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

Lene Thorsen1,2 | Hege S. Haugnes3,4 | Sophie D. Fosså3,5 | Marianne Brydøy6 | Torgrim Tandstad7 | Torbjørn Wisløff4,8 | Gunhild M. Gjerset1 | Elisabeth Edvardsen9,10 | Karl-Otto Larsen9 | Per Morten Sandset5,11 | Carola E. Henriksson5,12 | Truls Raastad10 | Helene F. S. Negaard13

1National Advisory Unit on Late Effects after Cancer Treatment, Department of Oncology, Oslo University Hospital, Oslo, Norway
2Department of Clinical Service, Oslo University Hospital, Oslo, Norway
3Department of Oncology, University Hospital of North Norway, Tromsø, Norway
4Institute of Clinical Medicine, University of Tromsø – The Arctic University, Tromsø, Norway
5Institute of Clinical Medicine, University of Oslo, Oslo, Norway
6Department of Oncology and Medical Physics, Haukeland University Hospital, Bergen, Norway
7Clinic of Oncology, St. Olavs Hospital, Trondheim, Norway
8Norwegian Institute of Public Health, Oslo, Norway
9Department of Pulmonary Medicine, Oslo University Hospital, Oslo, Norway
10Department of Physical Performance, Norwegian School of Sports Sciences, Oslo, Norway
11Department of Haematology, Oslo University Hospital, Oslo, Norway
12Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway
13Department of Oncology, Oslo University Hospital, Oslo, Norway

Correspondence
Lene Thorsen, National Advisory Unit on Late Effects after Cancer Treatment, Department of Oncology, Oslo University Hospital and Department of Clinical Service, Oslo University Hospital, Oslo, Norway. Email: lka@ous-hf.no

Funding information
AKTIV Against Cancer; The Research Council of Norway, Grant/Award Number: 218312; The South-Eastern Norway Regional Health Authority, Grant/Award Number: 2010063

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...
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.

**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\(_{2\text{peak}}\)) 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\(_{2\text{peak}}\) measured...
during a CPET using a continuous graded exercise protocol on a treadmill until exhaustion. Peak heart rate (HRpeak) 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 HRpeak, followed by HIIT; that is, 2 to 4 intervals of 2 to 4 minutes at 85% to 95% of HRpeak, (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. HRpeak obtained during the pre-intervention CPET was used to calculate the training zones. The HR and the Borg Rating of Perceived Exertion Scale17 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 VO₂ peak during chemotherapy by 14 mL/kg/min in the control arm.
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 VO₂ 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*               |                          |                     |        |        |        |
| IIA                  | 8                        | 3                   | 1      | 1      | 1      |
| IIB                  | 1                        | 4                   | 1      |        |        |
| 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 scoreb (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)       | 4.7    | 5.0    | 6.3    |
| HDL-cholesterol (mmol/L) | 1.6 (0.8-1.8)        | 1.1 (0.8-1.7)       | 1.6    | 1.7    | 1.0    |
| LDL-cholesterol (mmol/L)| 2.9 (2.4-7)           | 3.5 (2.3-4.9)       | 2.8    | 3.0    | 4.7    |
| Triglycerides (mmol/L)| 1.4 (0.6-1.7)           | 0.9 (0.8-1.9)       | 1.6    | 1.4    | 1.6    |
| Glucose (mmol/L)     | 5.5 (4.6-6.2)           | 5.4 (4.9-6.9)       | 5.1    | 5.1    | 5.9    |
| HbA1c (%)            | 5.0 (4.8-5.2)           | 5.3 (5.0-5.6)       | 4.9    | 5.0    | 5.1    |
| Other variables relevant to thrombosis (median [range] or n) | | | | | |
| VO₂peak (mL/kg/min)  | 43.0 (33-56)            | 41.6 (30-51)        | 35.0   | 46.3   | 32.8   |
| % of expected (%)    | 102 (67-120)            | 91 (76-104)         | 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                   |        |        |
| Meeting PA guidelines precancerh |         |                     |        |        |        |
| Yes                  | 8                        | 6                   | 1      | 1      |
| No                   | 1                        | 2                   |        |        |
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, 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 prepamulated 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...
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/m². 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 2 | Number of intervals and minutes when the cases reached high-intensity training zone (85%-95% of peak heart rate) for each session |
| --- | --- | --- |
| Week | First chemotherapy cycle | Second chemotherapy cycle | Third chemotherapy cycle |
| | 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 |

3194 | THORSEN ET AL.
| References                  | Induction 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\(^{29}\)     | 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\(^{30}\)   | 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\(^{31}\)     | 2000-2009        | 193   | All stages, 41 adjuvant First and second line CBCT |                           | 4/193 (2.1) | 1/193 (0.5) |           |            |           |                           | Supradiacicular LN metastases, CVA                                          |
| Diedemann et al\(^{32}\)    | 1996-2008        | 8233  |                                      |                           | 25/8233 (0.3) | 20/8233 (0.2) |           |            |           |                           |                                                                             |
| de Haas et al\(^{33}\)      | 1977-2004        | 324   | Metastatic nonseminoma             |                           | 26/324 (8.0) | 3/324 (0.9)  |           |            |           |                           |                                                                             |
| Nuver et al\(^{34}\)        | 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\(^{35}\)      | 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 m²                                                           |
| Weij et al\(^{36}\)         | 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\(^{37}\)     | 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, and one where the design was not reported. 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). The reported rates of venous TE events presented in Table 3 consists of deep vein thrombosis and pulmonary embolism, except for one study which also includes superficial vein thrombosis. The reported incidence rate of pulmonary embolism ranged from 0% to 11%. Nine studies reported on the incidence rate of myocardial infarction ranging from 0% to 4%. Eight studies reported on the incidence rate of both pulmonary embolism or myocardial infarction, ranging from 0% to 15%

Among cancer patients in general, the following are identified as TE risk factors: Platelet count >350 × 10^9/L, hemoglobin <10 g/dL, leukocyte count >11 × 10^9/L, BMI > 35 kg/m², CBCT and TC. 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).

### 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. Platelet activation and aggregation are contributing factors in the mechanism of arterial thrombus formation. Proposed mechanisms for the increased risk of TE events during CBCT in TC patients are that CBCT induces endothelial damage and upregulation of procoagulant factors such as coagulation factor VIII. 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.

### 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. Studies have shown that HIT sessions are followed by a transient increase in platelet activation and aggregation. The increase in factor VIII and the degree of platelet activation and aggregation after exercise are associated with the intensity of the exercise. 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.

### 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. 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 HIT 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.

### Acknowledgements

The authors thank the patients for participating and the doctors, nurses, physiotherapists and trainers at the four hospitals and in the municipality involved in the TAST-trial. We will also thank Laima Taylor at the Institute for Cancer Genetics and Informatics at OUH for contributing to the randomization procedures and Hilde Iren Flaatten, Senior Medical Librarian, University of Oslo for performing the literature search.
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_suppl4551

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.

ORCID
Lene Thorsen https://orcid.org/0000-0002-7857-5475

REFERENCES
1. Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. J Cancer Surviv. 2010;4:87-100.
2. Loughney L, West MA, Kemp GJ, Grocott MPW, Jack S. Exercise intervention in people with cancer undergoing neoadjuvant cancer treatment and surgery: a systematic review. Eur J Surg Oncol. 2016;42:28-38.
3. Segal R, Zwaal C, Green E, et al. Exercise for people with cancer: a clinical practice guideline. Curr Oncol. 2017;24:e290-e315.
4. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin. 2012;62:243-274.
5. Segal R, Zwaal C, Green E, et al. Exercise for people with cancer: a consensus Statement from international multidisciplinary roundtable. Med Sci Sports Exerc. 2019;51:2375-2390.
6. Loughney LA, West MA, Kemp GJ, Grocott MPW, Jack S. Exercise interventions for people undergoing multimodal cancer treatment that includes surgery. Cochrane Database Syst Rev. 2018;(12):CD012280.
7. Adamson L, Quist M, Andersen C, et al. Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial. BMJ. 2009;339:b3410.
8. Andersen C, Rorth M, Ejlersen B, et al. The effects of a six-week supervised multimodal exercise intervention during chemotherapy on cancer-related fatigue. Eur J Oncol Nurs. 2013;17:331-339.
9. Andersen C, Rorth M, Ejlersen B, et al. The effects of a six-week supervised multimodal exercise intervention during chemotherapy on cancer-related fatigue. Eur J Oncol Nurs. 2013;17:331-339.
10. Hornsby WE, Douglas PS, West MJ, et al. Safety and efficacy of aerobic training in operable breast cancer patients receiving neoadjuvant chemotherapy: a phase II randomized trial. Acta Oncol. 2014;53:65-74.
11. van Waart H, Stuiver MM, van Harten WH, et al. Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: results of the PACES randomized clinical trial. J Clin Oncol. 2015;33:1918-1927.
12. Mijwel S, Backman M, Bolam KA, et al. Adding high-intensity interval training to conventional training modalities: optimizing health-related outcomes during chemotherapy for breast cancer: the OptiTrain randomized controlled trial. Breast Cancer Res Treat. 2017;168:79-93.
13. Feldman DR, Bosl GJ, Sheinfeld J, Motzer RJ. Medical treatment of advanced testicular cancer. JAMA. 2008;299:672-684.
14. Sprauten M, Haugnes HS, Brydoy M, et al. Chronic fatigue in 812 testicular cancer survivors during long-term follow-up: increasing prevalence and risk factors. Ann Oncol. 2015;26:2133-2140.
15. Haugnes HS, Bosl GJ, Boer H, et al. Long-term and late effects of germ cell testicular cancer treatment and implications for follow-up. J Clin Oncol. 2012;30:3752-3763.
16. Christensen JF, Andersen JL, Adamsen L, et al. Progressive resistance training and cancer testis (PROTRACT)—efficacy of resistance training on muscle function, morphology and inflammatory profile in testicular cancer patients undergoing chemotherapy: design of a randomized controlled trial. BMC Cancer. 2011;11:326.
17. Borg G. Perceived Exertion and Pain Scales. Champaign, IL: Human Kinetics; 1998.
18. Thorsen L, Kirkegaard C, Loge JH, et al. Feasibility of a physical activity intervention during and shortly after chemotherapy for testicular cancer. BMC Res Notes. 2017;10:214.
19. International Germ Cell Cancer Collaborative Group. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol. 1997;15:594-603.
20. Lubberts S, Boer H, Altena R, et al. Vascular fingerprint and vascular damage markers associated with vascular events in testicular cancer patients during and after chemotherapy. Eur J Cancer. 2016;63:180-188.
21. Nuver J, Smit AJ, van der Meer J, et al. Acute chemotherapy-induced cardiovascular changes in patients with testicular cancer. J Clin Oncol. 2005;23:9130-9137.
22. Cantwell BM, Mannix KA, Roberts JT, Ghani SE, Harris AL. Thromboembolic events during combination chemotherapy for germ cell malignancy. Lancet. 1988;2:1086-1087.
23. Paffenholz P, Grein K, Heidegger I, et al. Predictors of thrombosis in testicular cancer during platinum-based chemotherapy. World J Urol. 2019;37:1907-1916.
24. Heidegger I, Porres D, Veek N, Heidenreich A, Pfister D. Predictive factors for developing venous thrombosis during Cisplatin-based chemotherapy in testicular cancer. Urol Int. 2017;99:104-109.
25. Bezan A, Posch F, Ploner F, et al. Risk stratification for venous thromboembolism in patients with testicular germ cell tumors. PLoS One. 2017;12:e0176283.
26. Gonzalez-Billalabeitia E, Castellano D, Sobrevilla N, et al. Prognostic significance of venous thromboembolic events in disseminated germ cell cancer patients. J Natl Cancer Inst. 2017;109:djw265.
27. Gizz M, Oberic L, Massard C, et al. Predicting and preventing thromboembolic events in patients receiving cisplatin-based chemotherapy for germ cell tumours. Eur J Cancer. 2016;69:151-157.
28. Solari L, Kronig M, Ihorst G, et al. High rates of thromboembolic events in patients with germ cell cancer undergoing cisplatin-based polychemotherapy. Urol Int. 2016;96:399-405.
29. Srikanthan A, Tran B, Beausoleil M, et al. Large retroperitoneal lymphadenopathy as a predictor of venous thromboembolism in patients with disseminated germ cell tumors treated with chemotherapy. J Clin Oncol. 2015;33:582-587.
30. Srikantan A, Tran B, Beausoleil M, et al. Large retroperitoneal lymphadenopathy as a predictor of venous thromboembolism in patients with disseminated germ cell tumors treated with chemotherapy. J Clin Oncol. 2015;33:582-587.
32. Piketty AC, Flechon A, Laplanche A, et al. The risk of thromboembolic events is increased in patients with germ-cell tumours and can be predicted by serum lactate dehydrogenase and body surface area. Br J Cancer. 2005;93:909-914.
33. Weijl NI, Rutten MF, Zwinderman AH, et al. Thromboembolic events during chemotherapy for germ cell cancer: a cohort study and review of the literature. J Clin Oncol. 2000;18:2169-2178.
34. Dieckmann KP, Gerl A, Witt J, Hartmann JT, German Testicular Cancer Study Group, et al. Myocardial infarction and other major vascular events during chemotherapy for testicular cancer. Ann Oncol. 2010;21:1607-1611.
35. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008;111:4902-4907.
36. Barni S, Labianca R, Agnelli G, et al. Chemotherapy-associated thromboembolic risk in cancer outpatients and effect of nadroparin thromboprophylaxis: results of a retrospective analysis of the PROTECHT study. J Transl Med. 2011;9:179.
37. Bertina RM. The role of procoagulants and anticoagulants in the development of venous thromboembolism. Thromb Res. 2009;123 Suppl 4:S41-S45.
38. Jackson SP. Arterial thrombosis—insidious, unpredictable and deadly. Nat Med. 2011;17:1423-1436.
39. Dieckmann KP, Struss WJ, Budde U. Evidence for acute vascular toxicity of cisplatin-based chemotherapy in patients with germ cell tumour. Anticancer Res. 2011;31:4501-4505.
40. Nuver J, de Haas EC, van Zweeden M, Gietema JA, Meijer C. Vascular damage in testicular cancer patients: a study on endothelial activation by bleomycin and cisplatin in vitro. Oncol Rep. 2010;23:247-253.
41. Wilcox JN, Smith KM, Schwartz SM, Gordon D. Localization of tissue factor in the normal vessel wall and in the atherosclerotic plaque. Proc Natl Acad Sci USA. 1989;86:2839-2843.
42. Mackman N. Role of tissue factor in hemostasis and thrombosis. Blood Cells Mol Dis. 2006;36:104-107.
43. El-Sayed MS, El-Sayed Ali Z, Ahmadizad S. Exercise and training effects on blood haemostasis in health and disease: an update. Sports Med. 2004;34:181-200.
44. Wang JS. Intense exercise increases shear-induced platelet aggregation in men through enhancement of von Willbrand factor binding, glycoprotein Ib/IIa activation, and P-selectin expression on platelets. Eur J Appl Physiol. 2004;91:741-747.
45. Mockel M, Ulrich NV, Heller G Jr, et al. Platelet activation through triathlon competition in ultra-endurance trained athletes: impact of thrombin and plasmin generation and catecholamine release. Int J Sports Med. 2001;22:337-343.
46. Li N, He S, Blomback M, Hjemdahl P. Platelet activity, coagulation, and fibrinolysis during exercise in healthy males: effects of thrombin inhibition by argatroban and enoxaparin. Arterioscler Thromb Vasc Biol. 2007;27:407-413.
47. Andrew M, Carter C, O’Brodovich H, Heigenhauser G. Increases in factor VIII complex and fibrinolytic activity are dependent on exercise intensity. J Appl Physiol (1985). 1986;60:1917-1922.
48. Hansen JB, Wilsgard L, Olsen JO, Osterud B. Formation and persistence of procoagulant and fibrinolytic activities in circulation after strenuous physical exercise. Thromb Haemost. 1990;64:385-389.
49. Ahmadizad S, Nouri-Habashi A, Rahmani H, et al. Platelet activation and function in response to high intensity interval exercise and moderate continuous exercise in CABG and PCI patients. Clin Hemorheol Microcirc. 2016;64:911-919.

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

How to cite this article: Thorsen L, Haugnes HS, Fosså SD, et al. Thromboembolic events after high-intensity training during cisplatin-based chemotherapy for testicular cancer: Case reports and review of the literature. Int. J. Cancer. 2020;147:3189-3198. https://doi.org/10.1002/ijc.33151