



CLINICAL PRACTICE ARTICLE

Thromboembolic events during neoadjuvant chemotherapy in muscle invasive bladder cancer – any correlation to the central venous access? A clinical practice article [version 1; peer review: 1 approved with reservations]

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Abstract

Patients with muscle invasive bladder cancer have a generally known 5-year overall survival of approximately 58% with neoadjuvant chemotherapy (NAC). During the last decades, addition of Cisplatinum-based NAC in fit patients prior to radical cystectomy (RC), has significantly improved OS, compared to RC only. However, some published studies following NAC addition, describe an intermediate risk increase of thromboembolic events (TEEs). Placement of central venous access (CVA) before NAC has also been suggested as being a potential risk factor for thrombosis. We present a combination of images and cases from the Northern Swedish health region where three patients developed venous TEE after CVA placement for NAC-administration and found that the time until curable RC was prolonged circa one month each, with an addition of one RC cancelled. These are serious events and to our knowledge, there are no current guidelines on prevention of TEE before RC. The aim with this report was to provide examples of these events and conclude that further prospective trials are warranted on prevention and future guidelines regarding venous anticoagulant treatment for TEE that occur pre-RC in NAC-patients.

Keywords

Cystectomy, Thromboembolism, Urinary Bladder Neoplasm, Neoadjuvant Therapy, Central Venous Access

Open Peer Review

Approval Status ?


1

version 1

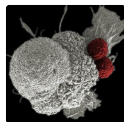
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[view](#)

1. **Katsuhiko Ito** , Kyoto University, Kyoto, Japan

Any reports and responses or comments on the article can be found at the end of the article.



This article is included in the **Oncology** gateway.

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Introduction

Muscle invasive bladder cancer (MIBC) accounts for circa 25% of all urinary bladder cancer. The 5-year overall survival (OS) is approximately 58% after three cycles of cisplatin-based neoadjuvant chemotherapy (NAC) and radical cystectomy (RC).¹ Both NAC and the risk of thromboembolic events (TEEs) has increased during the last decades. Evidence suggests that chemotherapy, in combination with the already hypercoagulable state induced by cancer, could contribute to thrombosis.^{2,3} It has also been suggested that placement of central venous access (CVA) before NAC could initiate thrombosis as well, with the potential mechanism being endothelial injury of veins.⁴ In a recent randomized controlled trial, it is also suggested that a much smaller caliber vein, where a CVA in the form of a peripherally inserted central catheter-line (PICC) is inserted, could be related to the risk of the device causing venous thrombosis. A five times higher risk (11%) of thrombosis from PICC-line was seen compared to (2%) the risk from totally implanted (PORTs), which are directly inserted in larger vessel, either the jugular or subclavian vein.⁵ To our knowledge, there are no clear guidelines on prevention of venous TEE during NAC before cystectomy. We report on three male patients with MIBC from the Swedish Northern health region, who all developed venous TEE after CVA placement, during NAC. The uniqueness of the report includes a combination of clinical information, images and existing sources on the subject presented here in a combined format.

Case 1

A 71-year-old Caucasian, male patient presented with gross hematuria. His medical history included ischemic heart disease, anti-platelet medication and prostatectomy due to prostate cancer 10 years prior to the hematuria. His previous occupation was a laborer within the steel industry before retirement. He was staged cT3N0M0 after transurethral resection of bladder (TURB) and received a PICC-line via the basilic vein in the right arm, prior to first NAC-cycle with methotrexate/vinblastine/Adriamycin/cisplatin (MVAC). Within two weeks he developed neutropenic fever, septic infection and chest pain correlated to deep breathing. A computed tomography (CT) pulmonary angiogram (CTPA) displayed multiple pulmonary embolism (PE) on a lobar artery level, to the right middle and inferior lobe (Figure 1A,B). Physical examination showed no sign of swelling in upper or lower extremities and he remained respiratory and circulatory stable. He received venous anticoagulant treatment with anti-Xa; Tinzaparin, with a daily dosage of 16000 IE (equivalent to 144 mg) for a predetermined period of six months. He received the last NAC-cycle and the RC one month delayed (Table 1). According to the most recent follow-up the patient remains in remission (Table 1).

Case 2

A Caucasian, male patient aged 74, also presenting with gross hematuria, had anti-platelet medication due to ischemic stroke in 2018, and a well-treated HIV-infection. Before retirement, he had worked for a large telephone company. The tumor was staged cT2N0M0 and he also received PICC-line via the right basilic vein and MVAC. A routine CT-scan after two cycles displayed multiple PE in the right lung (Figure 2A). The patient had symptoms of fatigue and shortness of breath, but he was respiratory and circulatory stable and physical examinations showed no signs of swelling in upper or lower extremities. He received treatment with anti-Xa; Tinzaparin at the dosage of 16000 IE to be evaluated during a period of six months. Due to deteriorated health, RC was cancelled and alternative curable treatment was recommended from a multidisciplinary conference, including urologist and oncologist. The last MVAC cycle was replaced by fluorouracil/mitomycin to be followed by radical radiotherapy. Initial dosage was 2 Gray, increased gradually to target

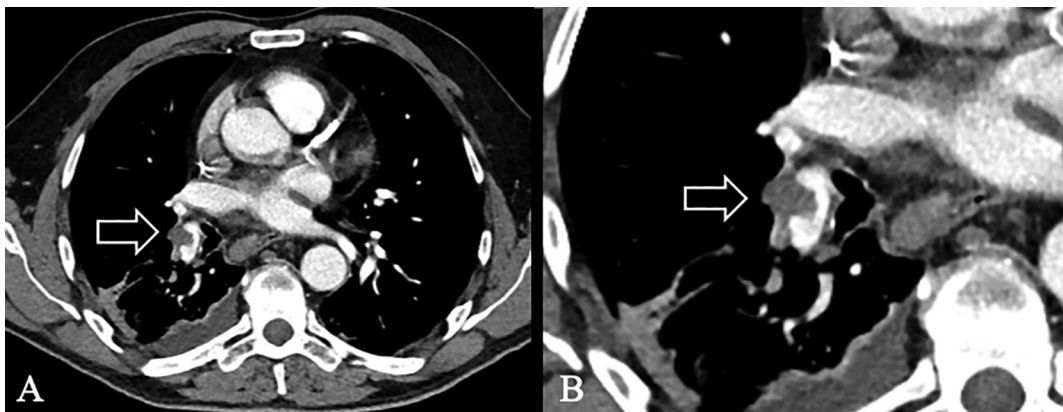


Figure 1. Image of pulmonary embolism (PE) in computed tomography pulmonary angiogram (CTPA). (A) CTPA of our first patient. PE was seen in the right lung on a lobar artery level, to the middle and inferior lobe. (B) Enhancement of PE in (A).

Table 1. Basic descriptive information of each patient. Date of diagnosis; muscle invasive bladder cancer. Age of diagnosis. cTNM stage (clinical tumor-node-metastasis). Histopathology of tumor. Smoking history in pack-years. Types of neoadjuvant chemotherapy (NAC); methotrexate/vinblastine/Adriamycin/cisplatin (MVAC), fluorouracil/mitomycin (FUMI). Number of NAC-cycles. Time from first cycle to thromboembolic event (TEE). Type of TEE. Anti-Xa Treatment; type of antithrombotic medication. Time from first NAC-cycle to radical cystectomy (RC). Radical cystectomy (RC) delayed due to TEE. pTNM stage (pathological tumor-node-metastasis: response outcome of primary tumor; stable disease; pT2-T4aN0M0, partial response; pTa, pTis, pT1.

	Patient 1	Patient 2	Patient 3
Age at diagnosis	71	74	69
cTNM stage	T3N0M0	T2N0M0	T2N0M0
Histopathology	Urothelial, nested variant	Urothelial	Urothelial, papillary
Smoking history	25 pack yrs	40 pack yrs	40 pack yrs
Type of NAC regimen	MVAC	MVAC + FUMI	MVAC
Number of NAC-cycles	3	2+1	3
Time 1 st NAC ----> TEE	12 days	22 days	30 days
Type of TEE	PE	PE	PE
Anti-Xa Treatment	16000 IE	12000 IE	12000 IE
Time 1 st NAC----> RC	3 months	No RC	4 months
RC delayed due to TEE	Yes	Cancelled	Yes
pTNM post RC	Stable disease (pT2bN0M0)	-----	Partial response (pT1N0M0)

dose of 68 Gray during 34 sessions under a period of 50 days. Follow-up CTPA after two months detected no residual PE, but the initial symptoms persisted up to a year post-TEE. According to the most recent follow-up the patient remains in remission (Table 1).

Case 3

A Caucasian male aged 69, was admitted due to suspected prostate cancer, but TURB revealed MIBC stage cT3N0M0. He had type 2 diabetes and essential hypertension. He worked in agriculture prior to retirement. The patient also received PICC-line via the right basilic vein and MVAC. After the second cycle, he developed neutropenic fever and back pain. CT scan displayed a centrally peripheral saddle PE (Figure 2B). Physical examination showed no sign of swelling in upper or lower extremities and besides symptoms such as fever, fatigue and pain, he was respiratory and circulatory stable. He received treatment with anti-Xa; Tinzaparin with the dosage of 12000 IE (equivalent to 192 mg) for a predetermined

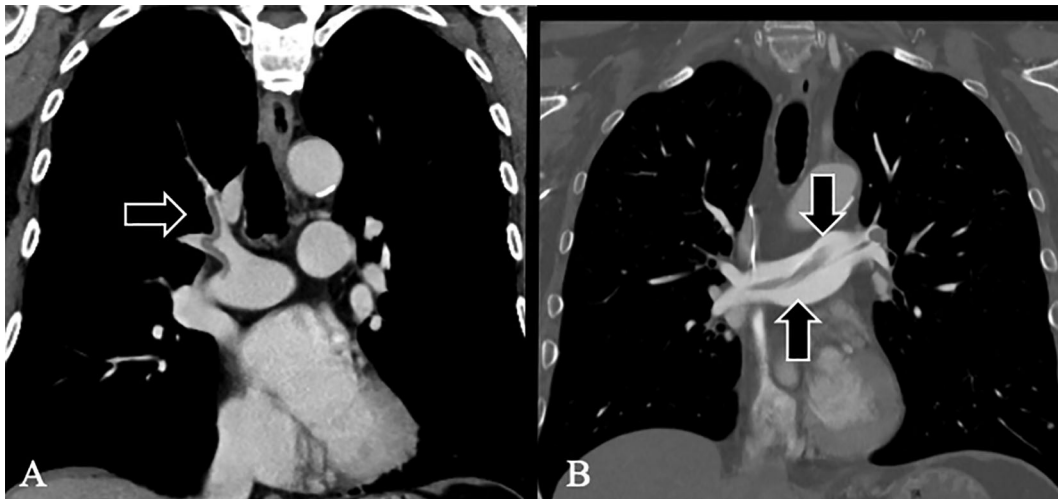


Figure 2. Image of pulmonary embolism (PE) in computed tomography (CT) chest with intravenous contrast. (A) CT chest of our second patient, with PE displayed in the right lung. (B) CT chest of our third patient, with a saddle PE displayed centrally, peripherally.

period of six months. He was fit to continue his third MVAC cycle one week post-TEE but RC was ultimately delayed one month. According to the most recent follow-up the patient remains in remission (Table 1).

Discussion

Our patients all received TEE of venous type; PE within 12-30 days after CVA (Table 1). Evidence that NAC could be a contributing factor for thrombosis has been suggested.^{2,3} Significant higher TEE ORs before RC were seen in NAC-patients compared to NAC-eligible NAC-naïve.⁴ In Zareba *et al*, TEEs had connection with CVA and preoperative TEE was associated with shorter OS (Hazard ratio 3.26; 95% confidence interval: 1.12–9.44; $p = 0.03$). NAC-patients also had a 3-fold higher incidence of TEE than NAC-naïve.³ In addition, there is a 70-fold higher risk of TEE during cancer in general.² A potential connection between TEE and the placement of CVA with following endothelial damage has also been proposed by previous studies.^{3,4} In a recent randomized controlled trial, it is also suggested that a smaller caliber vein, where PICC-line is inserted, could be related to a five times higher risk of having venous thrombosis from the device, compared to from a CVA of totally implanted (PORTs), which are directly inserted in larger vessel. Recommendations are to use PORTs rather than PICC-line on NAC-patients. PICC-line is however less staff-demanding and more common.⁵ To our knowledge, there are no current guidelines on prevention of TEE before RC, even though evidence suggests that incidental TEE of venous origin can cause significant mortality and morbidity without proper treatment. The time from diagnosis to RC was significantly longer among NAC-patients compared to NAC-naïve ($p < 0.001$).³ Our patients had similar delays, including one cancelled RC (Table 1). Prolonged time from diagnosis to RC could potentially allow metastatic dissemination. Our first and second patient had anti-platelet medication prior to diagnosis, but none had specific venous anticoagulants such as anti-Xa. Studies on whether prophylaxis on thrombosis during NAC can reduce the risk of TEE or not, have shown conflicting results.^{2,3} But in patients with pancreatic cancer, dalteparin achieved an 85% risk-reduction from a 23% TEE incidence rate to 3.4%.²

Conclusion

Evidence from literature suggests that NAC and malignancy increase the risk for TEE in MIBC-patients. CVA induced thrombosis during NAC, from endothelial damage or insertion in small caliber veins, has also been suggested as a potential mechanism for TEE. There are no current guidelines on prophylactic venous anticoagulation treatment and results from previous studies are conflicting. Time before curable operation can be prolonged if TEE arises. Further prospective trials are warranted on prevention and for developing future guidelines pre-RC regarding TEE in NAC-patients.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Consent

Written informed consent for publication of clinical details and images were specifically obtained from the patients included in this report.

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Current Peer Review Status: ?

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? **Katsuhiko Ito** 

The Department of Urology, Kyoto University, Kyoto, Japan

This is a case series to report the three patients with pulmonary thrombosis during neoadjuvant chemotherapy for urothelial carcinoma. All three patients had a central venous catheter, which the authors considered to be the cause of the emboli. This is an informative paper to raise the caution of the embolic event during the neoadjuvant phase.

My suggestion was as follows.

1. Why not check the venous thrombus around the catheter and in the leg vein via CT or ultrasound. The physical examination can not rule out the existence of a thrombus. If a massive thrombus remains, the management will be changed.
2. BMI, performance status, Hb, platelet, leucocyte, and in-hospital/ambulant setting are well-known risk factors and should be described.
3. Although there are no specific guidelines on the prevention of thromboembolism for NAC (neoadjuvant chemotherapy) before radical cystectomy. The guidelines showed that generally, patients with a high risk of thrombosis should receive prophylaxis before chemotherapy (1). The author should mention it.
4. *"But in patients with pancreatic cancer, dalteparin achieved an 85% risk-reduction from a 23% TEE incidence rate to 3.4%.²"*
The citation in this sentence seems inappropriate and makes readers confused.

References

1. Key N, Khorana A, Kuderer N, Bohlke K, et al.: Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. *Journal of Clinical Oncology*. 2020; **38** (5): 496-520 [Publisher Full Text](#)

Is the background of the cases' history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the conclusion balanced and justified on the basis of the findings?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Urology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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