Incidence, Characteristics and Implications of Thromboembolic Events in Patients with Muscle Invasive Urothelial Carcinoma of the Bladder Undergoing Neoadjuvant Chemotherapy

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Purpose: Neoadjuvant chemotherapy and pelvic surgery are significant risk factors for thromboembolic events. Our study objectives were to investigate the timing, incidence and characteristics of thromboembolic events during and after neoadjuvant chemotherapy and subsequent radical cystectomy in patients with muscle invasive bladder cancer.

Materials and Methods: We performed a multi-institutional retrospective analysis of 761 patients who underwent neoadjuvant chemotherapy and radical cystectomy for muscle invasive bladder cancer from 2002 to 2014. Median followup from diagnosis was 21.4 months (range 3 to 272). Patient characteristics included the Khorana score, and the incidence and timing of thromboembolic events (before vs after radical cystectomy). Survival was calculated using the Kaplan-Meier method. The log rank test and multivariable Cox proportional hazards regression were used to compare survival between patients with vs without thromboembolic events.

Results: The Khorana score indicated an intermediate thromboembolic event risk in 88% of patients. The overall incidence of thromboembolic events in patients undergoing neoadjuvant chemotherapy was 14% with a wide variation of 5% to 32% among institutions. Patients with thromboembolic events were older (67.6 vs 64.6 years, $p = 0.02$) and received a longer neoadjuvant chemotherapy course (10.9 vs 9.7 weeks, $p = 0.01$) compared to patients without a thromboembolic event. Of the thromboembolic events 58% developed preoperatively and 72% were symptomatic. On multivariable regression analysis the development of a thromboembolic event was not significantly associated with decreased overall survival. However, pathological stage and a high Khorana score were adverse risk factors for overall survival.

Conclusions: Thromboembolic events are common in patients with muscle invasive bladder cancer who undergo neoadjuvant chemotherapy before and after radical cystectomy. Our results suggest that a prospective trial of thromboembolic event prophylaxis during neoadjuvant chemotherapy is warranted.

Abbreviations and Acronyms

CT = computerized tomography

DVT = deep vein thrombosis

MIBC = muscle invasive bladder cancer

MVAC = methotrexate, vinblastine, doxorubicin and cisplatin

NAC = neoadjuvant chemotherapy

PE = pulmonary embolism

RC = radical cystectomy

TEE = thromboembolic event

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LEVEL I evidence suggests that platinum based NAC in combination with RC is associated with a significant survival advantage in patients with MIBC compared to RC alone.[1] This patient population is at risk for TEEs for several reasons. The risk of a TEE is increased as much as 70-fold in patients with cancer in general,[2–4] likely due to the malignancy induced hypercoagulable state[5] and immobilization.[6,7] In the particular population under study the TEE risk is further compounded by NAC, especially platinum based chemotherapy,[8] as well as pelvic surgery.[9] In a Danish population based study the risk of venous thromboembolism in patients with bladder cancer within 3 months of diagnosis was 70-fold higher than in the general population with a particularly high risk after RC.[2] A meta-analysis of 24,861 patients with bladder cancer documented a 1-year 5.3 standardized incidence ratio for venous thromboembolism compared with that of the general population.[10]

While guidelines exist that support prolonged postoperative TEE prophylaxis in surgical patients with cancer who undergo abdominal or pelvic surgery,[9] to our knowledge there are currently no guidelines or practice recommendations related to TEE prophylaxis in patients with MIBC during the NAC treatment course. Guidelines for patients with cancer in general also do not include recommendations on thromboprophylaxis during chemotherapy.[11] This is probably due to limited data related to the incidence and natural history of TEE in this patient population.

Our initial study based on data from McMaster University showed an overall TEE incidence of 8.4% in all 202 patients undergoing RC, which increased to 19.1% in patients treated with both NAC and RC.[12] The objectives of the current study were to investigate the incidence, characteristics and implications of TEE during and after NAC and subsequent RC for MIBC in a multi-institutional retrospective study. We present data that indicate a high incidence of TEE at the time of NAC administration when no standard TEE prophylaxis is practiced, as well as postoperatively.

MATERIALS AND METHODS

Patient Population

The study was approved at the lead institution (McMaster University, Juravinski Hospital) by the Hamilton Integrated Research Ethics Board under study number 12-243-C as well as by institutional review boards at all other centers. Ten tertiary centers, including 3 each in Canada and Europe, and 4 in the United States, were approached to identify patients who underwent NAC and subsequent RC for MIBC from 2002 to 2014. The 21 patients already on anticoagulant medication were excluded from study.

The incidence of TEE was the primary end point of this study. A TEE was defined as a venous, arterial or central venous port site thrombosis, or DVT, stroke or PE. The incidence of TEE was determined retrospectively in 761 consecutive patients. The timing of TEE was measured from the start of NAC and categorized as preoperative (before RC), early postoperative (within 1 month after RC) or late postoperative (within 6 months after RC). If more than 1 TEE developed, the time and type of the first event were used for analysis. TEEs were classified as clinical (symptomatic) or incidental (detected by imaging performed for unrelated reasons, such as CT for staging). Postoperative prophylaxis was administered in the more contemporary patients in the study. However, type and duration varied across institutions, ranging from warfarin, Fragmin® (dalteparin), or unfractionated or low molecular weight heparin for the duration of hospitalization to up to 6 weeks postoperatively. Those data were not specifically captured.

The Khorana score, which was established to assess the risk of TEE in patients with cancer treated with chemotherapy, was determined prior to NAC in all patients. The Khorana score is based on baseline hemoglobin, platelet and leukocyte counts as well as on body mass index and tumor site.[13] Other patient characteristics for which data were collected included age, gender, antiplatelet and anticoagulant medication use, history of prior TEE, type and duration of NAC, histology, pathological stage, complete response after NAC (pT0N0), disease progression and survival.

Statistical Analysis

Categorical and continuous variables were compared between patients with and without a TEE using the chi-square test and the Wilcoxon rank sum test, respectively. Kaplan-Meier survival curves and the log rank test were used to compare survival between patients in whom TEE did and did not develop. Multivariable Cox proportional hazards regression was used to determine the HR and 95% CI of cancer specific and overall survival, and assess the association between TEE development and these outcomes after adjusting for age, Khorana score and pathological stage. Statistical analyses were performed using SPSS®, version 23 with $p < 0.05$ considered significant.

RESULTS

At 10 tertiary centers across North America and Europe a total of 761 patients were identified who underwent NAC and subsequent RC for MIBC. Median followup from MIBC diagnosis was 21.4 months (range 3 to 272) in all patients and 25.6

months (range 3 to 272) in survivors. Table 1 lists patient characteristics stratified by TEE status.

One TEE developed in 101 patients each and 2 TEEs, separated in time, developed in 4 each. The incidence of any TEE across the 10 institutions was 13.8% (fig. 1, *A*). Of the TEEs 71.6% were detected clinically whereas 28.4% were detected incidentally by imaging performed for unrelated reasons, most commonly chest CT for restaging. Of the 99 TEEs for which the type of TEE was known 49 (49.5%) were DVT and 33 (33.3%) were PE while 4 patients presented with a DVT and PE simultaneously. Seven TEEs presented as arterial emboli, 6 were port site thromboses, of which 1 was fatal, and none of the patients experienced a stroke. Of the 99 TEEs for which the timing of the TEE was known 57 (57.6%) occurred before RC, 19 (19.2%) occurred within 1 month of RC and 27 (27.3%) occurred between 1 and 6 months following RC (fig. 1, *B*). The type and timing of the TEE was not available for 6 patients. Also, we observed a broad, statistically significant 5.4% to 32.1% variation in TEE incidence among the 10 institutions ($p < 0.001$). Figure 2 shows the cumulative hazard plot of TEE occurrence with time.

Patients in whom a TEE developed were on average older (age 67.6 vs 64.6 years, $p = 0.02$) and had longer NAC courses (10.9 vs 9.7 weeks, $p = 0.01$). Gender, Khorana score, NAC regimen and pathological TNM stage did not differ significantly between patients with and without TEE (table 1). The preNAC Khorana risk score was 1 or 2 in 88% of patients for whom it was available, indicating intermediate TEE risk.

Mean overall survival in patients in whom TEE did and did not develop was 43.4 (95% CI 31.5–55.2) vs 68.7 months (95% CI 62.8–74.7, $p = 0.06$). There was also only a trend toward decreased cancer specific survival ($p = 0.07$). Development of a TEE preoperatively was not significantly associated with overall survival whereas a postoperative TEE that occurred more than 30 days after RC was associated with worse overall survival ($p = 0.03$). On multivariable regression analysis a TEE was not significantly associated with decreased overall survival (table 2). However, pathological stage and a high Khorana score were adverse risk factors for overall survival.

DISCUSSION

Our data clearly demonstrate that TEEs are common in patients with MIBC who undergo NAC followed by RC with 58% of TEEs developing preoperatively during or after NAC. To our

Table 1. *Patient characteristics*

	NonTEE		TEE		p Value
Total No. pts	656		105		—
	Preop				
Median age at diagnosis (IQR)/761 pts	64.6 (57.3–71.3)		67.6 (59.4–73.0)		0.02 (Wilcoxon rank sum test)
No. gender (%)/761 pts:					0.39 (Fisher exact test)
M	494	(75.3)	75	(71.4)	
F	162	(24.7)	30	(28.6)	
No. Khorana score (%)/594 pts:					0.79 (Wilcoxon rank sum test)
1	315	(62.8)	58	(62.4)	
2	129	(25.8)	22	(23.6)	
3	51	(10.2)	11	(11.8)	
4	6	(1.2)	2	(2.2)	
No. antiplatelet medication (%)/594 pts	92	(18)	25	(24)	0.02 (Fisher exact test)
Median wks NAC (IQR)/614 pts	9.7	(7.0–12.0)	10.9	(7.7–12.9)	0.01 (Wilcoxon rank sum test)
No. NAC cycles (%)/710 pts:					0.10 (Fisher exact test)
1–3	267	(43.6)	34	(34.7)	
4–8	345	(56.4)	64	(65.3)	
No. NAC regimen (%)/745 pts:					0.34 (Fisher exact test)
MVAC	150	(23.4)	16	(15.5)	
Gemcitabine/cisplatin	371	(57.8)	70	(68.0)	
Gemcitabine/carboplatin	48	(7.5)	7	(6.8)	
Cisplatin/etoposide	21	(3.3)	4	(3.9)	
Cisplatin	9	(1.4)	0		
Other	43	(6.7)	6	(5.8)	
	Postop				
No. pathological stage (%)/726 pts:					0.42 (Fisher exact test)
pT0	151	(24.3)	22	(21.4)	
pTa-pT2	194	(31.2)	27	(26.0)	
pT3-pT4	106	(17.0)	19	(18.3)	
pTxN+	171	(27.5)	36	(34.6)	
Median No. lymph nodes removed (IQR)/745 pts	21	(12–39)	23	(14–40)	0.09 (Wilcoxon rank sum test)
No. progression (%)/630 pts	166	(30.9)	40	(43.5)	<0.001 (log rank test)
No. dead at last followup (%)/754 pts	201	(30.8)	39	(38.6)	0.06 (log rank test)

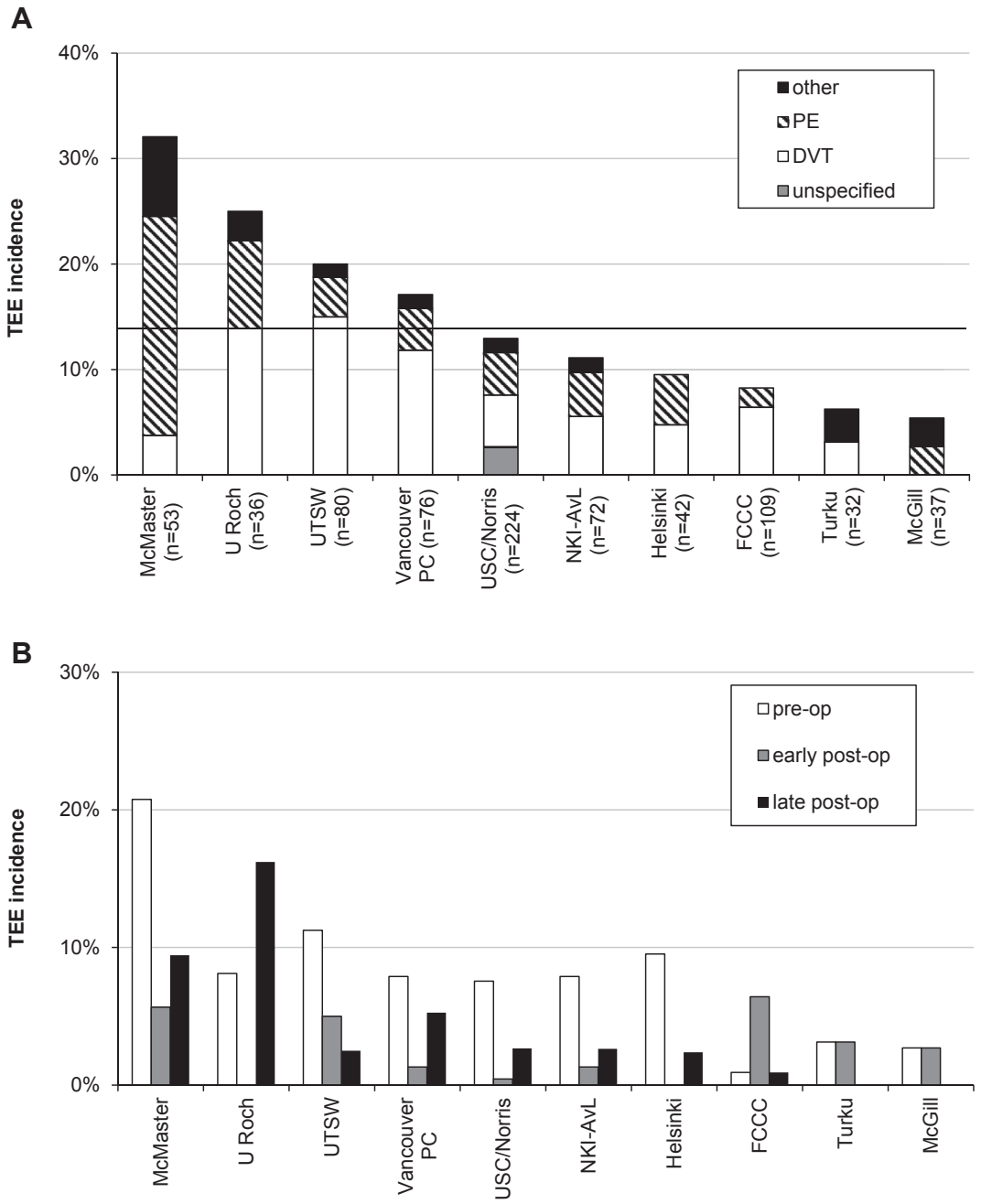

Figure 1. *A*, incidence of any TEE by institution and TEE type. Institution and total number of patients contributed by each institution are listed in decreasing order of TEE incidence. Horizontal line indicates 13.8% incidence across all centers. *B*, TEE timing relative to RC by center. *McMaster*, McMaster University. *U Roch*, University of Rochester. *UTSW*, University of Texas Southwestern Medical Center. *Vancouver PC*, Vancouver Prostate Centre. *NKI-AvL*, Netherlands Cancer Institute-Antoni van Leuwenhoek Hospital. *Helsinki*, Helsinki University Hospital. *FCCC*, Fox Chase Cancer Center. *Turku*, Turku University Hospital. *McGill*, McGill University.

knowledge this is a novel observation because the literature related to TEEs in patients with bladder cancer has to date focused on those with metastatic disease,[10,14] those who receive primary chemotherapy[15] or those undergoing RC.[16,17] Studies of the risk of TEE during NAC are currently lacking.

VanDlac et al reported a TEE rate of 6% in American patients undergoing RC with a mean time from RC to TEE of 15.2 days.[17] Risk factors were age, operative time, sepsis and length of hospital stay. Although the study did not factor in the potential effect of NAC, the reported overall incidence exactly mirrors our postoperative incidence of 6%. Similarly, in a retrospective study of patients with bladder cancer undergoing RC Sun et al reported a post-RC symptomatic TEE incidence of 6.4% in a

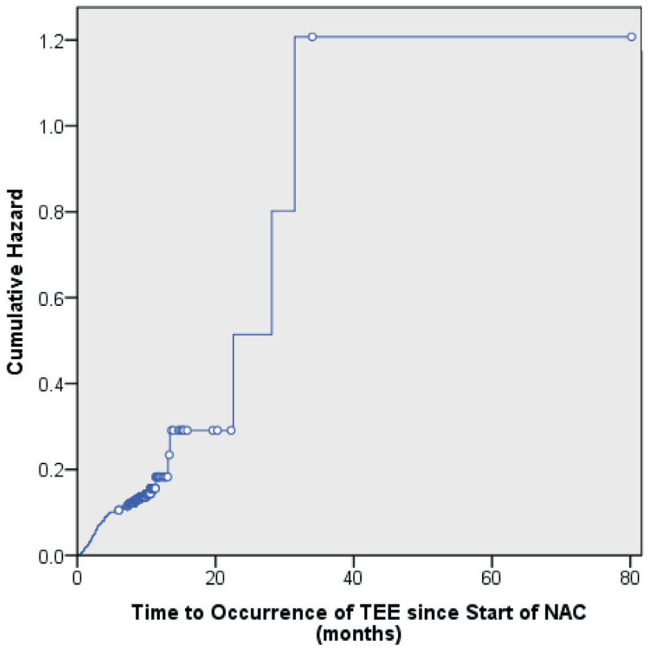

Figure 2. Cumulative hazard plot shows TEE development vs time from NAC start to TEE. University of Southern California-Norris Comprehensive Cancer Center data are not shown as data were unavailable on time from NAC start to RC in patients without TEE. Censoring occurred 6 months after RC (open circles) in patients without TEE. Median time from NAC start to RC was 3.53 months (range 1.22 to 74.2).

subgroup of 388 patients despite the use of unfractionated heparin prophylaxis.[18] The most recent AUA (American Urological Association) Best Practice Statement published in 2009 only addresses venous thromboembolism prophylaxis during the postoperative period[19] and compliance with these recommendations among AUA members is reportedly low.[20] Likewise, even with the use of thromboprophylaxis after RC a median TEE rate of 2.0% (range 0% to 6.4%) in the early postoperative period was documented in our study. Importantly, TEEs continued to develop even after 30 days following RC, which is past the time of extended TEE prophylaxis recommended in guidelines for patients who undergo pelvic surgery for cancer.[9]

Table 2. *Univariable and multivariable regression analyses with respect to overall survival*

	Univariable		Multivariable	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age	1.02 (1.01–1.03)	0.004	1.01 (1.00–1.03)	0.15
TEE:				
None	Referent		Referent	
Any development	1.40 (0.99–1.97)	0.06	0.99 (0.67–1.45)	0.94
TNM pathological stage:				
pT0	Referent		Referent	
pTa-pT2	1.94 (1.10–3.41)	0.002	1.70 (0.95–3.05)	0.08
pT3-pT4	6.51 (3.80–11.18)	<0.001	5.08 (2.85–9.04)	<0.001
pTxN+	10.25 (6.15–17.09)	<0.001	8.46 (4.99–14.36)	<0.001
Khorana score:				
1	Referent		Referent	
2	1.46 (1.05–2.05)	0.03	1.36 (0.97–1.92)	0.08
3	1.63 (1.07–2.48)	0.02	1.11 (0.72–1.72)	0.63
4	4.20 (1.84–9.60)	0.001	5.56 (2.40–12.88)	<0.001

In patients with metastatic or locally advanced solid tumors who are treated with chemotherapy several placebo controlled studies have demonstrated that pharmacological thromboprophylaxis results in a statistically significant reduction in TEEs without significantly increasing the risk of bleeding.[21–24] In contrast, other studies showed no significant benefit.[25] Currently, to our knowledge there are no recommendations for routine outpatient TEE prophylaxis in patients with cancer during systemic chemotherapy but this is an active area of research and recommendations may change.[26] Notably, most of the aforementioned studies, which were performed in different or diverse advanced cancer populations and were not limited to bladder cancer, demonstrated a 3.4% to 4.4% TEE incidence in the placebo group.[21–23,25] This rate is remarkably lower than the 7.6% preoperative rate in our study, suggesting that outpatients with MIBC who undergo NAC are at high risk for TEE and should be the subject of a trial to investigate whether TEE prevention is justified. In patients with pancreatic cancer, in whom the rate of TEE is substantially higher, dalteparin has achieved an 85% risk reduction from a 23% TEE incidence rate in patients who received gemcitabine alone to 3.4%.[24] Risk reductions due to thromboprophylaxis in the other studies range from 49% to 85%.[21–23]

While the overall risk of TEE in our patients undergoing NAC followed by RC was 13.8%, representing 1 of 7 patients, we noted a wide and statistically significant variation (5.4% to 32.1%) in TEE incidence among the institutions. There are several possible reasons for these large differences. While TEE prophylaxis was not administered to any patients during NAC, the duration of the NAC course, the number of cycles and the regimens differed among the institutions. Indeed, the duration of NAC was significantly increased in patients with vs without a TEE, potentially putting patients at higher risk for TEE at centers where longer courses of NAC are administered. A delay in NAC due to the development of a TEE may also have caused the longer duration but delays were not captured in our study.

Different NAC regimens could also account for some of the differences, although we did not find a statistically significant difference in regimens between patients in whom a TEE developed and those in whom it did not. Nevertheless, in Helsinki and Turku all patients except 1 were treated with cisplatin/gemcitabine. At the other centers the

regimens were more variable. While the type of MVAC regimen (dose-dense vs regular) was infrequently recorded in our database, treatment with dose-dense MVAC, for which the duration of chemotherapy is generally shorter, may also explain some differences, although a smaller percent of patients with a TEE were treated with MVAC (15.5% vs 23.4%). In a recent analysis of SEER (Surveillance, Epidemiology and End Results) data on stage 2-3 bladder cancer in patients older than 65 years Gupta et al reported a 43% higher risk of TEE within the first year in patients who received platinum based chemotherapy compared to those who did not receive it.[15] Therefore, it is reasonable to believe that platinum based NAC may potentiate long-term thrombogenicity.

None of the current patients underwent routine Doppler ultrasound to exclude DVT unless clinically indicated. However, we suspect that different practices with respect to imaging performed for restaging near the completion of NAC and before RC may account for the large differences in the preoperative TEE incidence. For example, at McMaster University, where the largest number of preoperative TEEs in general and PEs in particular was detected, CT of the chest is often done routinely for restaging following NAC. In a prospective analysis of 407 oncology patients who underwent CT chest imaging for unrelated indications PE was found in up to 11% who had recently received chemotherapy.[27] The detection of unsuspected PE on staging CT in patients with cancer may have an impact on survival and complications that is similar to that of symptomatic PE.[28,29] O'Connell et al documented that in patients with cancer the finding of unsuspected PE on routine staging CT had a negative impact on survival, particularly if the PE was located more proximal than the subsegmental arterial branches.[30]

Because the use of restaging chest CT at the end of NAC at most other centers participating in this study was variable, we suspect that the incidence of TEE may actually be higher than the overall 13.8% rate reported. Given the high incidence of incidentally detected PE during NAC in our study at McMaster University[12] and its significant association with adverse clinical outcomes,[28–30] routine addition of the chest to the post-NAC restaging abdominal and pelvic CT should be considered. Since the incidence of silent DVTs in our patient population is also unknown, the value of not only routine restaging chest CT but also lower extremity Doppler ultrasound would be best addressed within the framework of a prospective prevention trial. Moreover, since the use of anticoagulants in patients with cancer treated with chemotherapy has been shown to confer a tangible survival benefit,[26] consideration of a prospective prevention trial of prophylaxis during the NAC treatment period is warranted. Our data may assist in planning such a trial. We also suggest that at the end of NAC preoperative chest CT and lower extremity Doppler ultrasound imaging be incorporated into the protocol to maximize event detection.

This study has several limitations, most notably its retrospective nature and the nonuniform use of chest imaging and TEE prophylaxis, which varied throughout the study duration at each institution. Prophylaxis regimens to prevent TEEs within the first month after RC are now mostly routine but they were not used consistently or frequently at many institutions during the early period of this study. The comorbidities and disease characteristics of these patients may be different than those in the general patient population with MIBC, given the referral nature of most participating institutions, leading to an inflated TEE rate. There were some missing data elements, particularly in the timing of RC with respect to the start of NAC, which limited the determination of risk factors for the development of TEE. We also did not capture delays or dose reductions in the administration of NAC.

CONCLUSIONS

This multicenter retrospective study shows that TEEs are common in patients with bladder cancer who undergo neoadjuvant chemotherapy followed by radical cystectomy. Further investigation is warranted in a prospective trial testing thromboprophylaxis during NAC and preoperative imaging.

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