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EDITORIAL – PANCREATIC TUMORS

Differences in DVT Rates in Patients Treated With and Without Preoperative Chemotherapy Prior to Distal Pancreatectomy: Is it the Therapy or Disease Burden?

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Venous thromboembolism (VTE) is a well-known complication after major oncologic surgery, with randomized trials and national guidelines supporting the use of perioperative and extended VTE prophylaxis after major oncologic surgery, including pancreatectomy.[1,2] Multiple efforts have been implemented to reduce the incidence of postoperative VTE, given the association of VTE with increased morbidity and cost. These have included standard chemical prophylaxis regimens, mechanical prophylaxis (e.g. sequential compression devices), early ambulation protocols, and extended (i.e. 28-day) prophylaxis regimens. Prior studies examining the American College of Surgeons National Surgical Quality Improvement (NSQIP) database have reported the incidence of VTE within 30 days after major pancreatic surgery to be approximately 3%.[3,4] Receipt of chemotherapy, especially platinum-based agents, is a known risk factor in and of itself for VTE. While treatment paradigms have shifted towards increased use of neoadjuvant chemotherapy for many cancer types, including pancreatic adenocarcinoma, the impact of preoperative therapy on perioperative VTE rates has not been well-characterized.[5]

In this retrospective analysis of the NSQIP database from 2014 to 2020, Robbins and colleagues evaluated the association of neoadjuvant therapy (NAT) with postoperative VTE events after distal pancreatectomy in patients with pancreatic ductal adenocarcinoma, including 1414 patients treated with NAT and 2913 patients who underwent upfront surgery.[6] Multivariable analysis suggested that patients receiving NAT experienced a 73% increased odds of 30-day postoperative deep venous thrombosis (DVT) requiring treatment compared with those who underwent upfront surgery. The absolute 30-day DVT rate was relatively low (3.5% in NAT and 2.3% in upfront surgery), consistent with prior estimates using the NSQIP database, and there was no difference in rates of pulmonary embolism (PE). In contrast to most existing literature, DVT and PE were analyzed as separate outcomes in this study, rather than combined into a single VTE outcome.

Like all database analyses, there are inherent limitations to this study, many of which the authors acknowledge. The anatomic classification of these tumors (i.e. anatomically resectable, borderline resectable, or locally advanced) remains unknown, and the specific preoperative chemotherapy regimens and number of cycles are not captured within the dataset. Additionally, the authors chose to categorize receipt of either neoadjuvant chemoradiation and/or neoadjuvant chemotherapy as NAT, thereby limiting any analysis of differential risk for postoperative VTE based on treatment modality.

Although existing data are limited to just a few retrospective, single-institution studies, there appears to be an increased risk of VTE during neoadjuvant chemotherapy for patients with pancreatic ductal adenocarcinoma, reported to be as high as 10%.[7,8] Unfortunately, NSQIP does not capture pre-existing preoperative VTE; thus, these patients could

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not be excluded from the primary study analysis. Although the misclassification rate of VTE in NSQIP is low (approximately 5%), the presence of preoperative VTE has been previously identified to be the most common reason for VTE misclassification.[9] Furthermore, the authors are unable to report the type and location of DVT, which may have important implications. Mesenteric venous thrombosis can occur prior to surgery due to tumor involvement of splenic vein or splenoportal confluence, or in the postoperative setting when vein resection and reconstruction is required. However, none of these data are available in NSQIP. Finally, and perhaps most importantly, there are no data regarding perioperative, in-hospital, or post-discharge VTE chemoprophylaxis use and compliance.

Prior studies using NSQIP data to compare VTE rates among patients with pancreatic cancer treated with or without preoperative therapy have reported conflicting findings. In one study of 3408 patients undergoing pancreatectomy, patients in the neoadjuvant cohort had higher rates of DVT (4.1% vs. 2.6%).[10] However, two other studies that used propensity matching methodology to analyze outcomes with or without NAT found no significant difference in rates of VTE, and lower rates of postoperative complications, such as postoperative pancreatic fistula, among patients who received preoperative therapy.[11,12] The limited (i.e. 30-day) follow-up time in NSQIP is a major limitation, as VTE events may occur later within the postoperative period. In one study of 384 patients with pancreatic cancer undergoing pancreatectomy, the cumulative incidence of VTE increased for 2 years following surgery, reaching 30% in the neoadjuvant cohort and 20% in the upfront surgery cohort.[13]

While the primary finding in the study by Robbins and colleagues is that rates of DVT appear higher in patients undergoing distal pancreatectomy following receipt of preoperative therapy, the important question is why? Clearly, the group receiving preoperative therapy had more advanced disease, given increased rates of an open surgical approach, vascular resection, blood transfusion, and increased operative times. Furthermore, DVT rates were higher in patients who experienced postoperative complications. Not surprisingly, prior studies have noted that postoperative complications, particularly organ space infections and/or blood transfusions, increase the risk for post-pancreatectomy VTE.[3,4] Similarly, increased operative time has been consistently associated with increased rates of VTE.[14] It seems very likely that the drivers for the observed increased DVT rates may actually be the result of selection bias in the neoadjuvant cohort, reflecting more infiltrative tumors requiring a more technically challenging resection. Only three additional variables were included in the multivariable analysis (operative year, nodal status, and operative time), which do not adequately capture these underlying confounders. While the authors performed stepwise selection of variables for their final model, this method has been challenged and may result in the omission of important, explanatory covariates.[15,16]

Future studies should leverage more detailed databases to help understand some of the questions remaining after this study. Analyses linking registry or administrative data with electronic health records or multi-institutional collaborative data may be able to address the underlying confounders by capturing additional data, such as anatomic resectability, chemotherapy regimens, number of cycles, and use of perioperative prophylaxis.

On a national level, extended prophylaxis after major cancer operations remains persistently underutilized.[17,18] Factors contributing to underutilization may include cost and lack of desire for patients to perform self-injections of low-molecular-weight heparin (LMWH). Recent literature suggests that direct oral anticoagulants (DOACs) may be an acceptable alternative to LMWH without an increased bleeding risk, but further research on the safety and efficacy of DOACs following pancreatectomy is needed.[19] Additional studies should also examine whether all patients need a full 28-days of prophylaxis, or if patients can be safely risk-stratified to shorter and longer duration prophylaxis. Postoperative complications and receipt of NAT may be clinically relevant factors to consider in this stratification. Finally, implementation studies will be necessary to ensure adequate adoption of standardized VTE prophylaxis on a systems level.

In conclusion, Robbins and colleagues have utilized a large national database to report increased rates of VTE, specifically DVT, after preoperative chemotherapy followed by distal pancreatectomy for patients with pancreatic adenocarcinoma. Despite the limitations, their work highlights the need for an increased focus on improving adoption of and compliance with extended VTE prophylaxis and further confirmatory work using more detailed multi-institutional databases with longer follow-up.

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