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Thromboembolic events after high-intensity training during cisplatin-based chemotherapy for testicular cancer: Case reports and review of the literature

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Abstract

The randomized "Testicular cancer and Aerobic and Strength Training trial" (TAST-trial) aimed to evaluate the effect of high-intensity interval training (HIIT) on cardiorespiratory fitness during cisplatin-based chemotherapy (CBCT) for testicular cancer (TC). Here, we report on an unexpected high number of thromboembolic (TE) events among patients randomized to the intervention arm, and on a review of the literature on TE events in TC patients undergoing CBCT. Patients aged 18 to 60 years with a diagnosis of metastatic germ cell TC, planned for 3 to 4 CBCT cycles, were randomized to a 9 to 12 weeks exercise intervention, or to a single lifestyle counseling session. The exercise intervention included two weekly HIIT sessions, each with 2 to 4 intervals of 2 to 4 minutes at 85% to 95% of peak heart rate. The study was

Abbreviations: AEs, adverse events; (B)EP, (bleomycin) etoposide and cisplatin; CBCT, cisplatin-based chemotherapy; CPET, cardiopulmonary exercise test; CRF, cardiorespiratory fitness; CT, computed tomography; dRVVT, diluted Russell's viper venom test; DXA, dual-energy X-ray absorptiometry; HI(I)T, high-intensity (interval) training; HR, heart rate; RCT, randomized controlled trial; TAST, testicular cancer and aerobic- and strength training; TC, testicular cancer; TE, thromboembolic events.

prematurely discontinued after inclusion of 19 of the planned 94 patients, with nine patients randomized to the intervention arm and 10 to the control arm. Three patients in the intervention arm developed TE complications; two with pulmonary embolism and one with myocardial infarction. All three patients had clinical stage IIA TC. No TE complications were observed among patients in the control arm. Our observations indicate that high-intensity aerobic training during CBCT might increase the risk of TE events in TC patients, leading to premature closure of the TAST-trial.

KEYWORDS
cisplatin-based chemotherapy, high-intensity training, testicular cancer, thromboembolic events

1 | INTRODUCTION

The potential benefits of exercise training during and after cancer treatment have increasingly gained interest. Current evidence suggests that exercise is safe and effective to maintain or improve physical fitness and patient-reported outcomes both during and after treatment.[1-3] Cancer patients and survivors are therefore generally recommended to avoid inactivity and follow the public guidelines for physical activity if feasible.[4-6] However, the optimal intensity of exercise during cancer treatment remains unclear; particularly, the efficacy, feasibility and safety of high-intensity training (HIT) across subgroups of cancer patients.[7]

Previous randomized controlled trials (RCTs) examining effects and safety of HIT during chemotherapy have demonstrated beneficial effects and few adverse events (AEs).[8-12] Notably, only a small minority of patients in these studies were treated with cisplatin.

Cisplatin-based chemotherapy (CBCT) is standard treatment for metastatic germ cell testicular cancer (TC).[13] During CBCT, TC patients frequently experience reduced cardiorespiratory fitness (CRF) and muscle strength. Furthermore, TC survivors who have received CBCT are at risk of chronic fatigue and development of metabolic syndrome.[14,15] Given the risk of acute and long-term AEs after treatment of metastatic TC, identification of risk-reducing interventions is of high relevance. To the best of our knowledge, only one study has examined the effects of exercise during chemotherapy for TC, suggesting that high-intensity strength training was safe.[16]

In the "Testicular cancer and Aerobic and Strength Training trial" (TAST-trial), we aimed to evaluate the effects of high-intensity interval training (HIIT) on CRF in TC patients during CBCT. Here, we report on the unexpected high number of thromboembolic (TE) events among the patients randomized to the intervention.

What's new?

Exercise is widely acknowledged to be beneficial for cancer patients, but certain subgroups may experience adverse effects. Patients with testicular cancer who take cisplatin-based chemotherapy often experience reduced cardiovascular function. In this study, the authors observed an increase in thromboembolic events among testicular cancer patients taking cisplatin who engaged in HIIT twice a week. In a randomized trial, 3 out of 9 patients in the exercise arm experienced TE events, including myocardial infarction and pulmonary embolism, compared with 0 of 10 patients in the control arm. The study was cut short due to the increased risk.

2 | METHODS

2.1 | Study design and patients

The TAST-trial was a two-arm (1:1 ratio) national multicenter RCT, comparing change in CRF measured by peak oxygen uptake (VO_{2peak}) in TC patients who during CBCT underwent a training program including HIIT, to controls who received a single lifestyle counseling session. The randomization was computerized in an equal allocation and the patients were stratified by study center.

Patients were recruited at four university hospitals in Norway: Oslo University Hospital, University Hospital of North of Norway, Haukeland University Hospital and St. Olavs University Hospital, from November 2015 to November 2016. Inclusion criteria were men aged 18 to 60 years with metastatic germ cell TC and with a treatment plan of 3 or 4 cycles of cisplatin combined with etoposide (EP) or with etoposide plus bleomycin (BEP). The BEP/EP regimens were given in 3-week cycles and consisted of cisplatin 20 mg/m^2 Day 1 to 5, etoposide 100 mg/m^2 Day 1 to 5, and for BEP, bleomycin 30 mg Day 1, 5 and 15. Exclusion criteria were major physical or mental comorbidity, or not able to perform a maximal cardiopulmonary exercise test (CPET); that is, unable to cope with the equipment, or developing arrhythmias, cardiac ischemia or infarction, severe exercise-induced hypoxemia, or systolic blood pressure above 250 mmHg.

2.2 | Study assessments

All participants underwent the same assessments before and after the intervention period. The primary outcome was VO_{2peak} measured during a CPET using a continuous graded exercise protocol on a treadmill until exhaustion. Peak heart rate (HR_{peak}) assessed by 12-leads electrocardiography (ECG) was also measured during the CPET. If the rest and exercise-ECGs were normal and no cardiac symptoms occurred, no further cardiac examinations were performed. For safety reasons, pulmonary function, blood pressure and saturation were also measured before, during and after CPET, all under supervision of an exercise physiologist and a physician. Other assessments included, muscle strength tests, dual-energy X-ray absorptiometry (DXA) scan, routine blood tests and questionnaires.

After the discontinuation of the TAST-trial, the cases were assessed with regard to individual susceptibility for TE complications. Laboratory investigations were performed 3 to 10 months after the TE events for deficiencies of the natural anticoagulants (protein S, protein C and antithrombin), presence of lupus anticoagulant (subtest diluted Russell's viper venom test (dRVVT) and silica clotting time, anti-cardiolipin antibodies and anti-beta2 glycoprotein I abs) and the presence of point mutations in the coagulation factor (F)V gene (c.1601G>A; FV Leiden) and in the prothrombin gene (c.*97G>A). The prechemotherapy computed tomography (CT) scans were re-evaluated for signs of thrombosis in large vessels or pulmonary embolism.

2.3 | Intervention arm

Because CRF was the primary outcome of the trial, we composed an intervention that emphasized high-intensity aerobic exercise. The intervention included two one-to-one supervised sessions per week for 9 or 12 weeks depending on the number of chemotherapy cycles. Walking uphill on a treadmill was the primary choice of exercise, but ergometer-cycling, rowing and out-door walking were possible alternatives. Each session consisted of 10 minutes warm-up at 60% to 70% of HR_{peak}, followed by HIIT; that is, 2 to 4 intervals of 2 to 4 minutes at 85% to 95% of HR_{peak}, (high-intensity zone); separated by 2 minutes' active recovery, and followed by 10 minutes' cool-down (Figure 1). Thereafter, an optional 15 minutes strength training was performed, depending on the patient's energy level. HR_{peak} obtained during the pre-intervention CPET was used to calculate the training zones. The HR and the Borg Rating of Perceived Exertion Scale[17] were registered each minute during the HIIT. If the patients felt unwell before or during a session, the physiotherapists/personal trainers were instructed to make individual adaptations regarding the intensity, duration and/or number of intervals. If the patient's condition was not compatible with HIIT, the planned session was postponed or canceled.

2.4 | Control arm

During the first chemotherapy cycle, patients in the control arm received a 30-minute counseling session on general lifestyle recommendations.

2.5 | Sample size calculation

Based on our experience from a pilot study,[18] we expected reductions in VO_2 peak during chemotherapy by 14 mL/kg/min in the control

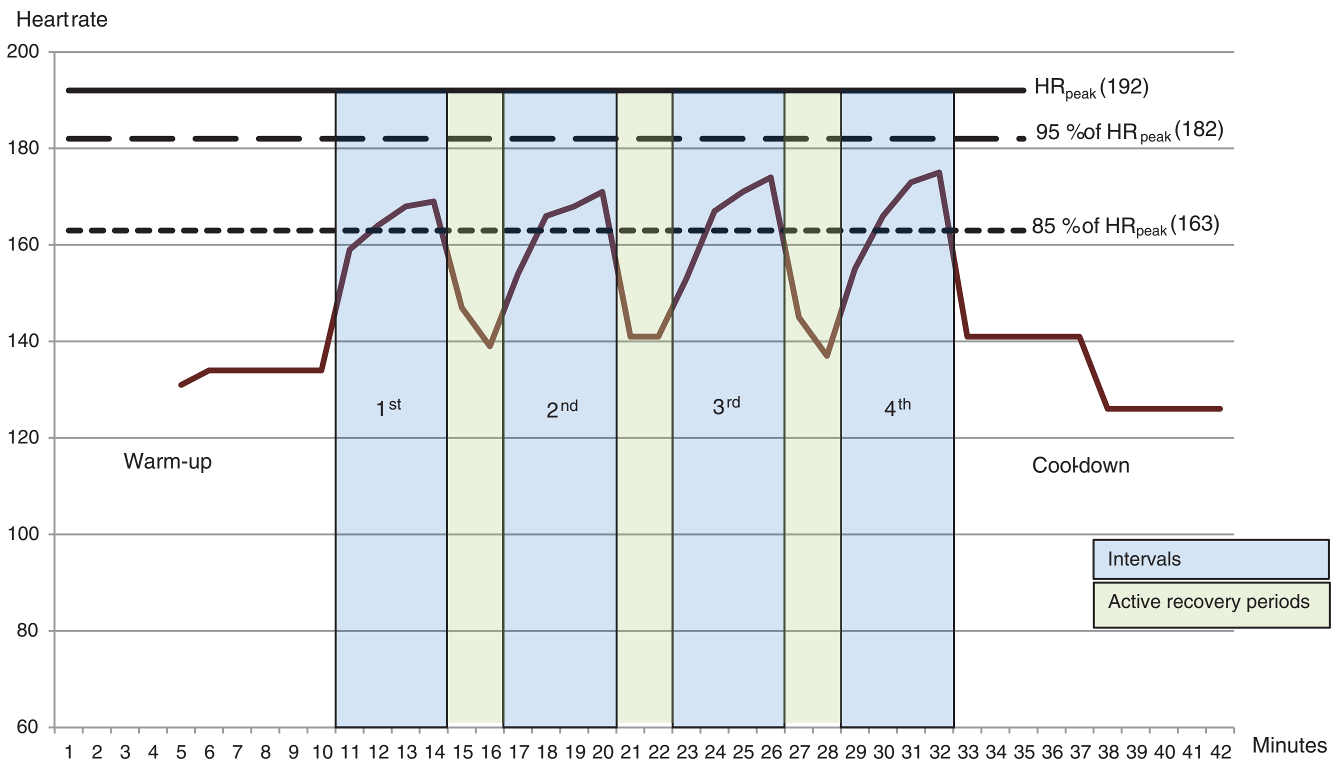

FIGURE 1 Typical session including 10 minutes warm-up, four intervals of high-intensity (85%-95% of HR_{peak}) physical exercise separated by active recovery, and 10 minutes cool-down. HR, heart rate; HR_{peak}, peak heart rate (beat·min^{-1}) [Color figure can be viewed at wileyonlinelibrary.com]

group and 9 mL/kg/min in the exercise group, with a SD of 5 mL/kg/min for both groups. Upfront sample size calculations showed that we needed 47 patients in each group to detect a mean group difference in change of VO_2 peak during chemotherapy of 5 mL/kg/min with a SD of 7 mL/kg/min (two-sided significance level of 5%, power of 90% and 10% dropout).

TABLE 1 Baseline characteristics of the patients in the intervention- and control arm, and of each case who developed a thromboembolic event

	Intervention arm (n = 9)	Control arm (n = 8)	Case 1	Case 2	Case 3
Age, year (median [range])	31 (21-50)	31 (25-56)	21	43	30
Cancer characteristics (n or median [range])					
Histology					
Seminoma	2	4			
Nonseminoma	7	4	1	1	1
Stage[a]					
IIA	8	3	1	1	1
IIB	1	4			
IIC	0	1			
Tumor markers					
hCG (IU/L)	3.2 (0.1-7.6)	4.1 (0.1-31.1)	3.4	6.3	3.5
AFP (kU/L)	3 (1-117)	6 (2-1294)	3	5	117
LDH (U/L)	172 (137-348)	183 (161-329)	196	148	140
Prognosis group					
Good	9	7	1	1	1
Intermediate	0	1			
Poor	0	0			
Treatment (n)					
BEP × 3	8	5	1	1	1
EP × 4	1	3			
Khorana score[b] (n)					
0-2	9	8	1	1	1
≥3	0	0			
Lipids and glucose (median [range])					
Cholesterol (mmol/L)	4.7 (3.3-6.3)	5.0 (3.6-6.2)[c]	4.7	5.0	6.3
HDL-cholesterol (mmol/L)	1.6 (0.8-1.8)	1.1 (0.8-1.7)[c]	1.6	1.7	1.0
LDL-cholesterol (mmol/L)	2.9 (2-4.7)	3.5 (2.3-4.9)[c]	2.8	3.0	4.7
Triglycerides (mmol/L)	1.4 (0.6-1.7)	0.9 (0.8-1.9)[c]	1.6	1.4	1.6
Glucose (mmol/L)	5.5 (4.6-6.2)	5.4 (4.9-6.9)[c]	5.1	5.1	5.9
HbA1c (%)	5.0 (4.8-5.2)[d]	5.3 (5.0-5.6)[e]	4.9	5.0	5.1
Other variables relevant to thrombosis (median [range] or *n*)					
VO_{2peak} *(mL/kg/min)*	43.0 (33-56)[f]	41.6 (30-51)[g]	35.0	46.3	32.8
% of expected (%)	102 (67-120)[f]	91 (76-104)[g]	67	109	68
BMI (kg)	24.9 (21.6-31.7)	28.9 (21.4-32.5)	29.9	24.8	31.7
Smoking					
No (never/stopped)	7	7		1	1
Yes, occasionally	2	1	1		
Meeting PA guidelines precancer[h]					
Yes	8	6	1	1	
No	1	2			1

TABLE 1 (Continued)

	Intervention arm (n = 9)	Control arm (n = 8)	Case 1	Case 2	Case 3
Comorbidity (self-reported)					
Yes	5[i]	3[j]	1[k]		1[l]
No	4	5		1	

Abbreviations: AFP, alpha-fetoprotein; BEP, bleomycin, etoposide and cisplatin; BMI, body mass index; EP, etoposide and cisplatin; HbA1c, glycated hemoglobin; hCG, human chorionic gonadotropin; HDL, high-density lipoprotein; IU/L, international units per liter; kU/L, kilounits per liter; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; mmol/L, millimole per liter; PA, physical activity; RPLN, retroperitoneal lymph node; U/L, units per liter.

[a]Stage according to Royal Marsden Hospital Stadium.

[b]Cancer site (testicular cancer = 1), prechemotherapy platelet count ≥350 × 10^9/L, hemoglobin <100 g/L, prechemotherapy leukocyte count >11 × 10^9/L, body mass index ≥35 kg/m^2 (Khorana et al[35]).

[c]n = 7.

[d]n = 8.

[e]n = 6.

[f]n = 7.

[g]n = 7.

[h]Minimum 150 minutes of moderate intensity PA or 75 minutes of high-intensity PA per week.

[i]Psychological distress (n = 2), muscle and skeletal disease (n = 2) and chronic lung disease (n = 1).

[j]Hypertension (n = 1), muscle and skeletal pain/disorder (n = 2), mild/moderate asthma (n = 1) and epilepsy (n = 1).

[k]Psychological distress.

[l]Muscle and skeletal pain/disorder.

3 | RESULTS

The TAST-trial was prematurely discontinued after inclusion of 19 of the planned 94 patients, due to an unexpected high number of TE events among the patients in the intervention arm. This decision was made by the principal investigator in accordance with recommendations from the safety evaluation committee.

During the 12 months inclusion period, nine patients were randomized to the intervention arm and 10 to the control arm. After randomization, one patient withdrew and another was excluded due to change in planned chemotherapy, leaving eight patients in the control arm. Three of nine patients (33%, 95% confidence interval [CI] 7%-70%) in the intervention arm developed TE complications, as compared to none in the control arm. Two of the patients developed pulmonary embolism and one patient myocardial infarction. All three patients had nonseminoma TC, Royal Marsden Hospital clinical Stage IIA, and were classified as International Germ Cell Cancer Collaborative Group good prognosis group.[19]

Two patients, both in the control arm, received anticoagulants at study entry: One patient as treatment for renal vein thrombosis, the other as thromboprophylaxis due to inferior caval vein compression. Baseline characteristics of the patients are presented in Table 1.

3.1 | Case reports

3.1.1 | Case 1

A 21-year-old man completed four of seven planned supervised exercise sessions before being diagnosed with pulmonary embolism. He preferred to switch between ergometer cycle, treadmill and rowing machine. In the four completed sessions, 9 of the 16 planned intervals were in the HIIT zone (Table 2 and Figure S1A).

On Day 10 of the second BEP cycle (7 days since last exercise session), he experienced cough and thoracic pain. The CT scan at the local emergency department revealed cryptogenic organizing pneumonia, and treatment with prednisolone and azithromycin was initiated. On Day 15 of the second BEP cycle, repeat CT scan showed thrombosis of the left internal and common iliac veins, and a large embolism in the right pulmonary artery. He received dalteparin subcutaneously for 6 months.

Potential risk factors for venous TE

Re-evaluation of the prechemotherapy CT scan did not reveal venous thrombosis or pulmonary embolism. The patient's grandfather had a provoked deep vein thrombosis after orthopedic surgery. The patient was heterozygous for the FV Leiden mutation, increasing his risk of venous TE twofold to sixfold. Lupus anticoagulant was weakly positive in one subtest (dRVVT), and still weakly positive after 13 and 30 weeks. Taken together, this patient had a modestly increased risk of venous TE. All other coagulation analyses were within reference ranges.

3.1.2 | Case 2

A 43-year-old man completed nine of 10 planned supervised exercise sessions before diagnosed with pulmonary embolism. He preferred to walk uphill on the treadmill. In the nine completed sessions, 13 of 40 planned intervals were in the HIIT zone (Table 2 and Figure S1b).

On Day 15 of the second BEP cycle (3 days since last exercise session), a preplanned evaluation CT scan detected large thrombotic masses in the inferior caval vein and bilateral pulmonary embolism. In retrospect, the patient had experienced increasing inspiratory thoracic

TABLE 2 Number of intervals and minutes when the cases reached high-intensity training zone (85%-95% of peak heart rate) for each session

	First chemotherapy cycle						Second chemotherapy cycle						Third chemotherapy cycle					
Week	**1**		**2**		**3**		**1**		**2**		**3**		**1**		**2**		**3**	
Case 1																		
Day	2	4	9	11			3											
Intervals (n)	2	3	2	2			0											
Minutes (n)	5	8	6	7			0											
Case 2																		
Day	3	5	10	12	15	19	1	3		12								
Intervals (n)	0	1	2	1	4	1	2	1		1								
Minutes (n)	0	1	5	2	6	1	4	1		1								
Case 3																		
Day	3	5		12	17	19	1	3	10		17	19	1	3				
Intervals (n)	2	4		2	4	4	4	1	3		3	3	4	4				
Minutes (n)	6	12		6	11	12	10	1	8		10	8	15	12				

pain and dyspnea from day seven of the second BEP cycle, which he had not reported to health professionals. He received dalteparin subcutaneously for 10 months, thereafter warfarin for 4 months.

Potential risk factors for venous TE

Re-evaluation of the prechemotherapy CT scan did not reveal venous thrombosis or pulmonary embolism. This patient had no hereditary factors for venous TE events, and all coagulation analyses were within reference ranges.

3.1.3 | Case 3

A 30-year-old man completed 12 of 14 planned supervised exercise sessions prior to a myocardial infarction. He preferred to walk uphill on the treadmill. In the 12 completed sessions, 38 of 48 planned intervals were in the HIIT zone (Table 2 and Figure S1c).

He experienced chest-pain from Day 6 of the third BEP cycle (3 days since last exercise session). After 12 hours of persistent pain, he consulted his oncologist. He was immediately referred to the local emergency department where he was diagnosed with ST-segment elevation myocardial infarction. Peak troponin I was 8541 ng/L (<35 ng/L). Angiography showed a clinically nonsignificant stenosis of the left anterior descending artery. Coronary angiography indicative of thromboembolic rather than atherosclerotic origin in TC patients during CBCT has been described previously.[20] He was given ticagrelor for 3 months and long-term acetylsalicylic acid and atorvastatin.

Potential risk factors for arterial TE

He had hereditary risk factors for cardiovascular disease, as one parent had angina pectoris, and several family members had hypercholesterolemia. All coagulation analyses were within reference ranges. His body mass index was 32 kg/m^2. He had no signs of hypertension (blood pressure 110/75 mmHg) or hyperglycemia. He was a never-smoker. Although within reference ranges, the lipid profile at baseline was unfavorable (Table 1). Taken together, this patient had a modest increased risk of arterial TE.

All three cases completed three cycles of BEP as planned, achieving durable complete remissions.

4 | DISCUSSION

Three of nine patients in the intervention arm experienced a TE event, that is, pulmonary embolism and myocardial infarction. Since the risk of pulmonary embolism or myocardial infarction are expected to be low in patients with TC during or shortly after CBCT, our observations indicated a substantially higher rate than reported in the literature (33% vs 0-15%). Pretreatment, none of the cases had any TC-specific risk factors for TE events, such as large abdominal lymph nodes, elevated LDH or central venous access. In accordance with national guidelines for treatment of TC in Norway, they did not receive primary thromboprophylaxis. Case 1 and 3 had predisposing factors for venous and arterial TE events, respectively.[20] Although we are fully aware that the TE events in the intervention arm might have been a play of chance, we find it hard to ignore that the HIIT might have contributed to the unexpected high number of TE events. Proposed mechanisms for possible interactions between CBCT and high-intensity aerobic exercise that can potentiate the risk of TE events are described after a review of the literature.

4.1 | TE events during CBCT—review of the literature

Within the three main concepts; testicular neoplasms, cisplatin and thromboembolism; MeSH terms with variations were searched in titles, abstracts and author keywords in MEDLINE (Ovid) and Embase

TABLE 3 Studies with thromboembolic events as an endpoint in testicular cancer patients during cisplatin-based chemotherapy included in the review of the literature

References	Inclusion period	n	Stage of disease Metastatic treatment lines	TEE, n (%)	VTE, n (%)	PE, n (%)	ATE, n (%)	MI, n (%)	PE/MI, n (%)	Risk factors
Paffenholz et al[23]	2003-2018	255	All stages, 66 Stage I First and second line CBCT	52/255 (20.4)	49/255 (19.2)	24/255 (9.4)	3/255 (1.2)	1/255 (0.4)	25/255 (9.4)	Clinical stage ≥ IIC, ↑LDH, febrile neutropenia, CVA
Heidegger et al[24]	2003-2015	153	All stages, 30 Stage I First, second and third line CBCT		26/153 (17.0)	11/153 (7.2)				Lugano stage ≥ IIC
Bezan et al[25]	2000-2013	300	Metastatic disease CBCT		37/300 (12.3)					Clinical stage IIC and III
Gonzalez-Billalabeitia et al[26]	2004-2014	658	Metastatic disease First line CBCT		72/658 (10.9)	21/658 (3.2)				
Gizzi et al[27]	2001-2014	279	All stages, 47 Stage I First line CBCT	28/279 (10.0)	26/279 (9.3)	0/279 (0.0)	2/279 (0.7)	0/279 (0.0)	0/279 (0.0)	↑LDH, RPLN metastases
Solari et al[28]	2008-2013	93	All stages, 30 Stage I First, second and third line CBCT	22/93 (23.6)	22/93 (23.6)	10/93 (10.7)	8/93 (8.6)	4/93 (4.3)	14/93 (15.1)	>40 years, LN metastases
Lubberts et al[20]	2006-2012	73	Metastatic disease First line CBCT	8/73 (11.0)	4/73 (5.5)	4/73 (5.5)	4/73 (5.5)	0/73 (0.0)	4/73 (5.5)	vWF and FVIII
Srikanthan et al[29]	2000-2010	324	Metastatic disease First line CBCT	31/324 (9.6)	31/324 (9.6)	11/324 (3.4)				RPLN >5 cm, ↑Khorana score
Honecker et al[30]	2000-2009	193	All stages. 41 adjuvant First and second line CBCT		4/193 (2.1)	1/193 (0.5)				Supraclavicular LN metastases, CVA
Dieckmann et al[34]	1996-2008	8233					25/8233 (0.3)	20/8233 (0.2)		
de Haas et al[31]	1977-2004	324	Metastatic nonseminoma		26/324 (8.0)	3/324 (0.9)				
Nuver et al[21]	1998-2004	65	Metastatic nonseminoma	6/65 (9.2)	4/65 (6.2)	2/65 (3.1)	2/65 (3.1)	2/65 (3.1)	4/65 (6.2)	
Piketty et al[32]	1992-1998	177	All stages, 25 Stage I First line CBCT	29/177 (16.4)	28/177 (15.8)	3/177 (1.7)	1/177 (0.6)	0/177 0.0	3/177 (1.7)	↑LDH, BSA > 1.9 m^2
Weijl et al[33]	1979-1997	179	Metastatic disease First line CBCT	15/179 (8.4)	13/179 (7.3)	9/179 (5.0)	3/179 (1.7)	0/179 (0.0)	9/179 (5.0)	Liver metastasis, high dose corticosteroids
Cantwell et al[22]	NR	52	Newly diagnosed	10/52 (19.2)	7/52 (13.5)	2/52 (3.8)	3/52 (5.8)	1/52 (1.9)	3/52 (5.8)	RPLN >5 cm

Abbreviations: ATE, arterial thromboembolic events; BSA, body surface area; CBCT, cisplatin-based chemotherapy; CVA, central venous access; FVIII, factor VIII; LDH, lactate dehydrogenase; LN, lymph node; MI, myocardial infarction; N, number; PE, pulmonary embolism; RPLN, retroperitoneal lymph node; TEE, thromboembolic events; VTE, venous thromboembolic events; vWF, Von Willebrand factor.

1980 to 2019. The Medical Library at the University of Oslo performed the search in August 2019. The search was limited to English language. Detailed search strategies are described in Supporting Information File S1. After screening and assessing 567 unique abstracts and full-text articles for eligibility, 15 articles with TE events as an endpoint in TC patients during CBCT were included (Table 3). Studies limited to venous access-associated thrombosis were excluded. The selection process is further detailed in Figure S2.

The majority of studies were retrospective, apart from two studies with a prospective design,[20,21] and one where the design was not reported.[22] The studies were heterogeneous and study populations were often poorly described. Thus, the expected rate of TE events among TC patients in clinical stage IIA without elevated LDH or central venous access is not deductible. During CBCT, 14 studies reported on incidence rates of venous TE events, ranging from 2% to 24% (Table 3).[20-33] The reported rates of venous TE events presented in Table 3 consists of deep vein thrombosis and pulmonary embolism, except for one study[26] which also includes superficial vein thrombosis. The reported incidence rate of pulmonary embolism ranged from 0% to 11%.[20-24,26-33] Nine studies reported on the incidence rate of myocardial infarction ranging from 0% to 4%.[20-23,27,28,32-34] Eight studies reported on the incidence rate of both pulmonary embolism or myocardial infarction, ranging from 0% to 15%.[20-23,27,28,32,33]

Among cancer patients in general, the following are identified as TE risk factors: Platelet count >350 $\times 10^9$/L, hemoglobin <10 g/dL, leukocyte count >11 $\times 10^9$/L, BMI > 35 kg/m^2, CBCT and TC.[35,36] These risk factors do not seem to apply for TC patients receiving CBCT. In TC patients receiving CBCT, several studies identify retroperitoneal lymph nodes >5 cm, central venous access and elevated serum LDH as risk factors for TE (Table 3).[22-25,27,29,32]

4.2 | TE events during CBCT—possible mechanisms

Venous thrombi are formed when the physiologic balance between procoagulant and anticoagulant reactions is disrupted. Blood coagulation is initiated, followed by amplification and propagation phases involving activated platelets.[37] Platelet activation and aggregation are contributing factors in the mechanism of arterial thrombus formation.[38] Proposed mechanisms for the increased risk of TE events during CBCT in TC patients are that CBCT induces endothelial damage[39] and upregulation of procoagulant factors such as coagulation factor VIII.[20,40] As a hypothetical consequence, endothelial damage with subsequent exposure of the subendothelium and release of collagen and fibronectin to the blood could activate platelets. Moreover, CBCT-induced endothelial damage may lead to exposure of tissue factor, which can initiate blood coagulation.[41,42]

4.3 | The association of HIT and TE risk

Blood is known to be hypercoagulable immediately after strenuous exercise, mainly due to an increased level of coagulation factor VIII.[43] Studies have shown that HIT sessions are followed by a transient increase in platelet activation and aggregation.[44-46] The increase in factor VIII and the degree of platelet activation and aggregation after exercise are associated with the intensity of the exercise.[47-49] Furthermore, the degree of platelet activation after HIT is reported to be related to individual physical fitness, leaving untrained individuals in at higher risk than well-trained individuals.[43]

4.4 | Possible increased TE risk during CBCT combined with HIT

The limited existing data on HIT during CBCT have not included reports on TE events. Adamsen et al examined the effects of an exercise intervention including HIT during chemotherapy. Among 135 patients randomized to the intervention, seven TC patients received CBCT.[8] No patients had TE events during the six-week intervention (L. Adamsen, personal communication, July 2019). One could speculate whether high-intensity training adds to the risk of TE events of CBCT among TC patients, rendering them more prone to TE events. It is possible that exercise programs with lower intensity and more gradual increase in intensity might be more favorable than the HIIT program in the TAST-trial.

4.5 | Limitations

The small number of included patients in the TAST-trial is an obvious limitation. Possibly, this is an accidental observation unrelated to the HIIT, reflected in the wide CI. Furthermore, our observations are after high-intensity aerobic exercise, thus not representative for physical activity with low- and moderate intensity or strength training. We are unable to estimate an exact cut-off for the training intensity regarding the risk of TE events. Our observation is also limited to HIT during CBCT, not to training after completing CBCT. Future research on TC and exercise training may consider exercise protocols with lower intensity during CBCT or HIT interventions after completion of CBCT.

5 | CONCLUSION

It is well known that TC patients are at risk of TE events during CBCT. Two of the three cases with TE events had risk factors for such events. Our study raises the possibility that HIIT during CBCT adds to CBCT-induced hypercoagulability.

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CONFLICT OF INTEREST

Prof Wisloff has received funding for work with Varicella and Herpes Zoster vaccine from MSD, not relevant for this article. The other authors declare no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available on request from the corresponding author, and with permission from Regional Committee for Medical and Health Research Ethics. The data are not publicly available due to privacy and ethical restrictions. The present findings are previously published as an abstract/poster at the ASCO Annual Meeting 2017. DOI: 10.1200/JCO.2017.35.15_suppl.4551

ETHICS STATEMENT

The TAST-trial was approved by the Regional Committee for Medical and Health Research Ethics (2014/1169/REC South-East) and registered in ClinicalTrial.gov (NCT02577172). All participants signed an informed consent before inclusion, and the three cases have read this report and provided a written consent for publication.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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