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ORIGINAL ARTICLE

Do All Abdominal Neuroendocrine Tumors Require Extended Postoperative VTE Prophylaxis? A NSQIP Analysis

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Abstract

Background Venous thromboembolism (VTE) occurs at high incidence in abdominal cancer surgery; therefore, a 4-week postoperative VTE prophylaxis is advocated. However, most patients with neuroendocrine tumors (NETs) have more favorable prognoses. This study aimed to determine the incidence of VTE in patients with abdominal NETs, compare these rates to other abdominal malignancies, and identify VTE risk factors.

Methods The ACS-NSQIP database was queried to identify patients with abdominal NETs and other abdominal malignancies who underwent surgery from 2008 to 2015. A 30-day postoperative VTE incidence for each group was compared. Univariable and multivariable analyses were used to identify VTE risk factors.

Results Of the 7226 operations for patients with benign (2154) and malignant (5072) abdominal NETs, 144 patients experienced a VTE without significant differences between groups. Subgroup analysis revealed a spectrum of VTE rates. Compared to VTE rates of other abdominal malignancies, patients with benign (1.1% vs. 2.4%, $p < 0.001$) or malignant (1.7% vs. 2.4%, $p < 0.001$) non-pancreatic abdominal NETs had significantly lower rates, malignant pancreatic NETs (PNETs) (3.4% vs. 2.4%, $p = 0.03$) had significantly higher rates, and benign PNETs (3.2% vs. 2.4%, $p = 0.21$) had comparable rates. Multivariable analysis identified pre-operative albumin ($p < 0.001$), bleeding disorders ($p < 0.001$), operative time ($p < 0.001$), and having a PNET ($p = 0.04$) as risk factors for VTE in abdominal NET patients.

Conclusion Routine extended VTE prophylaxis after surgery may be necessary in PNETs, but probably unnecessary in other abdominal NETs. However, clinicians should use risk factors identified in this study when considering to forego extended VTE prophylaxis in NET patients.

Keywords Neuroendocrine tumors · Venous thromboembolism · NSQIP

Introduction

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism (PE), and is a common cause of morbidity and mortality in postoperative patients.[1,2] The incidence of VTE after abdominal and pelvic general surgery has been reported in 2–14% of patients.[3,4] The risk of postoperative DVT doubles, and PE triples in patients with cancer.[5] Multiple prospective studies and reviews have shown that prolonged prophylaxis reduces the incidence of VTE after major abdominal surgery, particularly for cancer.[4,6–8] Therefore, 4 weeks of postoperative VTE prophylaxis has been recommended by the American College of Chest Physicians (ACCP), National Comprehensive Cancer Network (NCCN), and American Society of Clinical Oncology (ASCO).[5,9–11]

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NETs arise from neural crest cells and account for 0.5% of malignancies.[12] They are found in multiple organs, most commonly the lung, pancreas, and gastrointestinal tract, and have a wide range of aggressiveness. Tumor extent and grade have shown to be the most important prognostic variables for patients with NETs, although primary tumor site is an important prognostic marker as well. According to one large study, patients with well-differentiated NETs have a far better survival than patients with moderately differentiated and poorly differentiated NETs, and by organ, patients with pancreatic NETs have especially poor survival and often present with advanced disease.[13] Regardless of stage and grade, most patients with NETs have a better prognosis than their counterparts with adenocarcinomas with 5-year survival rates of 65% and 32% respectively.[14]

Since NETs appear to have different tumor biology, patients with NETs may have different rates of VTE and may not need the same postoperative VTE prophylaxis as patients with other cancers.[13] The primary objective of this study was to investigate the incidence of postoperative VTE in patients with abdominal NETs and compare it to a contemporaneous cohort of patients with other abdominal malignancies. The secondary objective was to identify risk factors associated with VTE in NET patients to assist clinicians in selecting patients that could safely forego extended VTE prophylaxis.

Methods

The American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) is a nationally validated program that prospectively collects detailed clinical data of surgical patients from the pre-operative phase to 30 days postoperatively in the USA.[15] Approval for the use of the NSQIP patient-level data in this study was obtained from the institutional review board of Rush University Medical Center and NSQIP. The NSQIP dataset used for this study included data from the years 2008–2015.

International Classification of Diseases (ICD) codes version 9 were utilized to identify patients with NETs as well as other abdominal malignancies. The pediatric population is not accounted for, since NSQIP does not collect data on patients under the age of 18. Patients with NETs were identified using ICD codes 209-209.29, malignant NETs; 209.3, poorly differentiated NETs, which were considered malignant; and 209.4-209.69, benign NETs. Patients with abdominal NETs were then extracted from this group using ICD codes 209-209.17; 209.23-209.27; 209.4-209.57; 209.63-209.67 and subcategorized into benign (ICD codes 209.4-209.57, 209.63-209.67) and malignant (ICD codes 209-209.17, 209.23-209.27). For the remaining patients with an ICD code that did not specify a location, the "principal operative procedure CPT code description" listed in the NSQIP database was used to determine if the NET was benign or malignant. Patients with abdominal NETs, both benign and malignant, were further subcategorized into patients with pancreatic NETs (PNETs) vs. non-pancreatic abdominal NETs using the "principal operative procedure CPT code description" as well. Patients with abdominal malignancies other than NETs were identified using ICD codes 150-159.99 which includes malignant neoplasms of the esophagus, stomach, small intestine, colon, rectum, anus, liver, intrahepatic bile ducts, gallbladder and extrahepatic bile ducts, pancreas, retroperitoneum, and peritoneum.

The term VTE was defined as having a PE or DVT. The rates of postoperative VTE during hospitalization and following hospital discharge were examined. A Fisher exact test was used to evaluate whether a significant difference in VTE incidence existed between patients with benign and malignant NETs. Fisher exact tests were also used to determine the difference in VTE between patients with non-pancreatic abdominal NETs and PNETs, whether benign or malignant. Differences in VTE were also investigated with Fisher exact tests between patients with abdominal malignancies and patients with malignant abdominal NETs, malignant non-pancreatic abdominal NETs, and malignant PNETs as well as for patients with benign abdominal NETs, benign non-pancreatic abdominal NETs, and benign PNETs.

Welch's *t* tests were conducted to determine if significant differences existed between patients with and without VTE based on age, body mass index, pre-op white blood cell count, pre-op albumin, pre-op hematocrit, pre-op platelets, pre-op INR, pre-op PTT, pre-op PT, red blood cell count, and operative time. Fisher exact tests and nested logistic regression models with likelihood ratio tests were used to examine the same question for sex, race, type of anesthesia, diabetes, smoking, alcohol use, functional status, history of chronic obstructive pulmonary disease, history of congestive heart failure, history of myocardial infarction, history of hypertension requiring medication, history of cerebrovascular accident, history of renal failure, dialysis, wound infection, steroid use, bleeding disorder, pre-op blood transfusion, pre-op sepsis, pregnancy, operation in the previous 30 days, emergency surgery, wound class, ASA class, and lesion type benign or malignant as well as non-pancreatic abdominal NET or PNET. These same variables, with the exception of lesion type (benign or malignant), were then investigated in the same manner to determine if significant differences existed between patients with benign and malignant neoplasms. Given the large number of variables examined, the false discovery rate was controlled at 0.05 using the Benjamini-Hochberg procedure. Variables found to be significantly different when comparing patients with both benign versus malignant lesions and patients with VTE versus no VTE were included in nested multivariable regression models to predict VTE. All analyses were conducted in R 3.3.2 (Austria, R Core Team).[16]

Results

Our NSQIP database review found 8104 patients with NETs, and 7226 had abdominal NETs subcategorized as benign (2154) or malignant (5072). Of the patients with malignant NETs, 1163 had PNETs, while 3909 had non-pancreatic abdominal NETs. We also found 169,350 patients that had other abdominal malignancies.

The overall incidence of 30-day post-procedure VTE for patients with abdominal NETs was 2.0%. No significant difference in VTE rate was found when comparing patients with benign, malignant, and poorly differentiated NETs to each other (1.7% vs. 2.0% vs. 2.5% respectively, $p = 0.38$). There was, however, a significant difference between patients with non-pancreatic abdominal NETs and PNETs (1.5% vs. 3.3%, $p < 0.001$) whether they were benign (1.1% vs. 3.2%, $p = 0.001$) or malignant (1.7% vs. 3.4%, $p < 0.001$). These results are summarized in Fig. 1. Of patients with non-pancreatic abdominal NETs, 49.4% of the VTE events were PEs, this rate was 54.1% for patients with PNETs.

Patients with malignant NETs were also compared to patients with other malignant abdominal tumors, and did not have significantly different rates of VTE (2.1% vs. 2.4%, $p = 0.16$). When subcategorized, however, patients with malignant non-pancreatic abdominal NETs did have a significantly lower rate of VTE compared to patients with other abdominal malignancies (1.7% vs. 2.4%, $p < 0.001$). Conversely, patients with malignant PNETs had significantly higher incidence of VTE than patients with other abdominal malignancies (3.4% vs. 2.4%, $p = 0.03$).

Patients with benign NETs were also compared to patients with other abdominal malignancies, and did have significantly lower rates of VTE (1.7% vs. 2.4%, $p = 0.03$). When subcategorized, patients with benign non-pancreatic abdominal NETs did have a significantly lower rate of VTE compared to patients with other abdominal malignancies (1.1% vs. 2.4%, $p < 0.001$). However, patients with benign PNETs did not have significantly different incidence of VTE than patients with other abdominal malignancies (3.2% vs. 2.4%, $p = 0.21$).

When comparing NET patients with and without VTE via univariable analysis, older age, lower pre-op hematocrit, longer operative time, lower pre-op albumin, having a bleeding disorder, higher ASA class, and having a PNET were associated with an increase in 30-day post-procedure VTE (Table 1). On multivariable analysis, four variables were associated with a significant increase in VTE: (1) longer operative time, (2) lower pre-operative albumin, and (3) diagnosis of a bleeding disorder (4) having a PNET (Table 2).

Discussion

This is the first study to analyze the incidence of VTE in patients with abdominal NETs in a large prospective contemporary database and it shows that patients with benign or malignant non-pancreatic NETs have significantly lower

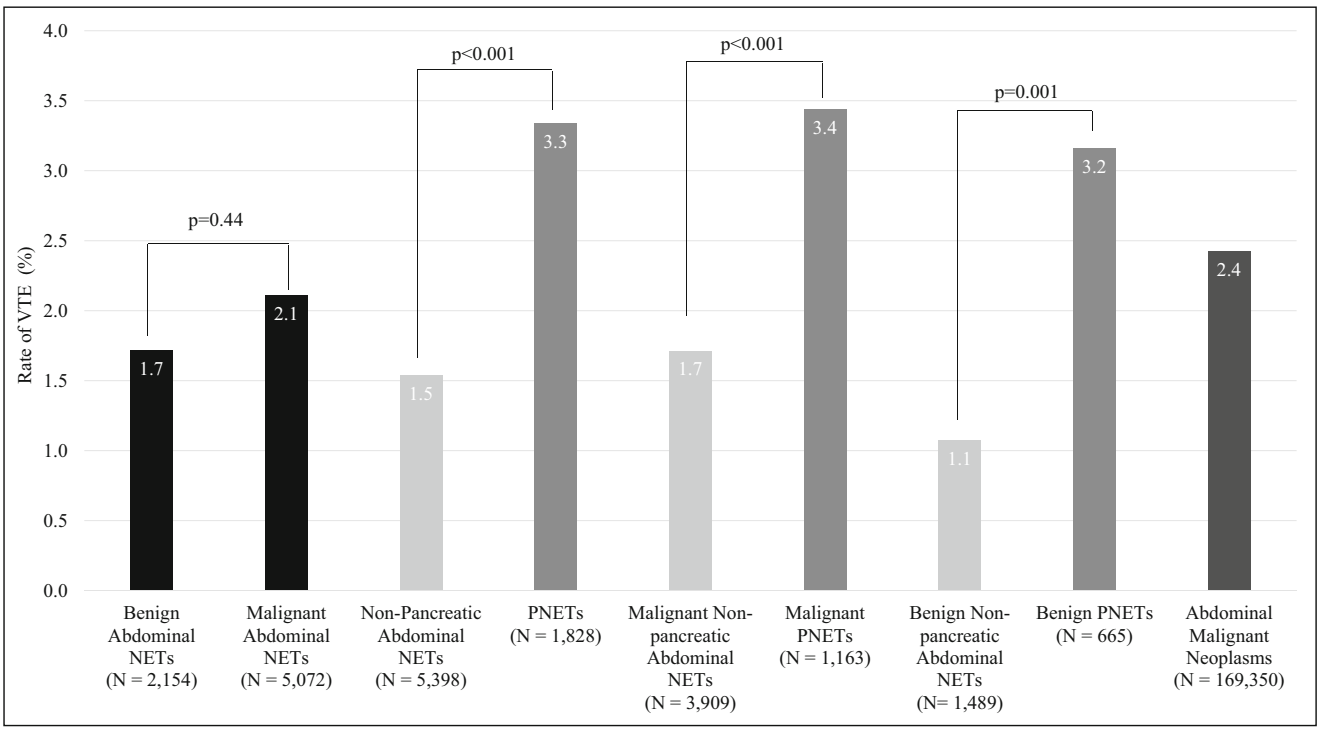

Fig. 1 Venous thromboembolism (VTE) rate for patients by type of neuroendocrine tumor (NET). The p value listed is for comparison between particular NET groups; VTE rate of patients with other abdominal malignant neoplasms is shown for reference

Table 1 Significant predictive variables of venous thromboembolism (VTE) in neuroendocrine tumor (NET) patients on univariable analysis as well as benign versus malignant versus poorly differentiated NETs

Variable	No VTE	VTE	*p* value
Age	59.5 (14.0)	62.7 (12.8)	0.02
Pre-op hematocrit	39.6 (5.2)	38.3 (6.2)	0.01
Operative time (min)	184.3 (118.0)	264.7 (169.1)	< 0.001
Pre-op albumin	4.0 (0.6)	3.7 (0.7)	< 0.001
Steroid			0.02
No	98.2%	1.8%	
Yes	94.6%	5.4%	
Bleeding disorder			< 0.001
No	98.2%	1.8%	
Yes	92.6%	7.4%	
ASA class			< 0.001
ASA class 1	99.6%	0.4%	
ASA class 2	98.6%	1.4%	
ASA class 3	97.9%	2.1%	
ASA class 4	100%	0%	
ASA class 5	100%	0%	
Pancreatic neuroendocrine tumor			< 0.001
Other neuroendocrine tumors	98.5%	1.5%	
Pancreatic neuroendocrine tumor	96.7%	3.3%	
Malignancy of neuroendocrine tumor			0.38
Benign	98.3%	1.7%	
Malignant	98.0%	2.0%	
Poorly differentiated	97.5%	2.5%	

Means and standard deviations are presented for all numeric variables. Bleeding disorder, ASA class, and steroid use are given as proportions

VTE rates than patients with benign or malignant PNETs or patients with other abdominal malignancies. The differences identified suggest that extended VTE prophylaxis could potentially be relaxed in benign and malignant non-pancreatic NETs.

PNETs often present with more advanced disease by stage and malignancy than non-pancreatic NETs and may contribute to higher rates of VTE among patients with NETs.[13] Although patients with malignant NETs have a VTE rate of 2.1%, the rate falls to 1.7% and is significantly lower than that of patients with other abdominal malignancies (2.4%) when patients with malignant PNETs (3.4%) are excluded. The reason why VTE rate for patients with benign NETs (1.6%) was not significantly different than for patients with malignant NETs (2.0%) is likely because the benign NET group included patients with benign PNETs that have a VTE rate of 3.2%. This study suggests that non-pancreatic vs. PNET type may be as or more important as having a benign vs. malignant NET in terms of patient risk of developing VTE. PNET was also shown to be an independent risk factor for VTE on multivariable analysis.

There is a progressive range of VTE rates as patient tumor type progresses from benign non-pancreatic abdominal NET to malignant PNET. On the low end of the spectrum, the VTE incidence of 1.1% for patients with benign non-pancreatic abdominal NETs is equivalent to the "high risk" general surgery VTE group that does not receive extended (i.e., 4 weeks) VTE prophylaxis as described in a previous study that validated the Caprini Score and its VTE risk levels (low, moderate, high, and highest).[2] Conversely, malignant PNETs had a significantly higher VTE rate (3.4%) compared to other abdominal malignancies (2.4%), a rate that falls into the "highest risk" Caprini Score category in the same validated study.[2] When compared to other NSQIP studies, PNETs have a similar or higher VTE rate than patients undergoing hepatectomies and pancreatectomies (2.8–3.2%), GI oncologic surgery (2.6%), and surgery for IBD and malignant colon cancer (2.74% and 1.74%) for all of which extended VTE prophylaxis has been advocated.[17–20] Therefore, although guidelines suggest all malignant cancers receive extended VTE prophylaxis, some patients with malignant NETs may be at less risk, like patients with malignant non-pancreatic abdominal NETs, while other patients with benign NETs may be more at risk, like patients with benign PNETs.

Our secondary aim was to identify risk factors associated with increased VTE rates in patients with abdominal NETs

Table 2 Odds ratios (OR) for significant predictive variables of venous thromboembolism in neuroendocrine tumor patients on multivariable analysis

Variables	OR	2.5%	97.5%	*p* value
Operative time (h)	1.27	1.19	1.36	< 0.001
Pre-op albumin (decreasing, per 1 unit)	2.12	1.60	2.81	< 0.001
Bleeding disorder (yes)	3.54	1.95	6.43	< 0.001
Pancreatic neuroendocrine tumor (yes)	1.53	1.01	2.31	0.04

undergoing surgery. Low pre-operative albumin and having a bleeding disorder were independent risk factors identified on multivariable analysis. Pre-operative albumin is a surrogate marker for the patient's depleted nutritional state, may lead to venous stasis, and is a known risk factor for VTE.[21,22] Having a bleeding disorder has also previously been shown to elevate risk of VTE in surgical patients in general.[9,22] Since the NSQIP database does not provide information specifying the type of bleeding disorder or whether adequate treatment has been provided, this finding is difficult to further interpret. However, extra consideration for VTE prophylaxis should be taken for patients with these risk factors since they were shown to increase the odds of VTE in NETs by 2.12 (low pre-operative albumin) and 3.54 (bleeding disorder).

Increased operative time was also identified as an independent risk factor. Increased operative time can lead to increase venous stasis which causes endothelial injury from venous wall distension.[23] Surgery also causes a hypercoagulable state due to inflammation and endothelial damage that triggers the clotting cascade.[23] In this study, the odds of VTE increased by 1.27 with each additional hour in the operating room. Therefore, all other things being equal, the calculated incidence of VTE in benign non-pancreatic abdominal NETs would equal that of other malignant neoplasms after an additional 3.3 h in the operating room.

This study has multiple limitations. First, the NSQIP database does not provide information on perioperative or postoperative use of sequential compression devices or pharmacologic prophylaxis. We assumed that because this study included patients from 2008 to 2015 and modern guidelines for extended VTE prophylaxis in cancer patients were published in 2004 and 2007 by the ACCP and ASCO respectively, that many patients received some amount of VTE prophylaxis as corroborated by Henke et al. and likewise assumed in other similar studies.[5,24–26] We attempted to overcome this limitation in our study by comparing the rate of VTE in all patients with abdominal NETs to the rates of VTE in all patients with malignant abdominal neoplasms presuming that they received a comparable treatment in the same time period. Second, we cannot completely exclude a surveillance bias, as clinicians could have considered patients with NETs less prone to VTE and therefore surveille them less frequently. Third, NSQIP does not clarify how VTEs were discovered and if they were symptomatic or not; however, this systematic bias applies to both the NET and control group. Fourth, ICD 9 codes limit describing NETs as benign, malignant, or poorly differentiated without direct information on tumor stage or grade.[27] Regardless, even with the assumption that, per the ICD coding system, "benign" NET means localized disease, "malignant" NET means metastasized disease (to lymph nodes or distant sites), and "poorly differentiated" NET means high-grade morphology, and we found no statistically significant differences among these subtypes. Finally, the NSQIP database limits the assessment of complications to the 30-day postoperative period, but VTE events may occur beyond the 30-day mark.

Conclusion

Patients with malignant non-pancreatic abdominal NETs appear to have a significantly lower rate of VTE while patients with malignant PNETs have a significantly higher rate of VTE when compared to patients undergoing surgery for other abdominal malignancies. Clinicians can use this information and the risk factors identified in this study when considering individualizing extended post-operative VTE prophylaxis in patients with abdominal NETs.

Authors' Contribution Each author above contributed substantially to the design of the work or the data acquisition, analysis, or interpretation. All authors contributed to the drafting and revising of the work and approved the final version of the manuscript.

Compliance with Ethical Standards

Disclosures None of the authors has any disclosures or competing interests.

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References

1. Caprini JA. Risk assessment as a guide for the prevention of the many faces of venous thromboembolism. *Am J Surg*. 2010;199(1): S3-S10.
2. Bahl V, Hu HM, Henke PK, Wakefield TW, Campbell DA, Caprini JA. A validation study of a retrospective venous thromboembolism risk scoring method. *Ann Surg*. 2010;251(2):344–350.
3. Spyropoulos AC, Hussein M, Lin J, Battleman D. Rates of symptomatic venous thromboembolism in US surgical patients: A retrospective administrative database study. *J Thromb Thrombolysis*. 2009;28(4):458–464.
4. Rasmussen M, Jorgensen L, Wille-Jorgensen P. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery (Review). *Cochrane Database Syst Rev*. 2009;(1):1–18.

5. Lyman GH, Khorana AA, Falanga A, Clarke-Pearson D, Flowers C, Jahanzeb M, Kakkar A, Kuderer NM, Levine MN, Liebman H, Mendelson D, Raskob G, Somerfield MR, Thodiyil R, Trent D, Francis CW. American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. *J Clin Oncol*. 2007;25(34): 5490–5505.
6. Bergqvist D, Agnelli G, Cohen AT, Eldor A, Nilsson PE, Moigne-Amrani AL, Dietrich-Neto F. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *N Engl J Med*. 2002;346(13):975–980.
7. Rasmussen MS, Jorgensen LN, Wille-Jørgensen P, Nielsen JD, Horn A, Mohn AC, Somod L, Olsen B. Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicenter randomized open-label study. *J Thromb Haemost*. 2006;4(11):2384–2390.
8. Fagarasanu A, Alotaibi GS, Hrimiuc R, Lee AYY, Wu C. Role of extended thromboprophylaxis after abdominal and pelvic surgery in cancer patients: A systematic review and meta-analysis. *Ann Surg Oncol*. 2016;23:1422–1430.
9. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, Samama CM. Prevention of VTE in nonorthopedic surgical patients. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 SUPPL.):227–277.
10. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schnemann HJ. Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl.):7–47.
11. Streiff MB, Bockenstedt PL, Cataland SR, Chesney C, Eby C, Fanikos J, Fogerty AE, Gao S, Goldhaber SZ, Hassoun H, Hendrie P, Holmstrom B, Kuderer N, Lee JT, Millenson MM, Neff AT. Venous thromboembolic disease clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2013;11(11):1402–1429.
12. Harris JW, Mark EB. Small Intestine. In: Townsend CM, Beauchamp RD, Evers BM, Mattox KL, ed. *Sabiston Textbook of Surgery The Biological Basis of Modern Surgical Practice*. 20th ed. Philadelphia: Elsevier Inc; 2016:1272–1276.
13. Yao JC, Hassan M, Phan A, Dogohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey J, Rashid A, Evans DB. One hundred years after "carcinoid": Epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol*. 2008;26(18):3063–3072.
14. Bilimoria KY, Bentrem DJ, Wayne JD, Ko CY, Bennett CL, Talamonti MS. Small bowel cancer in the United States. *Ann Surg*. 2009;249(1):63–71.
15. ACS-NSQIP. [Accessed February 1, 2017] The American College of Surgeons, 2008–2015. Available at http://site.acsnsqip.org.
16. R Core team. *R: A language and environment for statistical computing. R foundation for statistical computing , Vienna, Austria.* 2016. https://www.R-project.org/.
17. Tzeng CD, Curley SA, Vauthey J, Aloia TA. Distinct predictors of pre- versus post-discharge venous thromboembolism after hepatectomy: Analysis of 7621 NSQIP patients. *Hpb*. 2013;15(10):773–780.
18. Beal EW, Tumin D, Chakedis J, Porter E, Moris D, Zhang X, Abdel-Misih S, Dillhoff M, Manilchuk A, Cloyd J, Schmidt CR, Pawlik TM. Identification of patients at high risk for post-discharge venous thromboembolism after hepato-pancreato-biliary surgery: which patients benefit from extended thromboprophylaxis? *HPB*. 2018; 20:621–630.
19. Bellini G, Teng A, Kotecha N, Sutton E, Yang CK, Passeri M, Lee DY, Rose K. The identification of risk factors for venous thromboembolism in gastrointestinal oncologic surgery. *J Surg Res*. 2016;205(2):279–285.
20. Wilson MZ, Connelly TM, Tinsley A, Hollenbeak CS, Koltun WA, Messaris E. Ulcerative colitis is associated with an increased risk of venous thromboembolism in the postoperative period: The results of a matched cohort analysis. *Ann Surg*. 2015;261(6):1160–1166.
21. Kanth AM, Khan SU, Gasparis A, Labropoulos N. The distribution and extent of reflux and obstruction in patients with active venous ulceration. *Phlebol J Venous Dis*. 2014;30(5):350–356.
22. Rogers SO, Kilaru RK, Hosokawa P, Henderson WG, Zinner MJ, Khuri SF. Multivariable predictors of postoperative venous thromboembolic events after general and vascular surgery: results from the patient safety in surgery study. *J Am Coll Surg*. 2007;204(6): 1211–1221.
23. Kim JYS, Khavanin N, Rambachan A, McCarthy RJ, Mlodinow AS, De Oliveria GS, Stock MC, Gust MJ, Mahvi DM. Surgical duration and risk of venous thromboembolism. *JAMA Surg*. 2015;150(2):110.
24. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, Ray JG. Prevention of venous thromboembolism, the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest*. 2004;126(3 Suppl): 338S–400S.
25. Henke PK, ARya S, Pannucci C, Kubus J, Hendren S, Engelsbe M, Campbell D. Procedure-specific venous thromboembolism prophylaxis: A paradigm from colectomy surgery. *Surgery*. 2012;152(4): 528–536
26. Tzeng CD, Katz MHG, Lee JE, Fleming JB, Pisters PWT, Vauthey J, Aloia TA. Predicting the risks of venous thromboembolism versus post-pancreatectomy haemorrhage: analysis of 13771 NSQIP patients. *HPB*. 2014 Apr; 16(4):373–383
27. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO Classification of Tumours of the Digestive System, Fourth Edition. In: *International Agency for Research on Cancer*. Vol 3.; 2010:417.