Ann Surg Oncol (2019) 26:1503–1511
https://doi.org/10.1245/s10434-018-07148-z

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – PANCREATIC TUMORS

Risk of Venous Thromboembolism for Patients with Pancreatic Ductal Adenocarcinoma Undergoing Preoperative Chemotherapy Followed by Surgical Resection

Brian A. Boone, MD[1,2], Mazen S. Zenati, MD, PhD[1], Caroline Rieser, MD[1], Ahmad Hamad, MD[1], Amr Al-abbas, MD[1], Amer H. Zureikat, MD[1], Melissa E. Hogg, MD[1], Matthew D. Neal, MD[1], and Herbert J. Zeh III, MD[1,3]

[1]Department of Surgery, University of Pittsburgh, Pittsburgh, PA; [2]Division of Surgical Oncology, Department of Surgery, West Virginia University, Morgantown, WV; [3]Department of Surgery, UT Southwestern, Dallas, TX

ABSTRACT

Background. Pancreatic ductal adenocarcinoma (PDA) is associated with a hypercoagulable state, resulting in a high risk of venous thromboembolism (VTE). Risk of VTE is well established for patients receiving chemotherapy for advanced disease and during the perioperative period for patients undergoing surgical resection. However, data are lacking for patients undergoing neoadjuvant treatment followed by resection, who may have a unique risk of VTE because of exposure to both chemotherapy and surgery.

Methods. The study included patients with PDA who underwent neoadjuvant therapy followed by surgery from 2007 to June 2017. Development of VTE was evaluated from the start of treatment through the 90-day postoperative period. Risk factors including demographic, treatment, and laboratory variables were evaluated.

Results. The study investigated 426 patients receiving neoadjuvant therapy before surgical resection. Of these patients, 20% had a VTE within 90 days postoperatively (n = 87), and 70% of the VTE occurred during the postoperative period. The VTE included pulmonary embolism (30%), deep vein thrombosis (33%), and thrombosis of the portal vein (PV)/superior mesenteric vein (SMV) (40%). A pretreatment hemoglobin level lower than 10 g/dL and a platelet count higher than 443 were independently associated with VTE during neoadjuvant treatment. The independent predictors of postoperative VTE were a body mass index higher than 35 kg/m^2, a preoperative platelet-to-lymphocyte ratio higher than 260, resection with distal pancreatectomy with celiac axis resection/total pancreatectomy, PV/SMV resection, and longer operative times. Development of VTE was associated with worse overall and disease-free survival and an independent predictor of survival and decreased likelihood of receiving adjuvant chemotherapy.

Conclusions. Venous thromboembolism during neoadjuvant therapy and the subsequent perioperative period is common and has a significant impact on outcome. Further study into novel thromboprophylaxis measures or protocols during neoadjuvant treatment and the perioperative period is warranted.

Since the early observations of Trousseau in the mid-19th century, the unique biology and aggressiveness of pancreatic adenocarcinoma (PDA) has been associated with hypercoagulability,[1–4] resulting in a high risk of cancer-associated venous thromboembolic events (VTE).[5,6] The induction of a hypercoagulable state and increased risk of VTE during major abdominal surgery are well established and particularly profound for pancreatic surgery, with nearly 4% experiencing the development of VTE in the postoperative course.[7–9] Among pancreatic cancer patients receiving chemotherapy for advanced cancer, the VTE rate reaches 40%.[5,10–12]

Recently, the development of novel, more active chemotherapeutic regimens has led to increased use of preoperative chemotherapy, particularly for patients with borderline resectable disease.[13] Unfortunately, limited data

Electronic supplementary material The online version of this article (https://doi.org/10.1245/s10434-018-07148-z) contains supplementary material, which is available to authorized users.

First Received: 30 July 2018;
Published Online: 16 January 2019

B. A. Boone, MD
e-mail: Brian.boone@hsc.wvu.edu

are available regarding the rates of VTE and the associated risk factors for PDA patients undergoing neoadjuvant therapy followed by surgical resection, who are exposed to the risks associated with both chemotherapy and surgery.

We evaluated patients with PDA undergoing preoperative treatment followed by surgical resection to identify the rate of venous thromboembolism in this cohort. Additionally, we identified risk factors that may be useful in selecting patients at highest risk for VTE during this course of treatment. Finally, we examined the impact of VTE development during neoadjuvant treatment and the perioperative period on clinical outcomes, including survival and receipt of adjuvant chemotherapy.

METHODS

Study Design

The Institutional Review Board at the University of Pittsburgh approved the study (PRO17080318). This retrospective study reviewed all patients undergoing preoperative treatment followed by surgical resection for pancreatic adenocarcinoma at the University of Pittsburgh Medical Center from 2007 through June 2017. Patient demographics, treatment characteristics, and clinical outcomes were collected. Laboratory values from a complete blood count (CBC) were evaluated before chemotherapy treatment and after treatment (preoperatively). Existing VTE risk assessment scores (Khorana and Caprini) validated in the setting of cancer were calculated.[14,15]

Venous thromboembolism was defined as any venous blood clot, including deep vein thrombosis (DVT), pulmonary embolism (PE), and portal, superior mesenteric or splenic vein thrombosis. No formal screening process was used identify VTE in this retrospective study, so both symptomatic and incidentally discovered VTE were included.

Statistical Analysis

Continuous data are reported as mean ± standard deviation or median (interquartile range). Categorical variables are reported as frequency (n) and percentage (%). For continuous variables, comparisons were made using Student's t test when they were normally distributed and with Wilcoxon rank-sum test when distributed otherwise. For categorical variables, comparisons were made using Fisher's exact test. Uni- and multivariate logistic regression analyses were performed to identify factors predictive of VTE, receipt of adjuvant chemotherapy, and survival. To determine the impact of VTE, Kaplan-Meier was used to estimate median survival.

Statistical significance for survival was determined using the log-rank test. Cox proportional hazards models were used to identify predictors of survival after control was used for disease stage, margin, receipt of adjuvant chemotherapy, and other covariates. All tests used in the analysis were two-sided, with an alpha of 0.05, indicating statistical significance. Statistical analysis was performed with Stata 13.1 (Stata Corp LP, College Station, TX, USA).

RESULTS

Patient Demographics and Treatment Characteristics

The study investigated 426 patients who received neoadjuvant therapy followed by surgical resection for pancreatic adenocarcinoma. The patient demographics and characteristics for the entire cohort are reported in Table 1. The median age was 65 years, and 50% of the patients were female. Most of the patients had tumor-node-metastases (TNM) stage 2A (32%, $n = 128$) or 2B (45%, $n = 184$) disease. A variety of chemotherapy regimens were used including a gemcitabine-based regimen ($n = 128$), FOLFIRINOX ($n = 102$), gemcitabine/nab-paclitaxel ($n = 159$), and a combination of multiple regimens ($n = 34$).

Minimally invasive pancreatic resection was performed for 200 patients (47%), with 133 patients (31%) undergoing portal/superior mesenteric vein (SMV) resection. Of these patients, 54 (41%) had lateral wall resection of the vein, 46 (35%) had vein resection with primary end-to-end anastomosis, and 33 (25%) had vein resection requiring use of an interposition graft or patch for reconstruction.

Subcutaneous heparin was administered as thromboprophylaxis for a large majority of the patients (98%), in addition to encouragement for early ambulation and use of sequential compression devices. Thromboprophylaxis was administered within 12 h after surgery for 61% of the patients and within 24 h for 96% of the patients. Laboratory values associated with thromboinflammatory pathways are reported in Table S1.

VTE Event Rate During Neoadjuvant Therapy and Postoperative Course

For 20% of the patients ($n = 87$), VTE was discovered from the initiation of neoadjuvant chemotherapy through the 90-day postoperative period. The VTE events were evenly distributed between PE, DVT, and portal/mesenteric/splenic vein thrombosis (Fig. 1a). For 70% of the patients ($n = 61$) with a 90-day VTE, the VTE occurred in the postoperative period rather than during chemotherapy

TABLE 1 Patient demographics and treatment characteristics

	Entire cohort $n = 426$	No VTE $n = 339$ (80%)	VTE $n = 87$ (20%)	p
Patient characteristics				
Age	65.21 ± 70	64.79 ± 9.80	66.84 ± 9.17	0.078
Female	213 (50)	164 (48.4)	49 (56.3)	0.186
Caucasian	401 (94)	318 (93.8)	83 (95.4)	0.572
BMI	26.91 ± 5.41	26.76 ± 5.16	27.51 ± 6.28	0.248
BMI > 35	27 (8.7)	26 (7.7)	11 (12.6)	0.142
CCI age-adjusted	4.70 ± 1.55	4.623 ± 1.53	4.98 ± 1.62	0.059
Blood type B	50 (11.76)	37 (11)	13 (15)	0.302
Prior VTE	22 (5.2)	16 (4.7)	6(6.9)	0.413
FMHx VTE/ hypercoagulability	7 (1.7)	5 (1.5)	2 (2.3)	0.635
Active smoker	83 (20)	64 (19)	19 (22)	0.534
Ca 19-9				
At presentation	337 (111,1046)	363 (113, 1282)	276 (96, 1046)	0.126
Post neoadjuvant	55 (29, 161)	65 (30, 185)	40 (20, 85)	0.011
Treatment characteristics				
Surgical approach				
Whipple	327 (76.76)	267 (78.7)	60 (69.0)	
Distal	55 (12.91)	45 (13.3)	10 (11.5)	
Total	5 (1.17)	2 (0.59)	3 (3.4)	0.021
Central	1 (0.23)	1 (0.29)	0 (0)	
Appleby	38 (8.92)	24 (7.1)	14 (16.1)	
PV/SMV resection	133 (31.2)	99 (29.2)	34 (39.1)	0.076
OR time	394 ± 125	384 ± 113	432 ± 158	0.001
MIS	200 (47%)	158 (47%)	42 (48%)	0.781
Prophylaxis < 12 h postop	163 (38.9)	129 (38.6)	34 (40)	0.816
G-CSF treatment	124 (29)	96 (28)	28 (32)	0.539
Adjuvant chemotherapy	302 (73)	252 (77)	50 (58)	0.001
VTE risk assessment scores				
Khorana				
Pre-treatment	2.2 ± 0.5	2.2 ± 0.4	2.2 ± 0.5	0.823
Pre-operative	2.5 ± 0.6	2.5 ± 0.6	2.5 ± 0.7	0.535
Caprini	8.8 ± 1.2	8.7 ± 1.3	9.1 ± 1.1	0.004
Survival outcomes				
Overall survival	29.4 (27.6, 34.4)	32.3 (28.1, 40.1)	23.1 (17.9, 28.8)	0.002
Disease-free survival	19.6 (17.7, 22.5)	20 (18.5, 24.3)	16.7 (12.4, 21.5)	0.019
Follow-up	41.4 (33.9, 48.8)	39.6 (32.9, 48.8)	42.5 (36.2, 71.2)	0.132

Data presented as mean ± SD, *n* (%), or median (IQR). *BMI* body mass index, *CCI* Charlson co-morbidity index, *VTE* venous thromboembolism, *FMHx* family medical history, *PV/SMV* portal vein/superior mesenteric vein, *MIS* minimally invasive surgery

treatment (Fig. 1b). In 42 of these patients, the VTE was discovered after discharge from the hospital (69% of the patients with postoperative VTE and 48% of all the patients with VTE). The VTE event rate, stratified by treatment, is reported in Table S2.

The patients undergoing distal pancreatectomy with celiac axis resection (DP-CAR/Appleby) or total pancreatectomy had the highest rate of VTE (36.8% and 60%, respectively) and had a distribution of VTE events similar to the remainder of the cohort. Of 133 patients who had a portal vein (PV)/SMV resection, 34 had a VTE, resulting in a VTE rate of 25.6%. The VTE was most commonly PV/SMV/splenic vein thrombosis, accounting for 37% of the VTE in these patients. The type of vein resection and reconstruction had no impact on the development of a VTE or PV/SMV thrombosis. The rate of PV thrombosis after

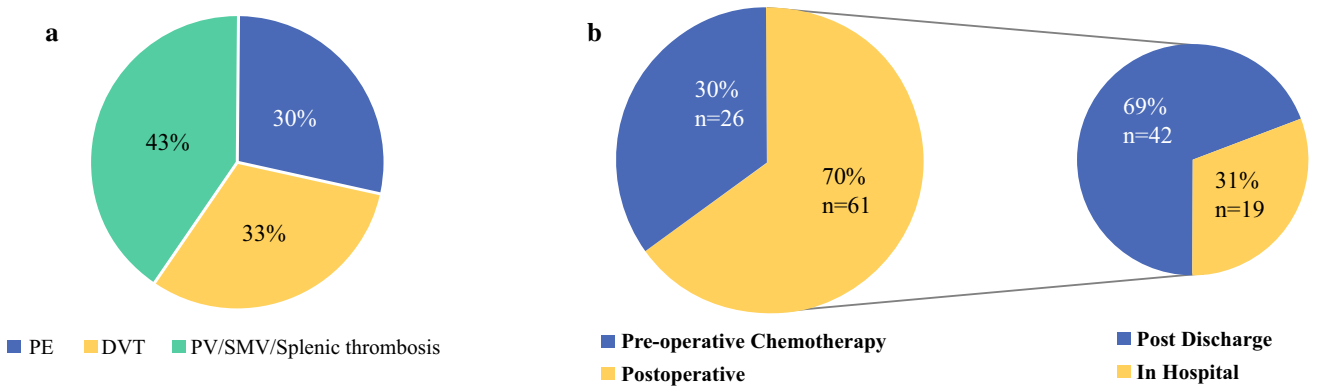

FIG. 1 Distribution of venous thromboembolism (VTE) events from initiation of neoadjuvant chemotherapy through the 90-day postoperative period. **a** The VTE events included pulmonary embolism (PE, $n = 26$), deep vein thrombosis (DVT, $n = 29$), and portal/mesenteric/splenic vein thrombosis ($n = 37$). **b** Timing of VTE throughout the treatment course

vein resection was 9.3% for lateral vein wall resection, 10.9% for resection with end-to-end anastomosis, and 21.2% when the use of an interposition graft or patch was required ($p = 0.27$). The VTE rate did not differ significantly based on the type of preoperative chemotherapy used.

The patients with a VTE had a significantly greater frequency of preoperative platelet/lymphocyte ratio higher than 260 (Table S1, 26% vs. 16%; $p = 0.047$), lower CA19-9 values after neoadjuvant therapy (median 40 vs. 65 U/mL; $p = 0.011$), longer operative times (432 ± 158 vs. 384 ± 113 min; $p = 0.001$), and a greater likelihood of undergoing total pancreatectomy or DP-CAR (Table 1). The patients with a VTE showed statistical trends toward older age ($p = 0.078$), a higher Charlson comorbidity index ($p = 0.059$), a greater frequency of preoperative anemia ($p = 0.056$), and a greater frequency of PV/SMV resection ($p = 0.076$).

VTE Prediction Scores Fail to Identify the High-Risk Cohort

Existing VTE prediction scores were calculated and evaluated for the patient cohort (Table 1). The mean Khorana score for the entire cohort was 2.2 ± 0.5 based on pre-treatment laboratory values and 2.5 ± 0.6 based on preoperative, postchemotherapy values, both of which fall into the intermediate risk category for this scoring system. The mean Caprini score was 8.8 ± 1.2, which is in the highest risk category. The Caprini score was statistically higher for the patients who had a VTE during treatment, but the differences in the score between the two groups were both in the highest risk category and clinically insignificant (9.1 ± 1.1 vs. 8.7 ± 1.3; $p < 0.004$). The Khorana score did not differ significantly between the patients with and those without VTE.

Predictors of VTE in Patients During Neoadjuvant Therapy

Uni- and multivariate logistic regression analysis were performed to identify risk factors for VTE that occurred during the neoadjuvant treatment period (Table 2). In the multivariate analysis, the independent predictors of VTE were pretreatment hemoglobin lower than 10 g/dL (odds ratio [OR] 6.54, 95% confidence interval [CI] 1.4–31.8; $p = 0.02$) and pretreatment platelet count higher than 443 (OR 5.63; 95% CI 0.773–41.0; $p = 0.088$). The patients who had a lower percentage decrease in CA19-9 in response to neoadjuvant treatment were protected from VTE (OR 0.04; 95% CI 0.002–0.809; $p = 0.036$).

Predictors of VTE in Patients During the Postoperative Period

Uni- and multivariate logistic regression analysis was performed to identify risk factors for VTE that occurred during the 90-day postoperative treatment period (Table 3). The independent predictors of VTE in the multivariate analysis were body mass index (BMI) higher than 35 kg/m^2 (OR 4.99; 95% CI 1.35–8.52; $p = 0.02$), preoperative platelet-to-lymphocyte ratio (PLR) higher than 260 (OR 3.56; 95% CI 1.4–9.1; $p = 0.01$), longer operative time (OR 1.005 per min; 95% CI 1.002–1.009; $p = 0.002$), resection with DP-CAR or total pancreatectomy (OR 9.39; 95% CI 2.4–36.4; $p = 0.001$), and PV/SMV resection (OR 3.086; 95% CI 1.3–7.32; $p = 0.01$). The patients with persistent elevation of CA19-9 above normal after treatment (OR 0.317, 95% CI 0.139–0.723; $p = 0.01$) and larger tumors (OR 0.673; 95% CI (0.139–0.723; $p = 0.01$) were protected from VTE. The timing of thromboprophylaxis administration did not have an impact on the development of VTE.

TABLE 2 Predictors of VTE during neoadjuvant therapy

Variable	Univariate			Multivariate[+]		
	OR	95% CI	*p*	OR	95% CI	*p*
Age > 65	2.336	0.961–5.68	0.06*	–	–	–
Gender (F)	0.849	0.383–1.88	0.69			
BMI > 35						
BMI	1.023	0.955–1.10	0.52			
Fam Hx VTE	2.67	0.300–23.8	0.38			
Active smoker	1.02	0.372–2.82	0.97			
CCI-AA	1.1	0.861–1.408	0.44			
Blood type B	1.395	0.460–4.23	0.56			
Pre-Tx labs						
Hgb < 10	2.45	0.676–8.89	0.17*	6.54	1.35–31.78	0.020
Platelets > 443	3.389	0.693–16.57	0.13*	5.63	0.773–40.99	0.088
NLR	0.989	0.893–1.10	0.84			
PLR	0.999	0.994–1.00	0.50			
Albumin	0.556	0.256–1.206	0.14*	–	–	–
Ca 19-9 after Tx						
Persistent elevation	0.666	0.254–1.74	0.41			
% Change	0.054	0.003–0.826	0.04*	0.04	0.002–0.809	0.036
G-CSF	0.327	0.072–1.50	0.15*	–	–	–
Caprini	1.18	0.894–1.56	0.24			
Khorana score (pre-op)	0.676	0.248–1.842	0.44			

Number of subjects 268, LR χ^2 (3), $p = 0.001$, Pseudo $R^2 = 0.122$

[+] $p < 0.20$ was the threshold for covariates inserted in the model for MVA

* Analysis on MVA, – Nonsignificance

Sequela of VTE During Neoadjuvant Treatment and Surgery

Only 58% of the patients with VTE received adjuvant chemotherapy compared with 77% of those who did not experience VTE ($p < 0.001$). The development of VTE was associated with significantly worse disease-free survival (median DFS, 16.7 vs. 20.0 months; $p = 0.019$) and overall survival (median OS, 23.3 vs. 32.3 months; $p = 0.002$) than the patients who did not experience VTE (Fig. 2a, b). The development of a PV/SMV thrombosis was associated with significantly worse overall survival (Fig. 2c; median OS, 20.1 vs. 31.7 months; $p = 0.0002$). The findings showed VTE to be an independent predictor of failure to receive adjuvant chemotherapy (OR 0.45; 95% CI 0.26–0.75; $p = 0.005$) and an independent predictor of overall survival (hazard ratio [HR] 1.53; 95% CI 1.1–2.1; $p = 0.01$) after control was used for CA19-9, disease stage, margin status, receipt of adjuvant chemotherapy, and other confounding variables.

DISCUSSION

Whereas the risk of VTE for pancreatic cancer patients undergoing surgical resection or chemotherapy for advanced disease is well studied, limited data are available for PDA patients undergoing neoadjuvant therapy, who are exposed to the risks associated with both chemotherapy and surgery. In the current analysis, 20% of the patients treated with neoadjuvant chemotherapy followed by surgery experienced VTE within 90 days after surgery. Krepline et al.[16] evaluated the incidence of VTE among resectable and borderline resectable PDA patients receiving neoadjuvant chemotherapy and demonstrated VTEs in 10% of the patients. Importantly, this analysis did not include assessment for VTE during the postoperative period, which is when a majority of VTE events occurred in the current study. This likely explains the lower rate of VTE compared with the current findings.

The development of VTE in cancer patients is an independent predictor of diminished response to therapy and decreased survival.[16–19] In the current study, the development of VTE was associated with worse survival

TABLE 3 Predictors of VTE during postoperative period

Variable	Univariate			Multivariate[+]		
	OR	95% CI	*p*	OR	95% CI	*p*
Age > 65	1.189	0.686–2.06	0.29			
Gender (F)	1.645	0.943–2.87	0.08*	–	–	–
BMI > 35	1.817	0.781–4.23	0.17*	4.991	1.35–8.52	0.02
Fam Hx VTE	1.113	0.128–9.70	0.92			
Active smoker	1.279	0.664–2.47	0.46			
CCI-AA	1.159	0.979–1.37	0.09*	–	–	–
Blood type B	1.408	0.642–3.09	0.39			
Pre-Tx labs						
Lymphocytes	0.782	0.554–1.10	0.16			
Hgb < 10	2.143	0.740–6.21	0.16*	–	–	–
NLR	1.037	0.989–1.09	0.13*	–	–	–
Pre-op labs						
Lymphocytes	0.578	0.417–0.800	0.001			
Hgb < 10	0.869	0.325–2.33	0.78			
NLR > 3	1.833	1.05–3.19	0.03*	–	–	–
PLR > 260	2.027	1.08–3.81	0.03*	3.555	1.40–9.05	0.01
Ca 19-9 after treatment						
Pre-op level	0.998	0.995–1.00	0.08*	–	–	–
Persistent elevation	0.478	0.240–.955	0.04*	0.317	.139–.723	0.01
% Decrease	0.789	0.345–1.80	0.57			
G-CSF	1.805	0.738–4.41	0.20*	–	–	–
Caprini score	1.197	0.983–1.46	0.07*	–	–	–
Khorana score (pre-op)	1.401	0.865–2.27	0.17*	–	–	–
Surgical resection						
Whipple	0.334	0.160–0.698	0.004			
Distal	0.231	0.074–0.719	0.01			
DP-CAR/total	3.130	1.51–6.48	0.002*	9.394	2.43–36.4	0.001
Portal/SMV resection	1.800	1.03–3.15	0.04*	3.086	1.30–7.32	0.01
OR time (per min)	1.004	1.002–1.006	0.001*	1.005	1.002–1.009	0.002
Tumor size	0.673	0.445–1.02	0.06*	0.382	.209–.697	0.002
R1 resection	1.580	0.828–3.02	0.17*	–	–	–
Stage	0.766	0.576–1.02	0.07*	–	–	–
> 24 h before prophylaxis	1.545	0.418–5.71	0.51			

Number of subjects 268, LR χ^2 (3), $p = 0.001$, Pseudo $R^2 = 0.122$

[+] $p < 0.20$ was the threshold for covariates inserted in the model for MVA

* Analysis on MVA,– nonsignificance

and decreased likelihood of receiving adjuvant chemotherapy, similar to previously published reports analyzing different patient cohorts.

The reasons why VTE had an impact on adjuvant therapy are difficult to determine objectively, but in this retrospective study, we suspected that the development of VTE is an indicator of general morbidity, delayed recovery, and deconditioning, resulting in a clinical judgment that the patient is unable to tolerate adjuvant therapy. Importantly, the development of VTE had an impact on survival independently of the receipt of adjuvant chemotherapy, suggesting a potential link between the pathophysiology of thromboembolism and the biology and aggressiveness of pancreatic cancer. Furthermore, in considering the impact of VTE on patients, we must also consider that bleeding risk associated with subsequent treatments for VTE are a significant source of morbidity and mortality at all stages of treatment. Anticoagulation in the perioperative period after pancreatic surgery is associated with elevated rates of complications.[20]

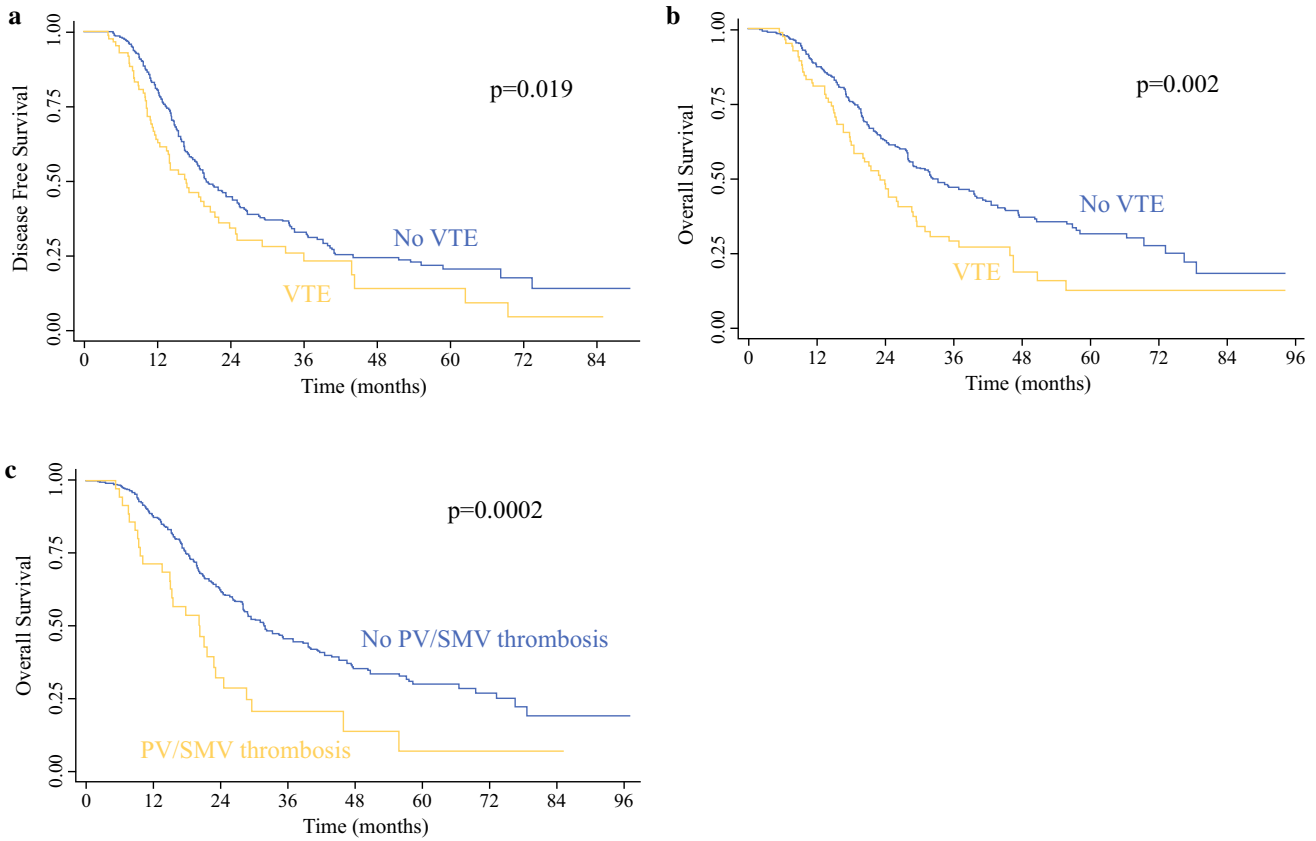

FIG. 2 Venous thromboembolism (VTE) is associated with worse survival outcomes. The development of venous thromboembolism during neoadjuvant therapy and the 90-day perioperative period resulted in significantly worse (**a**) disease-free survival (median 16.7 vs. 20.0 months; $p = 0.019$) and (**b**) overall survival (median 23.1 vs. 32.3 months; $p = 0.002$) than shown by the patients who did not experience VTE. VTE (yellow), no VTE (blue). (**c**) The development of portal vein thrombosis was associated with significantly worse overall survival (median 20.1 vs. 31.7 months; $p = 0.0002$)

Given the significant impact of VTE on clinical outcomes, identification of high-risk patients for appropriate tailoring of thromboprophylaxis regimens is an important goal. Unfortunately, predictive modeling scoring systems developed to identify high-risk patients in other cancers are ineffective at assessing risk for pancreatic cancer.[5,21] The current study confirmed these observations, as neither the Caprini nor Khorana scores were able to discriminate patients at highest risk for VTE. In the current study, anemia, elevated platelet-to-lymphocyte ratio (PLR), elevated platelet count, higher BMI, longer operative time, performance of DP-CAR or total pancreatectomy, and performance of vein resection were independent risk factors for VTE, with VTE rates reaching 60% for select subsets of patients. Because risk factors available to the medical team before the start of treatment were studied, these data can be used to tailor prophylactic measures appropriately throughout the course of treatment.

The identification of risk factors allows for selection of patients at highest risk to evaluate new thromboprophylaxis regimens and novel treatment targets. The use of chemical thromboprophylaxis during the neoadjuvant chemotherapy portion of treatment has been suggested,[16] but most VTEs in the current study occurred in the postoperative setting despite the use of standard mechanical and chemical thromboprophylaxis. Additionally, VTE was discovered after 69% of the patients with a postoperative VTE were discharged, suggesting a potential benefit of post-discharge thromboprophylaxis for high-risk patients.[22] These findings highlight the need for novel therapies and treatment strategies that target the biology of cancer-associated hypercoagulability.

Historically, patients with more advanced disease are thought to be at the highest risk for VTE.[5,10–12] Interestingly, the current analysis showed that the patients who had a lesser response to neoadjuvant therapy (persistently elevated posttreatment CA19-9 and larger tumors) were protected from VTE. To our knowledge, this is the first analysis to examine the impact of treatment response on VTE. Although it is not possible to provide a thorough explanation for this finding within the confines of the current analysis, these findings could suggest a potential

impact of neoadjuvant therapy on the complex thromboinflammatory signaling pathways in pancreatic cancer, and further exploration is warranted.

The current study had several limitations that limit its impact and application to clinical practice. Because this was a retrospective study with a relatively small number of patients, conclusions regarding procedures that are infrequently performed, such as DP-CAR and total pancreatectomy, must be interpreted with caution. Due to the retrospective nature of the study and the fact that no formal screening tests for VTE were performed, an overall VTE rate of 20% likely is an underestimate of its true incidence. Furthermore, the incidence of VTE is influenced by clinical practice patterns at our institution. We did not routinely use thromboprophylaxis during neoadjuvant chemotherapy, nor did we routinely discharge post-pancreatectomy patients receiving extended thromboprophylaxis. Although these practices will now be influenced by the findings of the current study moving forward, they certainly have an impact on the incidence of VTE in this cohort.

The goal of this study was to identify risk factors in patients exposed to chemotherapy and surgery. Therefore, all patients in the current study completed neoadjuvant treatment and proceeded to surgery. This selected out patients who experienced a VTE during neoadjuvant therapy and did not make it to surgical resection, either due to progressive disease or because of morbidity precluding surgery. Therefore, the percentage of VTEs that were postoperative was artificially elevated. It may be informative to compare cohorts of patients treated with and without neoadjuvant therapy. However, because neoadjuvant therapy is most commonly used for patients with more advanced disease, it was not possible for us to find a matched cohort for comparison in this single-institution analysis.

Despite these limitations, we demonstrated that patients undergoing neoadjuvant therapy followed by surgical resection are at high risk for the the development VTE during treatment, resulting in worse survival. We identified risk factors useful in anticipating VTE incidence that will allow for future study of risk mitigation through novel thromboprophylaxis treatment strategies in this patient population.

DISCLOSURE There are no conflicts of interest.

REFERENCES

1. Woei AJFJ, Tesselaar ME, Garcia Rodriguez P, Romijn FP, Bertina RM, Osanto S. Tissue factor-bearing microparticles and CA19.9: two players in pancreatic cancer-associated thrombosis? *Br J Cancer.* 2016;115:332–8.
2. Boone BA, Miller-Ocuin JL, Doerfler WR, Ellis JT, Lotze MT, Neal MD, Zeh HJ. Neutrophil extracellular traps promote hypercoagulability in pancreatic cancer through release of tissue factor and platelet aggregation. *Ann Surg Oncol.* 2017;S1:S110.
3. Pinzon R, Drewinko B, Trujillo JM, Guinee V, Giacco G. Pancreatic carcinoma and Trousseau's syndrome: experience at a large cancer center. *J Clin Oncol.* 1986;4:509–14.
4. Rickles FR, Edwards RL. Activation of blood coagulation in cancer: Trousseau's syndrome revisited. *Blood.* 1983;62:14–31.
5. Kruger S, Haas M, Burkl C, et al. Incidence, outcome, and risk stratification tools for venous thromboembolism in advanced pancreatic cancer: a retrospective cohort study. *Thromb Res.* 2017;157: 9–15.
6. Petterson TM, Marks RS, Ashrani AA, Bailey KR, Heit JA. Risk of site-specific cancer in incident venous thromboembolism: a population-based study. *Thromb Res.* 2015;135:472–8.
7. Molena D, Mungo B, Stem M, Feinberg RL, Lidor AO. Prevalence, impact, and risk factors for hospital-acquired conditions after major surgical resection for cancer: a NSQIP analysis. *J Gastrointest Surg.* 2015;19:142–51; discussion 151.
8. Tzeng CW, Katz MH, Lee JE, Fleming JB, Pisters PW, Vauthey JN, Aloia TA. Predicting the risks of venous thromboembolism versus post-pancreatectomy haemorrhage: analysis of 13,771 NSQIP patients. *HPB Oxf.* 2014;16:373–83.
9. Ramanathan R, Mason T, Wolfe LG, Kaplan BJ. Predictors of short-term readmission after pancreaticoduodenectomy. *J Gastrointest Surg.* 2018;22:998–1006.
10. Pelzer U, Opitz B, Deutschinoff G, et al. Efficacy of prophylactic low-molecular-weight heparin for ambulatory patients with advanced pancreatic cancer: outcomes from the CONKO-004 trial. *J Clin Oncol.* 2015;33:2028–34.
11. Shaib W, Deng Y, Zilterman D, Lundberg B, Saif MW. Assessing risk and mortality of venous thromboembolism in pancreatic cancer patients. *Anticancer Res.* 2010;30:4261–4.
12. Ishigaki K, Nakai Y, Isayama H, et al. Thromboembolisms in advanced pancreatic cancer: a retrospective analysis of 475 patients. *Pancreas.* 2017;46:1069–75.
13. Du L, Wang-Gillam A. Trends in neoadjuvant approaches in pancreatic cancer. *J Natl Compr Cancer Netw.* 2017;15:1070–7.
14. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood.* 2008;111:4902–7.
15. Bahl V, Hu HM, Henke PK, Wakefield TW, Campbell DA Jr, Caprini JA. A validation study of a retrospective venous thromboembolism risk scoring method. *Ann Surg.* 2010;251:344–50.
16. Krepline AN, Christians KK, George B, et al. Venous thromboembolism prophylaxis during neoadjuvant therapy for resectable and borderline resectable pancreatic cancer-Is it indicated? *J Surg Oncol.* 2016;114:581–6.
17. Larsen AC, Brondum Frokjaer J, Wishwanath Iyer V, et al. Venous thrombosis in pancreaticobiliary tract cancer: outcome and prognostic factors. *J Thromb Haemost.* 2015;13:555–62.
18. Sogaard KK, Schmidt M, Pedersen L, Horvath-Puho E, Sorensen HT. 30-year mortality after venous thromboembolism: a population-based cohort study. *Circulation.* 2014;130:829–36.
19. Sorensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. *N Engl J Med.* 2000;343:1846–50.
20. Menapace LA, Khorana AA. The role of thromboprophylaxis in cancer patients: emerging data. *Curr Opin Hematol.* 2010;17:450–6.
21. Munoz Martin AJ, Garcia Alfonso P, Ruperez Blanco AB, Perez Ramirez S, Blanco Codesido M, Martin Jimenez M. Incidence of venous thromboembolism (VTE) in ambulatory pancreatic cancer patients receiving chemotherapy and analysis of Khorana's predictive model. *Clin Transl Oncol.* 2014;16:927–30.

22. Beal EW, Tumin D, Chakedis J, et al. Identification of patients at high risk for post-discharge venous thromboembolism after hepato-pancreato-biliary surgery: which patients benefit from extended thromboprophylaxis? *HPB Oxf.* 2018;20:621–30.