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Venous thromboembolism in patients with cancer undergoing surgical exploration

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Abstract

Malignancy and surgery are both independent risk factors for venous thromboembolism (VTE) events. The current NCCN guidelines recommend VTE prophylaxis for up to 28 days after major abdominal or pelvic surgery for malignancy. We set out to evaluate the rate and timing of VTEs among patients with gastric, pancreatic, colorectal, and gynecologic malignancies who underwent surgery. We performed a retrospective review of the NSQIP database (2005–2013) focusing on patients with gastric, colorectal, pancreatic, and gynecologic malignancies. Our primary endpoint was a diagnosis of VTE within 30 days of surgery. We analyzed 128,864 patients in this study. On multivariable analysis, patients with pre-operative sepsis (OR 2.36, CI 2.04–2.76, $p < 0.001$), disseminated cancer (OR 1.73, CI 1.55–1.92, $p < 0.001$), congestive heart failure (OR 1.69, CI 1.25–2.28, $p = 0.001$), gastric cancer (OR 1.3, CI 1.09–1.56, $p = 0.004$), and pancreatic cancer (OR 1.2, CI 1.03–1.30, $p = 0.021$) were more likely to have a VTE. Of patients who had a VTE event, 34% occurred after discharge from surgery (gastric: 25%, colorectal 34%, pancreatic 31%, gynecologic malignancy 42%). Our study demonstrates that patients who undergo an operation for malignancy with pre-operative sepsis, disseminated cancer, congestive heart failure, gastric cancer, or pancreatic cancer are more likely to develop a VTE within 30 days of their operation. Of those patients who developed a VTE, approximately one-third occurred after discharge during a 30 day post-operative period. This data supports that further studies are needed to determine the appropriate length of post-operative VTE chemoprophylaxis in patients with cancer.

Keywords Cancer · Deep vein thrombosis · Neoplasm · Surgery · Venous thromboembolism · Discharge

Highlights

- Retrospective review of patients in the NSQIP database (2005–2013) who underwent surgery for gastric, colorectal, pancreatic, and gynecologic malignancies
- Patients with preoperative sepsis, disseminated cancer, gastric cancer or pancreatic cancer were more likely to develop a VTE within the 30 day postoperative period
- One-third of VTEs during a 30 day postoperative period occurred after discharge
- Further studies are needed to determine the appropriate length of postoperative VTE prophylaxis for patients with cancer

Introduction

Venous thromboembolism (VTE) is one of the most common cancer-associated complications, with an estimated 15% of patients affected [1, 2]. VTEs have significant personal and clinical impact, being associated with worse quality of life, longer hospital length of stay (LOS), increased cost, worse overall survival, and diminished response to treatment in some types of cancer [3–7]. Additionally, rates of VTE appear to correlate with cancer outcomes. For these reasons, there is active research into the prevention and management of thromboembolic disease in these patients.

It is well-established that surgery and malignancy independently represent substantial predisposing factors for

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VTE, and that patients who undergo abdominal or pelvic laparotomy in the setting of cancer are at particular risk [1, 8, 9]. However, current practice recommendations from the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), American College of Chest Physicians, and National Comprehensive Cancer Network (NCCN) still struggle to elucidate specific recommendations for VTE prophylaxis for patients with cancer undergoing surgery [10–13]. The guidelines that differentiate between prophylaxis for surgical and for non-surgical patients, agree on the use of low-molecular weight heparins for prevention and treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE), and recommend prophylaxis for hospitalized patients. However, many oncology patients do not receive appropriate VTE prophylaxis or treatment and have a persistently elevated risk in the outpatient setting [14, 15]. Current guidelines do not account for the different rates of VTE associated with different cancer types, and are further limited by the absence of data regarding optimal duration and timing of chemoprophylaxis.

Current management of surgical oncology patients requires consideration of multiple factors including tissue diagnosis, coordination with chemotherapy, and efforts to protect quality of life. Establishing standardized recommendations could have a significant effect on perioperative outcomes. In order to address this need, our team set out to evaluate the rate and timing of VTEs amongst cancer patients who underwent surgery using the National Surgical Quality Improvement Program (NSQIP) database.

Methods

We used the NSQIP database between the years 2005 and 2013 to perform a retrospective review of patients with a diagnosis of gastric, colon, rectal, pancreatic, ovarian, uterine, and cervical cancer. Patients with a colon or rectal cancer were grouped together as "colorectal cancer" and those with ovarian, uterine, or cervical cancer were grouped together as "gynecologic cancer." In the database, patients were listed as having either a PE or DVT within 30 days of surgery. Patients were analyzed based on having any VTE event, whether that manifested as a PE or DVT. Information on how long patients were hospitalized and when they were diagnosed with a VTE was analyzed. The difference between these two values was used to determine if the patient was still hospitalized when they were diagnosed with the VTE or if they had already been discharged from their initial surgery.

Each of the four cancer diagnoses (gastric, colorectal, pancreatic, gynecologic) were compared. The primary endpoint of the study was a diagnosis of a VTE within 30 days after surgery. Demographic data and risk factor variables included gender, age, body mass index (BMI), diabetes, smoking history, chronic obstructive pulmonary disorder (COPD), congestive heart failure (CHF), hypertension (HTN), end stage renal disease (ESRD), disseminated cancer, presence of sepsis preoperatively, and type of cancer diagnosis. BMI was calculated using the formula weight in kilograms divided by height in meters squared. BMI was split into three categories based on the World Health Organization (WHO) guidelines: underweight (< 18.5), normal weight (18.5–24.9), and overweight (≥ 25) [16]. For descriptive statistics, the "overweight" category encompassed the WHO categories of pre-obesity, obesity class I, obesity class II, and obesity class III. Patients with missing information for the variables listed above were excluded.

Analysis was undertaken to evaluate factors that influenced which patients had a VTE event. A univariable analysis with a Chi Square test for categorical variables and Independent t-test for continuous variables was performed to determine which factors should be included in the multivariable logistic regression. An association with $p < 0.10$ on univariable analysis was deemed significant and included in the multivariable model. For the multivariable model, a p value < 0.05 was considered statistically significant. The mean length of stay (LOS) for patients who had a VTE in the hospital versus those who had a VTE after discharge was calculated and evaluated with an Independent t-test. All analyses were performed using SPSS statistical software version 24 (IBM Statistics).

ACS NSQIP database collects information on preoperative risk factors, intraoperative variables, and 30-day postoperative mortality and morbidity outcomes for patients undergoing inpatient and outpatient surgery. This is a prospectively collected database. The American College of Surgeons National Surgical Quality Improvement Program and the hospitals participating in the ACS NSQIP are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

Results

Demographics

Of the 128,864 patients included in this study, the majority had colorectal cancer (n = 85,451, 66.3%), followed by pancreatic cancer (n = 18,095, 14.0%), gynecologic cancer (n = 16,934 13.1%), and gastric cancer (n = 8384, 6.5%). Only 3.6% of the study population had sepsis at the time of the operation and 10.1% of the population had disseminated cancer. Approximately half of the population (53.0%) had hypertension and a fifth of the population had diabetes (19.1%). Other co-morbidities listed in NSQIP were low amongst patients (COPD 5.1%, CHF 0.8%,

ESRD 0.2%). The majority of patients had a BMI over 25 (65.0%). The median operative time for the population was 169 min with gastric cancer and pancreatic cancer having the longest operative times (206 and 295 min, respectively). Demographic data for the total population and the four cancer types is available in Table 1. A small percentage of patients had a VTE during the 30 day postoperative period (n = 2843, 2.2%). Gastric cancer and pancreatic cancer had the highest rate of VTEs (gastric: n = 250, 3.0% and pancreatic: n = 567, 3.1%). Colorectal cancer included 1719 patients (2%) and gynecologic cancer included 307 patients (1.8%) with a VTE.

Variables associated with VTE event

A univariable analysis was performed to determine factors that were associated with VTE events. All factors met the $p < 0.10$ criteria to be included in the multivariable regression (Table 2). On multivariable regression, patients who were older (OR 1.02, CI 1.017–1.024, $p < 0.001$), male (OR 1.10, CI 1.02–1.19, $p = 0.019$), diagnosed with COPD

Table 1 Demographic data for population

Variables	Total population N (%)	Gastric cancer N (%)	Colorectal cancer N (%)	Pancreatic cancer N (%)	Gynecologic cancer N (%)
Median age (years)	65	66	66	66	61
Gender					
Male	59,500 (46.2%)	5231 (62.4%)	44,939 (52.6%)	9330 (51.6%)	0
Female	69,364 (53.8%)	3153 (37.6%)	40,512 (47.4%)	8765 (48.4%)	16,934 (100%)
BMI					
Underweight (< 18.5)	3792 (2.9%)	388 (4.6%)	2569 (3%)	599 (1.4%)	236 (1.4%)
Normal weight (18.5–24.9)	41,271 (32%)	3225 (38.5%)	27,352 (32%)	6837 (37.8%)	3857 (22.8%)
Over weight (25+)	83,801 (65%)	4771 (56.9%)	55,530 (65%)	10,659 (58.9%)	12,841 (75.8%)
Pre Op Diabetes					
Yes	24,669 (19.1%)	1529 (18.2%)	15,163 (17.7%)	5080 (28.1%)	2897 (17.1%)
No	104,195 (80.9%)	6855 (81.8%)	70,288 (82.3%)	13,015 (71.9%)	14,037 (82.9%)
Pre Op COPD					
Yes	6586 (5.1%)	457 (5.5%)	4812 (5.6%)	883 (4.9%)	434 (2.6%)
No	122,278 (94.9%)	7927 (94.5%)	80,639 (94.4%)	17,212 (95.1%)	16,500 (97.4%)
Smoking history					
Yes	21,073 (16.4%)	1636 (19.5%)	13,639 (16%)	3772 (20.8%)	2026 (12%)
No	107,791 (83.6%)	6748 (80.5%)	71,812 (84%)	14,323 (79.2%)	14,908 (88%)
Pre Op CHF					
Yes	1082 (0.8%)	64(0.8%)	898 (1.1%)	65(0.4%)	55 (0.3%)
No	127,782 (99.2%)	8320 (99.2%)	84,553 (98.9%)	18,030 (99.6%)	16,879 (99.7%)
Pre Op HTN					
Yes	68,347 (53%)	4491 (53.6%)	45,370 (53.1%)	10,141 (56%)	8345 (49.3%)
No	60,517 (47%)	3893 (46.4%)	40,081 (46.9%)	7954 (44%)	8589 (50.7%)
Pre Op ESRD					
Yes	254 (0.2%)	20 (0.2%)	173 (0.2%)	34 (0.2%)	27 (0.2%)
No	128,610 (99.8%)	8364 (99.8%)	85,278 (99.8%)	18,061 (99.8%)	16,907 (99.8%)
Pre Op Sepsis					
Yes	4586 (3.6%)	294 (3.5%)	3524 (4.1%)	485 (2.7%)	283 (1.7%)
No	124,278 (96.4%)	8090 (96.5%)	81,927 (95.9%)	17,610 (97.3%)	16,651 (98.3%)
Disseminated cancer					
Yes	13,063 (10.1%)	793 (9.5%)	9164 (10.7%)	1319 (7.3%)	1787 (10.6%)
No	115,801 (89.9%)	7591 (90.5%)	76,287 (89.4%)	16,776 (92.7%)	15,147 (89.4%)
VTE					
Yes	2843 (2.2%)	250 (3%)	1719 (2%)	567 (3.1%)	307 (1.8%)
No	126,021 (97.8%)	8134 (97%)	83,732 (98%)	17,528 (96.9%)	16,627 (98.2%)
Total operation time (median in min)	169	206	155	295	161

Table 2 Univariable analysis of risk factors for VTE events

Variable	No VTE N(%)	VTE N(%)	p value
Mean age (years)	64.5	67.1	< 0.001
Gender			
Male	58,067 (46.1%)	1433 (50.4%)	< 0.001
Female	67,954 (53.9%)	1410 (49.6%)	
BMI			
Underweight (< 18.5)	3709 (2.9%)	83 (2.9%)	0.001
Normal weight (18.5–24.9)	40,453 (32.1%)	818 (28.8%)	
Overweight (25+)	81,859 (65.0%)	1942 (68.3%)	
Pre Op Diabetes			
Yes	24,088 (19.1%)	581 (20.4%)	0.076
No	101,933 (80.9%)	2262 (93.2%)	
Pre Op COPD			
Yes	6394 (5.1%)	192 (6.8%)	< 0.001
No	119,627 (94.9%)	2651 (93.2%)	
Smoking history			
Yes	20,652 (16.4%)	421 (14.8%)	0.024
No	105,369 (83.6%)	2422 (85.2%)	
Pre Op CHF			
Yes	105 (0.8%)	47 (1.7%)	< 0.001
No	124,986 (99.2%)	2796 (98.3%)	
Pre Op HTN			
Yes	66,753 (53.0%)	1594 (56.1%)	0.001
No	59,268 (47.0%)	1249 (43.9%)	
Pre Op ESRD			
Yes	244 (0.2%)	10 (0.4%)	0.06
No	125,777 (99.8%)	2833 (99.6%)	
Pre Op Sepsis			
Yes	4364 (3.5%)	222 (7.8%)	< 0.001
No	121,657 (96.5%)	2621 (92.2%)	
Disseminated cancer			
Yes	12,614 (10.0%)	449 (15.8%)	< 0.001
No	113,407 (90.0%)	2394 (84.2%)	
Diagnosis			
Gastric cancer	8134 (6.5%)	250 (8.8%)	< 0.001
Colorectal cancer	83,732 (66.4%)	1719 (60.5%)	
Pancreatic cancer	17,528 (13.9%)	567 (19.9%)	
Gynecologic cancer	16,627 (13.2%)	307 (10.8%)	
Total operation time (mean time in minutes)	198	238	< 0.001

(OR 1.21, CI 1.04–1.41, p = 0.014), diagnosed with CHF (OR1.69, CI 1.25–2.28, p = 0.001), presence of disseminated cancer (OR 1.73, CI 1.55–1.92, p < 0.001), pre-operative sepsis (OR 2.36, CI 2.04–2.76, p < 0.001), and longer total operating time (OR 1.002, CI 1.002–1.002, p < 0.001) were more likely to develop a VTE (Table 3). A diagnosis of gastric (OR 1.30, CI 1.09–1.56, p = 0.004) or pancreatic cancer (OR 1.20, CI 1.03–1.30, p = 0.021) also significantly increased the likelihood of VTE compared to patients with a gynecologic malignancy (Table 3).

Table 3 Multivariable logistic regression for factors affecting VTE events

Variable	Odds ratio	Confidence interval	p value
Gender (ref: female)			
Male	1.10	1.02–1.19	0.019
Age	1.02	1.017–1.024	< 0.001
Smoker (ref: no)			
Yes	0.93	0.83–1.03	0.165
COPD (ref: no)			
Yes	1.21	1.04–1.41	0.014
CHF (ref: no)			
Yes	1.69	1.25–2.28	0.001
HTN (ref: no)			
Yes	0.95	0.87–1.03	0.194
Disseminated cancer (ref: no)			
Yes	1.73	1.55–1.92	< 0.001
Pre op Sepsis (ref: no)			
Yes	2.36	2.04–2.76	< 0.001
Diagnosis (ref: gynaecologic cancer)			
Gastric cancer	1.30	1.09–1.56	0.004
Colorectal cancer	0.95	0.83–1.08	0.422
Pancreatic cancer	1.20	1.03–1.30	0.021
Diabetes (ref: no)			
Yes	0.94	0.86–1.04	0.243
ESRD (ref: no)			
Yes	1.28	0.67–2.43	0.453
Total operation time	1.002	1.002–1.002	< 0.001
BMI (ref: < 18.5 underweight)			
Normal weight (18.5–24.9)	0.92	0.73–1.16	0.472
Overweight (25+)	1.15	0.91–1.44	0.240

Timing of VTE event

Next, we analyzed the timing of a patient's VTE event. Our goal was to determine if the VTE occurred before or after discharge. The majority of patients were diagnosed with a VTE prior to discharge (total population: n = 1866, 66.3%, gastric: n = 186, 75.0%, colorectal: n = 1118, 65.7%, pancreatic: n = 387, 69.0%, gynecologic: n = 175, 57.8%) compared to after discharge (total population: n = 948, 33.7%, gastric: n = 62, 25%, colorectal n = 584, 34.3%, pancreatic n = 174, 31%, gynecologic: n = 128, 42.2%). Even though more VTEs were diagnosed while admitted to the hospital, one-third of all patients were diagnosed after discharge. This can be found in Table 4.

The mean LOS for this patient population was 8 days and the mean LOS for the patients who had a VTE was 16 days.

Table 4 Number of patients with a VTE who were diagnosed before versus after discharge

Type of cancer	Number of patients with a VTE diagnosed prior to discharge	Number of patients with a VTE diagnosed after discharge
Gastric	186 (75.0%)	62 (25.0%)
Colorectal	1118 (65.7%)	584 (34.3%)
Pancreatic	387 (69.0%)	174 (31.0%)
Gynecologic	175 (57.8%)	128 (42.2%)
Total	1866 (66.3%)	948 (33.7%8)

Twenty nine patients were excluded from analysis because the length of stay was unknown

Patients who had a VTE diagnosed prior to discharge had a longer mean LOS compared to those who had a VTE diagnosed after discharge (gastric: 24 vs. 10 days, colorectal: 20 vs. 8 days, pancreatic 24 vs. 9 days, and gynecologic 15 vs. 4 days, respectively). The difference between the mean LOS for patients diagnosed with a VTE prior to discharge and after discharge was statistically significant for each cancer ($p < 0.001$ for each group).

Discussion

It is estimated that 20% of VTE cases occur in patients with cancer and that a large portion of them are diagnosed in the outpatient setting [17–20]. VTE events are associated with increased healthcare costs, recurrent thromboembolic events, bleeding complications from anticoagulation therapy, and delay in treatment [21–23]. Given the significant associated morbidity and mortality, insight into lowering the rate of VTEs is of particular interest. Our study utilizes a large national database to compare the rate of VTE events before and after discharge in patients with high-risk abdominal cancers. Previous work has attempted to look at this important issue, but did so over a much shorter time period with significantly fewer patients [24]. Based on our data, it is clear that a large proportion of patients develop VTEs after discharge and prolonged chemoprophylaxis should be strongly considered in patients with cancer requiring surgery.

Abdominal surgery and malignancy are both independent risk factors for VTE. A study in 2002 evaluated the level of fibrin monomers (FM) and fibrin-D-dimers (FD) in patients' plasma during the pre, peri, and postsurgical period. The investigators found elevated levels of FM and FD for 14 days after surgery, thereby representing a hypercoagulable state [25]. Malignant cells induce a hypercoagulable state through the manipulation of Virchow's triad: stasis of blood, vascular injury, and hypercoagulability [26]. The initial site of thrombosis is often in the valve sinus and secondary to abnormal/reduced blood flow or hypoxia leading to dysfunctional endothelium. One mechanism of malignancy induced VTE is through mechanical compression of the vein by tumors, resulting in venous stasis [27].

Because different malignancies confer different VTE rates, there are likely cancer specific mechanisms that play a role in VTE events, however, these mechanisms are largely unknown [27]. One class of mechanisms revolves around cancer cells that express and/or release factors that activate the coagulation pathway and platelets. For example, tissue factor is a tumor derived protein that can initiate the extrinsic pathway of the coagulation cascade. It is normally expressed on subendothelial cells, however, malignant tissue involving the endothelium can cause inappropriate expression. This has been observed in patients with pancreatic and ovarian cancer [27]. Some cancer cells release small membrane vesicles (microparticles) that act as procoagulants and some of these microparticles express tissue factor (specifically in pancreatic cancer). Other mechanisms include the expression of podoplanin on cancer-associated fibroblasts or the secretion of adenosine diphosphate (ADP) by cancer cells, both of which result in the activation and aggregation of platelets [27].

In addition to releasing procoagulants, the presence of a tumor results in the activation of inflammatory tissues and subsequent cytokine release. Tumor necrosis factor alpha (TNF-α) and interleukin-1β (IL-1β) are well known pro-inflammatory cytokines that exert prothrombotic effects and can be released in response to tumors. Both of these cytokines can induce expression of tissue factor (procoagulant), downregulate anti-thrombotic regulators (e.g. thrombomodulin), and inhibit the release of nitric oxide and prostacyclin. Nitric oxide and prostacyclin normally inhibit platelet adhesion and activation [27].

Finally, the tumor's hypoxic microenvironment promotes endothelial dysfunction and production of platelet activating factor. Platelet activating factor activates neutrophils and causes them to adhere to endothelium. The hypoxic environment causes the release of Weibel-Palade bodies from endothelial cells, which results in the release of von Willebrand factor and expression of P-selectin. This increases the procoagulant response [27].

It is thought that chemotherapy causes drug induced damage to the endothelium resulting in increased tissue factor expression and a procoagulant state. Other theories revolve around chemotherapy's effect on the liver and subsequent hepatotoxicity. This hepatotoxicity results in a decline in anticoagulant proteins (e.g. protein C, protein S, and antithrombin). Finally, chemotherapy results in apoptosis of tumor and endothelial cells, causing a cytokine release and expression of tissue factor [27]. Patients typically wait 6–8 weeks after a major operation before starting adjuvant chemotherapy, which falls outside of the 30 day follow up period available in the NSQIP database. It is well established in clinical trials that there is an increased risk of VTE in patients with cancer undergoing chemotherapy [28, 29]. However, there are limited studies focusing on patients with cancer undergoing surgery. As a result, there is little guidance to the duration of chemoprophylaxis in this patient population.

The 2017 NCCN guidelines recommend VTE prophylaxis for up to 4 weeks after surgery for high risk abdominal or pelvic cancer surgery [13]. These guidelines are based on two randomized control trials and limited retrospective studies [19, 30]. The first trial is a double blind, multicenter study that evaluated chemoprophylaxis after major abdominal or pelvic surgery for cancer. Both groups were given 6–10 days of enoxaparin. Afterwards, one cohort was given a placebo for 21 days and the other was given an additional 21 days of enoxaparin. This study found that the use of prolonged chemoprophylaxis was associated with a decrease in VTE rate from 12 to 4.8% with no difference in the rate of bleeding or complications. They concluded that enoxaparin for 4 weeks after abdominal or pelvic cancer surgery was safe and reduced VTEs [31]. A second clinical trial demonstrated that chemoprophylaxis for 28 days compared to 7 days in patients undergoing major abdominal surgery resulted in a 50% reduction in venographic VTEs [32]. The CANBESURE randomized study demonstrated that prolonged VTE chemoprophylaxis (or 28 days total) after abdominal or pelvic surgery for cancer reduces the number of major VTE events without increasing the risk of major bleeding [33]. This reinforces the previously reported data. Finally, a systemic review of the literature on prolonged chemoprophylaxis with low molecular weight heparin (LMWH) was published in 2009 [34]. This review evaluated clinical trials regarding prolonged chemoprophylaxis and found a consensus that 4 weeks of LMWH post operatively reduced the rate of VTE without increasing bleeding risk. While these studies demonstrate a decrease rate of VTEs with extended chemoprophylaxis after surgery, they cover a wide range of operations for both benign and malignant conditions. This results in vague guidelines that leave room for interpretation. Our own study demonstrated that about a third of VTEs in patients with gastric, pancreatic, colorectal, and gynecologic malignancies occur after discharge from surgery. This further supports the NCCN guidelines that chemoprophylaxis should be continued for up to 28 days.

The second major finding in our study was that there are high-risk populations who should be targeted for extended VTE chemoprophylaxis. We found that patients with disseminated cancer, pre-operative sepsis, gastric cancer, and pancreatic cancer were most likely to have a VTE event. The field of gynecologic oncology has tried to address the question of extended chemoprophylaxis in the past. A survey study in Europe found that 44% of gynecologic oncology surgeons prescribe VTE chemoprophylaxis for 4 weeks after surgery, 16% prescribe it for 6 weeks, and 5% prescribe it for longer than 6 weeks [35]. This means that 65% of the surgeons surveyed discharge patients home on chemoprophylaxis. As a result, we specifically compared patients with gastric and pancreatic cancer to those with a gynecologic malignancy in this study. Compared to gynecologic malignancy gastric cancer and pancreatic cancer were more likely to be associated with a VTE event. These findings are consistent with the literature [18, 36, 37]. Considering extended VTE prophylaxis is becoming a standard of care for gynecologic oncology patients, we should be exploring studies that can help make the current guidelines stronger.

As a retrospective review of a large database, there are limitations to this study. First, the NSQIP data available for these patients was limited to 30 days. We cannot tell if patients continued to have VTE events after 30 days or if there was a relationship between the rate of VTEs and time from surgery after 30 days. In a 2009 study, MD Anderson changed their guidelines so that all patients with a gynecologic malignancy who underwent a laparotomy were continued on LMWH for 28 days postoperatively. Prior to implementation of this protocol, the rate of VTE after surgery in this patient population was 2.7% compared with 0.6% after implementation of the guidelines. The study then looked at the development of a VTE within 90 days of surgery and found that the rate was still 3% [38]. This means that even though patients received prolonged chemoprophylaxis, it did not change the rate of VTE events after surgery. Instead, it merely delayed the VTE by a couple weeks. This speaks to the larger question about when to stop chemoprophylaxis after surgery. Another limitation of this paper is that medications are not included in the database so we do not know if a patient was on chemoprophylaxis during their hospital stay or after discharge. The third limitation is that patients who are diagnosed as an outpatient with a VTE may be missed by chart reviewers or difficult for the database to capture. This could falsely lower the rate of VTEs overall and the rate that occur after discharge as an outpatient. Fourth, as a large database, NSQIP is only representative of those hospitals that contribute to it. This presents a slight selection bias. Finally, as a large database that is created based on

hospital participation, there are missing variables and errors that can occur.

Our study shows that VTEs can occur after discharge from major abdominal surgery for gastric, colorectal, pancreatic, and gynecologic cancers during a 30-day follow up period. This supports that patients with cancer should be considered for prolonged chemoprophylaxis after surgery. We demonstrate that further investigation into chemoprophylaxis for patients after discharge from major cancer surgery is still needed. It would be beneficial to survey surgical oncologists in the United States to assess the typical practice patterns for VTE prophylaxis after discharge, similar to what has been done for gynecologic oncologists. Finally, to strengthen the guidelines, multicenter randomized clinical trials specifically targeting different patient populations will need to be undertaken to demonstrate efficacy and safety of chemoprophylaxis after discharge.

Conclusion

Our study demonstrates that patients who undergo an operation for malignancy with pre-operative sepsis, disseminated cancer, congestive heart failure, gastric cancer, or pancreatic cancer are more likely to develop a VTE within 30 days of their operation. Of those patients who developed a VTE, approximately one-third occurred after discharge during a 30 day post-operative period. This data supports that further studies are needed to determine the appropriate length of post-operative VTE chemoprophylaxis in patients with cancer.

Compliance with ethical standards

Conflict of interest None of the authors have any potential conflicts of interest or financial disclosures.

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