a prospective cohort study

Hereditary thrombophilia and VTE in colorectal cancer surgery

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Summary
Background Hereditary thrombophilia may play an important role in the rate of postoperative venous thromboembolism (VTE). We focused on the impact of hereditary thrombophilia on VTE incidence in colorectal cancer surgery patients within a 1-year postoperative period.
Methods Preoperatively, identifying of colorectal cancer patients with thrombotic mutations (PTM+) and without thrombotic mutations (PTM–) was performed by screening of factor V Leiden (FVL) and prothrombin G20210A mutation. Within prophylactic period (0–28 days postoperatively), coagulation markers (platelets, fibrinogen, D-dimer) were measured and symptomatic VTE was observed. Within post-prophylactic period (2–12 months after surgery), symptomatic VTE was observed.
Results In all, 202 patients were assessed and hereditary thrombophilia was detected in 9.9% (FVL 8.4%; prothrombin G20210A mutation 1.5%). In the prophylactic period, VTE incidence in PTM+ and PTM– was 0.0% and 1.6%, respectively ($p=0.730$). Levels of coagulation markers were comparable in both patient cohorts within 28 days postoperatively. In the post-prophylactic period, VTE incidence in PTM+ and PTM– was 15.0% and 5.5%, respectively ($p=0.125$), and detailed incidence of deep vein thrombosis (DVT) in PTM+ and PTM– was 15.0% and 3.3%, respectively ($p=0.048$). We observed significantly increased incidence of lower extremity DVT in such patients with FVL (17.6%).
Conclusion The standard regimen of extended-duration VTE prophylaxis is adequate for colorectal cancer patients with thrombotic mutations and more intensified VTE prophylaxis within the 28-day postoperative period is not justified. However, the ongoing postoperative pharmacologic prophylaxis (>28 days) should be considered in patients with hereditary thrombophilia, especially with FVL.

Keywords Factor V Leiden · Prothrombin mutation · Colorectal neoplasms · Venous thrombosis · Risk assessment

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Background

Colorectal cancer surgery is associated with an increased risk of postoperative venous thromboembolism (VTE). We can identify many risk factors that determine the overall risk of postoperative VTE. These risk factors are classified as patient related, cancer related, and surgery related. Hereditary thrombophilia

is considered as a significant patient-related risk factor. Factor V Leiden (FVL) and prothrombin G20210A mutation are the two most common genetic polymorphisms that predispose to VTE [1, 2]. The reported prevalence rates of FVL and the prothrombin G20210A mutation in the Czech population are 4.5% and 1.3%, respectively [3]. Outside of the healthy population, the risk of VTE is approximately 12- to 17-fold increased for patients with cancer who have the factor V Leiden or the prothrombin G20210A mutation [4]. In the Vienna Cancer and Thrombosis Study, a 2-fold increased risk of VTE was revealed in cancer patients with FVL compared to cancer patients without thrombotic mutation, the hazard ratio was 2.0 (95% confidence interval 1.0–4.0) [5]. Despite this fact, there is no evidence supporting a routine preoperative screening of hereditary thrombophilia in colorectal cancer patients. Similarly, there are no data for altering postoperative VTE prophylaxis in colorectal cancer patients with hereditary thrombophilia. So, standard regimen of routine 28-day postoperative pharmacologic prophylaxis with administration of low-molecular-weight heparin (LMWH) is used for colorectal cancer patients with thrombotic mutations. With regard to the lack of data, we focused on assessment of hypercoagulable status during 28-day postoperative period and analysis of 1-year postoperative VTE incidence in colorectal cancer patients with hereditary thrombophilia.

Methods

The study was performed as a prospective non-randomized study from June 2012 to March 2015. Altogether, 202 consecutive patients undergoing elective surgery for colorectal cancer were enrolled in our study. Inclusion criteria: elective surgery for colorectal cancer. Exclusion criteria: emergency surgery for complication of colorectal cancer, age <18 or >90 years, VTE in previous 6 months. Basic clinical parameters—gender, age, height, weight, body mass index (BMI)—were noted in every patient. A new adaptation of the Caprini risk assessment model was used to assess the VTE risk in every patient preoperatively [6]. Screening for hereditary thrombophilia, including genetic examination of FVL mutation and prothrombin G20210A mutation, was carried out in all patients before surgery. VTE prophylaxis comprised the use of elastic stockings and 28-days administration of LMWH (nadroparin calcium 0.3 ml/2850 IU anti-Xa s.c. per day) according to 9th ACCP recommendation. Postoperatively, the coagulation status was assayed by detection of platelet count (PLT), fibrinogen (Fbg), and D-dimer. Coagulation markers were measured within prophylactic period as scheduled: preoperatively, 1–3 h after surgery, on 1st postoperative day, on 4–5th postoperative day, on 7–10th postoperative day, and on 28–30th postoperative day. Symptomatic VTE was observed in 1-year postoperative follow-up, in the prophylactic period (0–28 days after surgery), and in the post-prophylactic period (2–12 months after surgery) separately. Wells' criteria were used for clinical diagnosis of deep vein thrombosis (DVT) [7]. Patients with a Wells score of >2 points warranted ultrasound examination of legs to verify deep vein thrombosis. When clinical suspicion of pulmonary embolism (PE) was observed, a computed tomography angiography was performed. VTE incidence and coagulation markers were compared between the cohort of patients with thrombotic mutation and the cohort of patients without hereditary thrombophilia.

Statistical analysis

Basic descriptive statistics within the two groups of colorectal cancer patients (with/without hereditary thrombophilia) were computed for all variables, which were subsequently tested for normality using Shapiro–Wilk tests. Differences in continuous variables (age, height, weight, BMI, Caprini score, length of surgery, coagulation markers: PLT, Fbg, D-dimer) between the two groups were examined by the Mann–Whitney test. Differences in categorical variables (gender, tumor stage, type of surgery, mortality, incidence of VTE: deep vein thrombosis, pulmonary embolism) were evaluated using odds ratio (OR) with 95% confidence interval (CI), chi-square test, or Fisher's exact test, where appropriate. For all statistical evaluations, p-values below 0.05 were considered to be statistically significant. Statistical analysis was performed using SPSS version 22 (IBM Corp., Armonk, NY, USA; [8]).

Results

Characteristics of study population

We assessed 202 patients with colorectal cancer. All these patients were classified as high risk for VTE according to the new adaptation of the Caprini risk assessment model (>5 points). Most of the patients (185/202; 91.6%) underwent radical surgery whereas a minor cohort of the patients (17/202; 8.4%) underwent palliative surgery. The surgical procedures performed on colorectal cancer were right hemicolectomy (n=55), resection of transverse colon (n=9), left hemicolectomy (n=16), sigmoid colectomy (n=32), low anterior resection (n=69), abdominoperineal resection (n=12), subtotal colectomy (n=6), and others (n=3). Open surgery was performed in 177 patients (87.6%) while laparoscopic surgery was performed in 25 patients (12.4%). The postoperative 28-day mortality rate was 5.9% (12 patients) and overall 1-year postoperative mortality rate was 16.3% (33 patients).

Hereditary thrombophilia was detected in 20 patients (9.9%). Heterozygous FVL mutation in 17 patients (8.4%) and heterozygous prothrombin G20210A mutation in 3 patients (1.5%) were proved. Homozy-

Table 1 Demographics and clinical characteristics of study patients

Characteristics	Colorectal cancer patients		*p*-value
	Hereditary thrombophilia neg	Hereditary thrombophilia pos	
Number of patients	182	20	–
Gender female/male	84/98	5/15	0.070
Age (years) mean (SD)	68.2 (10.0)	62.4 (12.6)	0.081
Height (cm) mean (SD)	170.6 (8.7)	173.6 (8.1)	0.106
Weight (kg) mean (SD)	81.4 (16.9)	79.6 (18.0)	0.518
BMI (kg/m^2) mean (SD)	27.9 (4.9)	26.3 (5.2)	0.082
Caprini score (points) mean (SD)	10.2 (1.7)	9.9 (1.7)	0.614
Stage/TNM (number)			
Stage Tis	12 (6.6%)	2 (10.0%)	0.781
Stage I	32 (17.6%)	5 (25.0%)	
Stage II	79 (43.4%)	7 (35.0%)	
Stage III	40 (22.0%)	5 (25.0%)	
Stage IV	19 (10.4%)	1 (5.0%)	
Surgery (number)			
Radical surgery	166 (91.2%)	19 (95.0%)	0.562
Palliative surgery	16 (8.8%)	1 (5.0%)	
Length of surgery (min.) mean (SD)	150.9 (61.6)	166.6 (74.8)	0.540
Mortality (number)			
Prophylactic period	10 (5.5%)	2 (10.0%)	0.418
Post-prophylactic period	19 (10.4%)	2 (10.0%)	0.951

BMI body mass index, *SD* standard deviation, *Tis* tumor in situ, *TNM* TNM classification 2011

gous genotype of thrombotic mutations as well as carriers of both FVL and prothrombin G20210A mutations were not observed in our cohort of patients.

Demographics and the clinical characteristics of patients with thrombotic mutations compared to patients without hereditary thrombophilia are reported in Table 1. The mean Caprini risk scores in both groups of patients were comparable (9.90, 10.24; $p=0.614$), as were other factors associated with risk of VTE (age, BMI, stage of malignancy, type of surgery, length of surgery, etc.).

Coagulation markers

Coagulation status was not assayed in all included 202 patients within the whole prophylactic period. Incomplete monitoring of coagulation markers in 31 patients was caused by early (<28 days) mortality ($n=12$), patient refusal to permit the taking of blood samples ($n=17$), and damage of blood samples in pre-analytic phase ($n=2$). Preoperatively, as well as during the prophylactic period, there were not any statistically significant differences in levels of coagulation markers, including PLT, Fbg, and D-dimer, in cohort of patients with thrombotic mutations compared to cohort of patients without hereditary thrombophilia (Table 2).

Venous thromboembolism

Incidence of VTE was assessed in a 202-patient study group. We observed 16 clinically apparent thrombotic events during the 1-year postoperative period so that overall 1-year incidence of VTE in all colorectal cancer patients was 7.9% (16/202). In the prophylactic period, VTE incidence was 1.5% (PE incidence 1.5%; DVT incidence 0.0%). In the post-prophylactic period, VTE incidence was 6.4% (PE incidence 2.0%; DVT incidence 4.4%). Detailed incidence rate of VTE in the early post-prophylactic period (2–6 months after surgery) and in the late post-prophylactic period (7–12 months after surgery) is reported in Table 3. In the early post-prophylactic period, we observed an increase of VTE incidence (5.4%). To investigate the risk for development of VTE in colorectal cancer patients after surgery, we present the odds ratio (OR) for every single postoperative period (Table 3).

Patients with thrombotic mutations had higher overall 1-year incidence of thrombotic events compared to patients without hereditary thrombophilia (15.0%, 7.1%, respectively); however, the difference wasn't statistically significant ($p=0.217$). In the prophylactic period, VTE incidence in cohort of patients with thrombotic mutations was comparable with the incidence of these thrombotic events in cohort of patients without hereditary thrombophilia (Table 4). In the post-prophylactic period, the cumulative VTE incidence was assessed due to the time-independent and constant prothrombotic effect of thrombotic mutations. Over the post-prophylactic period, we observed increased VTE incidence in patients with thrombotic mutations compared to patients without hereditary thrombophilia. However, the statistical

Table 2 Coagulation markers in patients with and without thrombotic mutations

Markers of coagulation		Colorectal cancer patients				*p* value
		Hereditary thrombophilia neg		Hereditary thrombophilia pos		
		Pts	Mean (SD)	Pts	Mean (SD)	
PLT (10^9/l)	PLT[a]	182	273.08 (97.44)	20	247.50 (82.56)	0.329
	PLT[b]	181	262.68 (100.31)	20	241.80 (77.69)	0.448
	PLT[c]	180	223.71 (81.11)	20	227.00 (84.60)	0.935
	PLT[d]	176	264.25 (90.71)	19	264.63 (92.15)	0.740
	PLT[e]	169	342.49 (113.08)	19	353.16 (124.52)	0.376
	PLT[f]	156	302.86 (116.61)	15	316.87 (130.97)	0.658
Fbg (g/l)	Fbg[a]	181	4.60 (1.00)	20	4.68 (1.02)	0.583
	Fbg[b]	181	3.59 (0.96)	20	3.56 (1.10)	0.931
	Fbg[c]	180	4.94 (0.90)	20	4.92 (1.10)	0.835
	Fbg[d]	176	6.82 (1.77)	19	6.54 (1.46)	0.528
	Fbg[e]	169	6.03 (1.50)	19	6.39 (1.69)	0.362
	Fbg[f]	156	4.76 (1.24)	15	4.64 (1.45)	0.430
D-dimer (µg/l)	D-dimer[a]	181	327.46 (577.77)	20	350.10 (313.84)	0.143
	D-dimer[b]	181	832.14 (754.91)	20	814.65 (586.89)	0.394
	D-dimer[c]	180	777.91 (877.30)	20	928.00 (1146.17)	0.576
	D-dimer[d]	176	1134.46 (1076.83)	19	1115.95 (1211.94)	0.836
	D-dimer[e]	169	1246.14 (1043.58)	19	1662.84 (1279.46)	0.143
	D-dimer[f]	156	419.70 (465.35)	15	578.80 (570.94)	0.061

Fbg fibrinogen, *PLT* platelets count, *Pts.* number of patients, *SD* standard deviation
Blood samples:
[a]preoperatively
[b]1–3 h after surgery
[c]on 1st postoperative day
[d]on 4–5th postoperative day
[e]on 7–10th postoperative day
[f]on 28–30th postoperative day

Table 3 Postoperative incidence of VTE in colorectal cancer patients

	Postoperative period			OR (95% confidence interval)		
	Prophylactic period	Post-prophylactic period				
	(0–28 days; 1)	Early (2–6 m; 2)	Late (7–12 m; 3)	Period 1 vs. 2	Period 2 vs. 3	Period 1 vs. 3
	Pts. (%)	Pts. (%)	Pts. (%)			
VTE	3 (1.5%)	11 (5.4%)	2 (1.0%)	3.82* (1.05–13.91)	0.17* (0.04–0.79)	0.66 (0.11–4.01)
DVT	0 (0.0%)	8 (3.9%)	1 (0.5%)	–[a]	0.12* (0.02–0.97)	–[a]
PE	3 (1.5%)	3 (1.5%)	1 (0.5%)	1.00 (0.20–5.01)	0.33 (0.03–3.20)	0.33 (0.03–3.20)

OR odds ratio, *Pts.* number of patients, *prophylactic period (1)* 0–28th day, *early post-prophylactic period (2)* 2–6 months, *late post-prophylactic period (3)* 7–12 months, *VTE* venous thromboembolism
[a]impossible to compute given the 0 in period 1
*statistically significant with $p < 0.05$

analysis revealed significant difference just for DVT incidence (Table 4).

With regard to VTE location, out of 16 patients, 9 patients (56.2%) had DVT and 7 patients (43.8%) had PE. Detailed locations of venous thromboembolism in patients with FVL and prothrombin G20210A mutation, and in patients without hereditary thrombophilia are reported in Table 5. DVT was a heterogeneous group of thrombotic events that encompassed the jugular vein thrombosis ($n = 4$) and lower extremity DVT ($n = 5$). Lower extremity DVT was classified as more proximal location of DVT, including thrombosis of the iliac-femoral vein ($n = 2$), and more distal location of DVT, including thrombosis of the femoral-popliteal calf vein ($n = 3$). We assessed the incidence of jugular vein thrombosis and lower extremity DVT separately. Detailed statistical analysis revealed non-significant differences in the incidence of jugular vein thrombosis between patients with FVL (0/17; 0%) and patients without hereditary thrombophilia (4/182; 2.2%; $p = 0.537$). However, a statistically significant increased incidence of lower extremity DVT was proven in the cohort of patients with FVL (3/17; 17.6%) compared to the cohort of patients without hereditary thrombophilia (2/182; 1.1%; $p < 0.001$). The same detailed statistical analysis of lower extremity DVT

Table 4 VTE incidence in colorectal cancer patients in the prophylactic and the post-prophylactic period

Venous thromboembolism	Colorectal cancer patients		*p*-value
	Hereditary thrombophilia neg. (182 patients)	Hereditary thrombophilia pos. (20 patients)	
Cumulative 1-year period			
VTE total (number)	13 (7.1%)	3 (15.0%)	0.217
Prophylactic period			
VTE (number)	3 (1.6%)	0 (0.0%)	0.730
PE	3 (1.6%)	0 (0.0%)	0.730
DVT	0 (0.0%)	0 (0.0%)	–[a]
Post-prophylactic period			
VTE (number)	10 (5.5%)	3 (15.0%)	0.125
PE	4 (2.2%)	0 (0.0%)	0.657
DVT	6 (3.3%)	3 (15.0%)	*0.048*

DVT deep vein thrombosis, *PE* pulmonary embolism, *VTE* venous thromboembolism, *prophylactic period* 0–28th days after surgery, *post-prophylactic period* 2–12 months after surgery
[a]no statistics are computed because DVT is a constant

Table 5 Location of venous thromboembolism in patients with and without thrombotic mutations

Characteristics	Colorectal cancer patients		
	Prothrombin G20210A (heterozygote)	Factor V Leiden (heterozygote)	Without thrombophilia
Number of patients	3	17	182
VTE (number)	0	3	13
Type of VTE			
PE	0	0	7
Lower extremity DVT	0	3	2
More proximal location	0	1	1
More distal location	0	2	1
DVT of jugular vein	0	0	4

DVT deep vein thrombosis, *PE* pulmonary embolism, *VTE* venous thromboembolism

incidence and jugular vein thrombosis incidence in patients with prothrombin G20210A mutation wasn't performed due to a low number of patients.

Discussion

The reported cumulative incidence of postoperative VTE in colorectal cancer surgery ranges from 2.2 to 5.4% and varies depending on patient population, duration of follow-up, and the method of detecting and reporting venous thrombotic events [9–11]. The observed overall postoperative 1-year incidence of VTE (7.9%) in our colorectal cancer patients is in line with previous data. Incidence of FVL (8.4%) and incidence of prothrombin G20210A mutation (1.5%) in our study population corresponds to the prevalence of thrombotic mutations in the Czech population [3]. Considering the risk of VTE, attention should be given to genotype of thrombotic mutations as well. Heterozygous allele of FVL and prothrombin G20210A mutation increase the risk of VTE by 3- to 7-fold and by 2- to 3-fold, respectively. Homozygous allele of FVL increases the risk of VTE by 80-fold [12, 13].

It is well recognized that extended (4 weeks) pharmacologic prophylaxis with LMWH administration significantly reduces 28-day postoperative VTE incidence in colorectal cancer surgery [14–16]. Therefore, we focused on assessment of impact of hereditary thrombophilia on thrombotic event incidence within two different periods of 1-year postoperative follow up—the prophylactic period (28 days postoperatively) and the post-prophylactic period (2–12 months after surgery).

Within the 28-day pharmacologic prophylaxis period we observed low incidence of VTE in the cohort of patients with thrombotic mutations as well as in the cohort of patients without hereditary thrombophilia (0.0%, 1.6%; $p = 0.730$; Table 4). Inpatient and early post-discharge (up to 28 days) incidence of symptomatic VTE in patients who had thrombotic mutations was significantly reduced secondary to extended pharmacologic prophylaxis. Moreover, assessment of hypercoagulability by detection of coagulation markers during the 28-day period didn't reveal any difference between the cohort of patients with thrombotic mutation and the cohort of patients without hereditary thrombophilia (Table 2). We can conclude that 4 weeks standard regimen of pharmacologic prophylaxis effectively reduced the risk of VTE in all colorectal cancer patients, including patients with thrombotic mutations. Based on our data, 28-day pharmacologic prophylaxis with standard LMWH dosing may

be recommended for patients with hereditary thrombophilia. Intensified pharmacologic prophylaxis of VTE in colorectal cancer patients with thrombotic mutations is not justified in the prophylactic period.

It is well known that the highest risk of postoperative venous thromboembolism occurs during the first few weeks after cancer surgery and the increased risk of VTE lasts for longer than 4 weeks postoperatively. Sweetland et al. reported the highest risk of VTE in the first 6 weeks after cancer surgery, and the risk was lower but still substantially increased 7–12 weeks after surgery [17]. In accordance with previous data, we observed a significantly increased risk for development of VTE within the early post-prophylactic period (OR = 3.82). The increased incidence of VTE during the 2–6 month period after surgery was mainly associated with an increase of DVT incidence. In the late post-prophylactic period (7–12 months after surgery) a drop of VTE risk was verified (OR = 0.17). An increased risk of VTE that lasts a few months beyond the 28-day prophylactic period is probably complex and multifactorial in etiology. Hypercoagulability status may persist in the early post-prophylactic period due to the subsiding effect of surgery and postoperative complications, effect of postoperative chemotherapy, effect of permanent intravenous devices, etc. Some of these factors have a temporary effect. Hereditary thrombophilia has a constant effect on blood coagulation in the postoperative period; therefore, a cumulative incidence of thrombotic events during the whole post-prophylactic period was assessed. Based on our results from the post-prophylactic period, an increased incidence of PE wasn't observed in patients with thrombotic mutations. However, a significantly increased incidence of DVT was revealed in the cohort of patients with thrombotic mutations compared to the cohort of patients without hereditary thrombophilia within the post-prophylactic period (15.0%, 3.3%; $p = 0.048$).

Moreover, it should be mentioned that DVT encompassed two subgroups of venous thrombosis with a little different etiology—jugular vein DVT and lower extremity DVT. DVT of the jugular vein is associated with indwelling of the central vein catheter (CVC), whereas lower extremity DVT is not associated with CVC. Even if thrombotic mutation may be an important risk factor in the development of CVC-related jugular vein thrombosis, many other CVC characteristics determine the risk of thrombosis, such as the type and material of the CVC, the location of CVC insertion, the duration of stay of the CVC, etc. [18–20]. Therefore, the relevant statistical analysis of impact of hereditary thrombophilia on jugular vein thrombosis incidence would require assessment of CVC characteristics. Lower extremity DVT is not provoked by CVC, so hereditary thrombophilia may play a more important role in the incidence of such lower extremity DVT. Focused analysis of DVT has revealed a statistically significant increased incidence of lower extremity DVT in patients with FVL compared to patients without hereditary thrombophilia (17.6%, 1.1%; $p < 0.001$). Increased incidence of such lower extremity DVT in the cohort of patients with FVL is in line with the factor V Leiden paradox. This term (FVL paradox) is used to describe the different risk of DVT and PE in carriers of FVL [21, 22]. FVL mutation is associated with a higher rate of thrombotic involvement of a more distal vein in a lower extremity. FVL is only weakly associated with PE due to a less proximal location of DVT. However, a similar paradox in carriers of other thrombotic mutations was not documented. Most of our patients with hereditary thrombophilia were carriers of FVL (Table 5). Our results verify the increased incidence of lower extremity DVT in patients with FVL within the post-prophylactic period. Thus, our data support the preoperative testing of thrombotic mutations because the results of genetic testing could be used for better individual thrombotic risk assessment. Knowledge of hereditary thrombophilia status seems to be more important beyond the 28-day postoperative period because ongoing pharmacologic prophylaxis of VTE may be considered in patients with thrombotic mutations.

Screening of hereditary thrombophilia in asymptomatic patients should be considered only in certain high thrombotic risk situations and the utility of thrombophilia testing in clinical practice is still a matter of debate [23, 24]. The latest results from a systematic review of hereditary thrombophilia screening and cost-effectiveness analysis of high-risk patient groups, including the use of oral estrogen preparations, pregnancy, and major orthopedic surgery, didn't support universal screening in these high-risk conditions [25]. Cancer surgery is a significant high thrombotic risk situation; however, screening of hereditary thrombophilia in patients undergoing colorectal surgery has not yet been assessed. Based on our data, testing of hereditary thrombophilia may help to identify colorectal cancer patients with a long-lasting increased risk of DVT after cancer surgery. The utility of hereditary thrombophilia screening in patients undergoing colorectal cancer surgery should be verified by cost–benefit analysis. The benefit of ongoing pharmacologic prophylaxis in the reduction of DVT and risk of bleeding related to LMWH therapy has to be validated in large prospective randomized trials. Additionally, the length of ongoing pharmacologic prophylaxis should be determined based on robust data. As was mentioned above, postoperative hypercoagulability is multifactorial and complex in etiology. We assume that universal screening is not necessary and selective screening of hereditary thrombophilia in high-risk patients should be considered. Great attention should be given to how to identify patients with persistent increased hypercoagulability longer than 4 weeks after surgery. In these patients, the testing of thrombotic mutations may play an important role. First, a reliable and famil-

iar diagnostic tool (risk assessment scoring model, coagulation markers, etc.) has to be determined.

There are two main limitations to consider in our study. First limitation is a low number of patients with hereditary thrombophilia resulting in lower power of the VTE incidence testing in this group. At least 90–100 patients with hereditary thrombophilia would be necessary for a valid assessment of VTE (power of 0.7). It would mean enrolling approximately 1400 patients with colorectal cancer to the study, because the incidences of monitored heterozygous alleles of FVL and prothrombin G20210A mutations in Czech population are 4.5% and 1.3%, respectively [3]. Second limitation is related to assessment of VTE incidence. The real VTE incidence was probably higher than we proved in our study group based on clinical suspicion. It is well recognized that a high rate of asymptomatic thrombotic events (3.0–17.7%) is revealed in colorectal cancer patients if screening of DVT by ultrasonography is performed in the postoperative period [26, 27]. However, most patients with asymptomatic VTE have calf vein thrombosis, for which the necessity of anticoagulation therapy is controversial. Another factor is the absence of detailed information about the cause of death in some patients. The autopsy was performed in most patients who died in the early postoperative period (<28 days), but in case of patient death in late postoperative period, the autopsy wasn't performed and accurate cause of death was not verified in most patients. This factor should be mentioned because VTE is the second leading cause of death in cancer patients (after cancer itself) [28].

Conclusion

We proved that the extended-duration (4 weeks) VTE prophylaxis with a standard regimen of LMWH administration effectively reduced the risk of VTE in patients with thrombotic mutations undergoing colorectal cancer surgery. Therefore, we assume that the standard regimen of 4 weeks VTE prophylaxis is adequate for colorectal cancer patients with hereditary thrombophilia and more intensified VTE prophylaxis within the 28-day postoperative period is not justified. In the post-prophylactic period, we observed increased incidence of symptomatic DVT in colorectal cancer patients with thrombotic mutations, especially symptomatic lower extremity DVT in patients with FVL. The ongoing postoperative pharmacologic prophylaxis (>28 days) should be considered in patients with hereditary thrombophilia undergoing colorectal cancer surgery. The selective screening of hereditary thrombophilia in patients undergoing colorectal cancer surgery may play a role in identifying high VTE risk patients requiring ongoing pharmacologic prophylaxis.

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Compliance with ethical guidelines

Conflict of interest J. Ulrych, T. Kvasnicka, V. Fryba, M. Komarc, I. Malikova, R. Brzezkova, J. Kvasnicka Jr, Z. Krska, J. Briza, and J. Kvasnicka declare that they have no competing interests.

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the ethics committee of General University Hospital in Prague. Informed consent was obtained from all patients for being included in the study.

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