Diploma Thesis

PRIMARY THROMBOPROPHYLAXIS AS RISK REDUCTION FOR THROMBOEMBOLIC EVENTS IN PATIENTS WITH TESTICULAR GERM CELL TUMOR UNDERGOING CISPLATINUM-BASED CHEMOTHERAPY

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Affirmation

I hereby declare that the following diploma thesis has been written only by the undersigned and without any assistance from third parties. Furthermore, I confirm that no sources have been used in the preparation of this thesis other than those indicated in the thesis itself.

Graz, 28.03.2023 *Gudrun Walser e.h.*

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Abbreviations

AFP	alpha fetoprotein
AJCC	American joint committee on cancer
AUC 7	7 times area under the curve
BEP	bleomycin, etoposide, cisplatin
BMI	body mass index
CI	confidence interval
CS	clinical stage
CTX	chemotherapy
DOAK	direct oral anticoagulant
EGGCT	extragonadal germ cell tumor
EP	etoposide, cisplatin
GCNIS	germ cell neoplasia in situ
GCT	germ cell tumor
HCG	human chorionic gonadotropin
IGCCCG	international germ cell cancer collaborative group
LDH	lactate dehydrogenase
N	number
NSGCT	non-seminomatous testicular germ cell tumor
OS	overall survival
PFS	progression free survival
PGC	primordial germ cell
PLAP	placental alkaline phosphatase
RLA	retroperitoneal lymphadenectomy
RPLN	retroperitoneal lymphadenopathy
RTX	radiotherapy
SGCT	seminomatous germ cell tumor
SHR	subdivided hazard ratio

TGCT	testicular germ cell tumor
TNM	tumor, nodes, metastasis
UICC	union internationale contre le cancer
ULN	upper limit of normal
VIP	etoposide, ifosfamid, cisplatin
VT	visceral thrombosis
VTE	venous thromboembolism

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Zusammenfassung

Hintergrund: Maligne Hodentumore sind die häufigste Tumorerkrankung bei jungen Männern zwischen 15 und 40 Jahren. Da Keimzelltumore sehr gut auf eine Cisplatin-basierte Behandlung ansprechen, haben die Patienten eine ausgezeichnete Überlebenswahrscheinlichkeit. Ein wichtiges Ziel in der Behandlung von Hodenkrebspatienten ist es daher, Therapiekomplikationen zu vermeiden. Eine Nebenwirkung, die gehäuft bei der Behandlung mit Cisplatin auftritt, sind venöse thromboembolische Ereignisse wie z.B. tiefe Beinvenenthrombosen oder Lungenembolien. In dieser Studie überprüften wir unsere Annahme, dass sich venöse thromboembolische Ereignisse bei Patienten mit malignen Hodentumoren unter Cisplatin-Therapie durch eine adäquate primäre Thromboseprophylaxe reduzieren lassen.

Patienten und Methoden: In dieser single-center Studie wurden Daten von 1052 Hodentumorpatienten, welche zwischen Januar 2000 und Dezember 2021 an der Abteilung für Onkologie der Medizinischen Universität Graz vorstellig wurden, retrospektiv analysiert. 346 Patienten erhielten eine Cisplatin-basierte Chemotherapie und wurden in diese Studie aufgenommen. Bei diesen Patienten wurde der Einsatz einer primärer Thromboseprophylaxe und das Auftreten von thromboembolischen Ereignissen untersucht.

Ergebnisse: 49 (14%) aus insgesamt 346 Patienten entwickelten eine venöse Thromboembolie (VTE). Die Hauptrisikofaktoren für die Entstehung einer VTE waren eine fortgeschrittene Tumorerkrankung (Stadium IIC-IIIC) (SHR für Stadium IIC-IIIC: 2.6 (95% CI: 5.0-24.7, p<0.001)) sowie eine retroperitoneale Lymphadenopathie (RPLN) mit einem Durchmesser über 5cm (SHR für RPLN: 2.36 (95% CI: 1,27-4.4. p<0.007)). Seit 2019 bekamen alle Hodenkrebspatienten an der Abteilung für Onkologie der Medizinischen Universität Graz eine primäre Thromboseprophylaxe begleitend zur cisplatinhältigen Chemotherapie. Die primäre Thromboseprophylaxe senkte das Risiko für eine venöse Thromboembolie um 52% (SHR=0.48, 95% CI: 0.24-0.97, p=0.032).

Schlussfolgerung: In dieser Studie konnte gezeigt werden, dass der Einsatz einer primären Thromboseprophylaxe bei Hodenkrebspatienten für die Dauer einer Cisplatin-basierten Chemotherapie zu einer signifikanten Reduktion von venösen

Thromboembolien führte. Die Verwendung einer möglichen primären Thromboseprophylaxe sollte bei diesen Patienten in Betracht gezogen werden.

Abstract

Background: Testicular germ cell tumors (TGCT) commonly occur in young man aged 15-40 years. Due to the application of cisplatinum-based chemotherapies, the overall survival rate of patients with metastatic TGCT is excellent. The prevention of treatment-related complications has therefore become increasingly important. Cisplatinum-based chemotherapy is associated with an increased risk of venous thromboembolism (VTE). We hypothesized that primary thromboprophylaxis in patients with TGCT undergoing cisplatinum-based chemotherapy can reduce the risk of VTE.

Patients and Methods: In this retrospective single-center cohort study we collected data from 1052 TGCT patients who were treated at the Department of Oncology at the Medical University of Graz between January 2000 and December 2021. 346 of these patients underwent cisplatinum-based chemotherapy either in adjuvant or in curative setting and were therefore included in this study.

Results: 49 (14.2%) out of the included 346 patients developed VTE. The most significant indicator for VTE were a higher clinical tumor stage (cs IIC-III) and a retroperitoneal lymphadenopathy (RPLN) greater than 5cm in diameter (SHR for clinical stage IIC-IIIC: 2.6 (95% CI: 5.0-24.7, p<0.001), SHR for RPLN: 2.36 (95% CI: 1,27-4.4. p<0.007)). Since 2017, the application of primary thromboprophylaxis constantly increased and since 2019, all patients with clinical stage IIC-III disease received primary thromboprophylaxis in addition to cisplatinum-based chemotherapy. Primary thromboprophylaxis reduced the relative risk for VTE by 52% after adjusting for clinical tumor stage (SHR=0.48, 95% CI: 0.24-0.97, p=0.032).

Conclusion: This study showed that the application of primary thromboprophylaxis in TGCT patients undergoing cisplatinum-based chemotherapy led to a significant reduction of VTE across all clinical tumor stages and should be considered on a risk-benefit ratio.

1 Introduction

Cancer patients have a 4 to 6 times increased risk for VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in comparison to the general population. (1, 2). VTE comes along with increased morbidity and mortality and sometimes causes a delay in cancer treatment (3, 4). In several randomized clinical trials, different cancer types were evaluated regarding the occurrence and prevention of VTE. However, TGCT patients were highly underrepresented in all these trials (1, 5-7).

Bezan et al (2017) and Srikanthan et al (2015) showed that a large RPLN and a higher clinical tumor stage are strongly associated with a higher risk of VTE in patients with TGCT (1, 8, 9). For this reason, TGCT patients treated at the Department of Oncology at the Medical University of Graz undergoing cisplatinum-based therapy were risk assessed and treated with primary thromboprophylaxis as described below. Since 2017, the application of primary thromboprophylaxis strongly increased and was finally applied in all patients with clinical stage IIC-III since 2019. This retrospective cohort study aimed to investigate the occurrence of VTE in TGCT patients between 2000 and 2021 with and without thromboprophylaxis (1).

1.1 Venous thromboembolic events in cancer patients

Many risk factors for the occurrence of VTE in cancer patients have been detected and have led to a more accurate application of primary thromboprophylaxis in this patient population. Risk factors include hospitalization, position of the primary tumor, higher tumor stage, comorbidities, higher risk according to Khorana score, the presence of a central venous catheter, previous VTE, a positive family history for VTE, a large RPLN and treatment procedures such as cytotoxic chemotherapy or antiangiogenic therapy (3, 8-11). Compared to the general population, the risk for VTE in cancer patients undergoing chemotherapy is approximately 6.5-fold greater (2). Several clinical trials showed a relative risk reduction of approximately 30-60% for VTE when applying primary thromboprophylaxis in high-risk cancer patients (1, 12). In the AVERT trial, cancer patients with a Khorana Score ≥ 2 and receiving outpatient chemotherapy were randomized to primary thromboprophylaxis with

apixaban or placebo. Out of the 563 patients included in this study, 4.2% of the patients receiving apixaban suffered from VTE whereas 10.2% of the placebo-group suffered from VTE (HR 0.41, p>0.001). This study included only 3 patients with testicular tumors (5).

Especially patients receiving cisplatinum-based chemotherapy were found to be very prone to VTE in comparison to patients receiving chemotherapies without cisplatinum (1, 13).

In 2017, Zahir et al. showed that the relative risk for the development of VTE in patients undergoing cisplatinum-based chemotherapy was 2.8 – 3.3 times higher compared to the control group treated with no cisplatinum-based chemotherapy (3). In another retrospective analysis from Moore et al in 2017, the incidence of VTE in cancer patients undergoing cisplatinum-based chemotherapy was 18.1% (14) compared to 7.3% in patients undergoing a non-cisplatinum based chemotherapy (3, 15). This shows a significantly higher incidence of VTE in cancer patients receiving cisplatinum-based chemotherapy than cancer patients receiving other forms of chemotherapy. The exact mechanisms are not yet known, but possible explanations are endothelial dysfunction, vasculitis or activation and aggregation of thrombocytes (1, 3, 16).

Several risk models have been developed to estimate the risk of VTE in cancer patients. One of the most popular risk scores is the Khorana Score (table 1) (2).

The Khorana Score contains 5 parameters: cancer type, platelet count before start of chemotherapy, hemoglobin level or the application of erythropoiesis stimulating agents (ESA) before start of chemotherapy, leukocyte level before start of chemotherapy and body mass index (2). The Khorana score was validated in a prospective, randomized clinical trial in 2008. 2701 outpatients with breast-, colorectal-, lung-, gynecologic-, gastric- and pancreatic- cancers as well as lymphomas and patients with cancers at other primary site initiating chemotherapy were included. The exact number of TGCT patients included in this trial is unknown (2).

To determine if the risk factors for VTE included in the Khorana Score are also applicable for TGCT patients undergoing cisplatinum-based chemotherapy, Srikanthan et al (2015) retrospectively analyzed data from 216 TGCT patients

undergoing cisplatinum-based chemotherapy for the occurrence of VTE. They found out, that the presence of a large RPLN greater than 5cm is a more accurate risk factor for the prediction of VTE in this patient population than the Khorana score (9).

In a further study from 2017, Bezan et al developed a risk stratification model for the occurrence of VTE in TGCT patients undergoing cisplatinum-based chemotherapy. They retrospectively analyzed 349 TGCT patients and concluded that the presence of a large RPLN and a higher clinical tumor stage (cs IIC – III) are more accurate risk factors for the prediction of VTE in TGCT patients than the size of the RPLN alone or the Khorana score (8).

Table 1 The Khorana Score: a predictive VTE risk-model for cancer patients treated with chemotherapy (2)

Patient characteristics	**Risk score**
Site of cancer • Very high risk (stomach, pancreas) • High risk (lung, lymphoma, gynaecologic, bladder, testicular	 2 Points 1 Point
Platelet < $350x10^9$/l (before chemotherapy)	1 Point
Hemoglobin < 100g/l or use of erythropoiesis stimulating factor (before chemotherapy)	1 Point
Leukocytes > $11x10^9$/l (before chemotherapy)	1 Point
BMI ≥ 35KG/m²	1 Point
Evaluation score (2) 0 points: low risk for VTE 1-2 points: intermediate risk for VTE 3-6 points: high risk for VTE	

1.2 Testicular germ cell tumors

Testicular germ cell tumors (TGCT) represent the most frequent malignancy among men aged 15 to 40 years (17). More than 80% of all TGCT are diagnosed in men below the age of 50 years (18). TGCT can either occur in the testes or less frequent extragonadal in the retroperitoneum, the mediastinum, or the midline of the brain (19). This specific distributional pattern possibly arises from the migration route of the precursor cells during embryogenesis (19, 20). The precursor cells, called primordial germ cells (PGC) migrate, while proliferating, through the midline of the body to the gonads. In further consequences this PGC will develop to sperms and eggs by passing several maturation processes (19, 20).

TGCT represent, with about 90%, the biggest group of all malignant testicular tumors. Other testicular tumors, such as lymphomas, leydig cell tumors, germ cord tumors or sertoli cell tumors represent 10% (21). TGCT can either be benign or malignant (22). The malignant form develops through malignant transformation of an intratubular precursor cell, named germ cell neoplasia in situ (GCNIS). Precursor cells are embryonic cells that possess the ability to differentiate in multiple different cell lineages (23).

About 5% of all patients with TGCT develop a GCT in the contralateral testicle during their lifetime. Another 5% already suffer from a GCNIS in the contralateral testicle at time of TGCT diagnosis (24). Nowadays, TGCT patients have an excellent 5-year survival rate of approximately 97% which is accounted to their very good response to cisplatinum-based chemotherapy (25, 26).

1.2.1 Classification

TGCT can be divided into seminomatous (SGCT) and non-seminomatous germ cell tumors (NSGCT), according to their histology (22). Subtypes of NSGCT are embryonal carcinoma, yolk sac carcinoma, choriocarcinoma, teratoma or mixed germ cell tumors. Mixed germ cell tumors contain different types of NSGCT or seminomatous tissues (19, 27). Every germ cell tumor containing non-seminomatous parts is classified as NSGCT. Pure SGCT only consist out of seminomatous tissue (28).

NSGCT

NSGCT account for approximately 40-45% of all TGCT and consist of non-seminomatous tissue. They typically occur at a mean age of 25 years and only 60% of them are clinical stage I at the time of diagnosis (22, 24, 29). The tumor markers for NSGCT are alpha fetoprotein (AFP), human chorionic gonadotropin (HCG) and lactate dehydrogenase (LDH). High levels of AFP and HCG are typically produced by yolk sac tumors or choriocarcinomas but can also be elevated in embryonal carcinomas (17, 26). Teratomas do not show elevated levels of HCG, only differentiation into hepatoid or mucinous tissue comes along with elevated levels of AFP (26).

NSGCT in clinical stage I have a very good survival rate of 98-100%. Risk factors for micro metastases and relapse include lymphatic and vascular tumor infiltration as well as the presence of an embryonal carcinoma itself (17, 24). Patients with clinical stage III and poor prognosis have a 5-year survival rate of approximately 65% (24).

SGCT

SGCT account for approximately 55-60% of all TGCT and contain only seminomatous tissue (24). They tend to occur later than NSGCT (22, 29). Around 80% of the SGCT are diagnosed in clinical stage I disease (26). Risk factors for micro metastases and relapse are a tumor size bigger than 4cm and the infiltration of the rete testis (17, 26).

Patients suffering from SGCT do not have elevated levels of AFP but can have elevated levels of HCG and high levels of LDH are possible. Due to the broad occurrence of the enzyme LDH, produced in different tissues like muscles, red blood cells, kidneys and liver, LDH is not specific for TGCT but can lead to its diagnosis (26). Even in patients having normal serum tumor markers, TGCT cannot be excluded due to their low sensitivity especially in SGCT (24).

TNM-Classification

For the classification of testicular germ cell tumors, the system from the international union against cancer (UICC) and the american joint committee on cancer (AJCC), both based on the TNM system, are used. The TNM system is used to determine the anatomical distribution of nearly every malignant tumor including regional distribution of the primary tumor (T), metastases of regional lymph nodes (N) and metastases in distant organs (M) as well as serum tumor markers (S) in TGCT patients. The TNM classification was revised in 2017 from the UICC and is shown in table 2 (22, 30, 31).

Table 2 TNM System of testicular germ cell tumors (30, 31)

pT - Primary tumor (pathology)	
pTX	Tumor cannot be evaluated
pT0	No evidence of primary tumor
pTis	Germ cell neoplasia in situ (GCNIS)
pT1	Tumor limited to the testicle (including rete testis infiltration), no evidence for vascular or lymphatic infiltration
pT2	Tumor limited to the testicle (including rete testis infiltration), with vascular or lymphatic infiltration or tumor with infiltration of the hilar soft tissue, the epididymis or the tunica vaginalis
pT3	Invasion of the spermatic cord (with/without vascular or lymphatic infiltration)
pT4	Invasion of the scrotum (with/without vascular or lymphatic infiltration)
N – regional lymph nodes	
NX	Regional lymph nodes cannot be evaluated
N0	No regional lymph node affection
N1	Regional lymph node metastasis ≤ 2cm or multiple lymph nodes ≤ 2cm
N2	Regional lymph node metastasis > 2cm and ≤ 5cm or multiple lymph node metastasis > 2cm and ≤ 5cm
N3	Regional lymph node metastasis > 5cm

M - distant metastases

M0 No distant metastasis

M1 Distant metastasis

M1a: metastasis in non-regional* lymph nodes or in the lung

M1b: non pulmonary visceral metastasis

*Regional lymph nodes include the retroperitoneal, paraaortal and paravertebral lymph nodes

S – serum tumor markers post orchiectomy

SX Serum tumor marker not available

S0 Serum tumor markers within normal limits

S1 – S3 At least increase of one tumor marker:

	LDH	HCG (mIU/mL)	AFP (ng/ml)
S1	< 1,5 x upper limit of normal	< 5000	< 1000
S2	1,5 – 10 x upper limit of normal	5000 - 50.000	1000 - 10.000
S3	> 10 x upper limit of normal	> 50.000	> 10.000

1.2.2 Diagnosis

In 90% of all cases the initial symptom is a non-painful swelling of one testicle (32) as well as a palpable knot or, less common, a size reduction of the affected testicle (30). Some patients also suffer from scrotal, back or flank pain (24). Mostly, the patient discovers the changes in his testicle by himself. In some cases alterations in the testicles are initially found during an urological examination either by ultrasound examination or by palpation (30). Increased tumor markers such as AFP, HCG and LDH confirm the suspicion of a testicular germ cell tumor (33). In SGCT elevated levels of LDH and HCG can be found. AFP levels must be within normal limits, otherwise the diagnosis of a SGCT must be discarded (30). If a TGCT is suspected the inguinal orchiectomy of the affected testicle and its histological examination is the first line treatment. Only in cases of high tumor volume and a life-threatening condition, chemotherapy is initiated before orchiectomy (22, 33).

After surgery, the patient undergoes a full body examination, called staging. This includes a complete urological examination with palpation and ultrasound of the testicles, urine analysis and computed tomography of the thorax, abdomen and pelvis. A blood analysis for the evaluation of the serum tumor markers AFP, HCG and LDH as well as a palpation of supraclavicular and pelvine lymph nodes are carried out (22). A profound anamnesis including symptoms, time of first palpation of the testicular knot, chronological progression of the symptoms, pre-existing conditions, use of medication, risk factors and family anamnesis is essential (22). Possible risk factors for the development of a TGCT are cryptorchidism, a TGCT on the contralateral testicle, close relative with TGCT such as father or brother (4-10 times increased risk), hypospadias, reduced sperm count, atrophy of the testicles and testicular dysgenesis syndrome (23, 25, 34).

1.2.3 Staging and Prognosis

The post-orchiectomy staging and categorization to a prognostic group is performed by using the classification of the international germ cell cancer collaborative group (IGCCCG) for advanced TGCT (24). Tumors can be categorized into stage 0, stage I (IA, IB), stage IS, stage II (IIA, IIB, IIC) and stage III (IIIA, IIIB, IIIC) disease as shown in table 3 (30).

Clinical stage 0 presents a GCNIS, which describes a precursor of testicular cancer without the ability to metastasize. In clinical stage I, the germ cell tumor is limited to the testicle without vascular or lymphatic invasion. In stage IS, increased post-orchiectomy serum tumor markers without radiological or clinical evidence of lymph node metastases or distant metastases can be found. Clinical stage II is defined by the presence of lymph node metastases and clinical stage III by distant metastases (30).

In 1997, the IGCCCG developed a prognostication tool for metastasized TGCT patients undergoing cisplatinum-based chemotherapy which resulted in three different prognostic groups: good prognosis group, intermediate prognosis group and poor prognosis group, whereas the poor prognosis group contains only patients with NSGCT (35). The IGCCCG prognostic groups for metastasized disease can be found in table 4.

For the allocation to a prognostic group, certain criteria in NSGCT patients were identified as disadvantageous: primary site of the tumor in the mediastinum, elevated levels of AFP, HCG and LDH as well as the presence of visceral metastases (e.g., brain, bone, liver) except lung metastases. In SGCT patients the presence of visceral metastases, except lung metastases, was found to be disadvantageous (35). In 1997, the 5-year survival rate was 91% in the good prognosis group, 79% in the intermediate prognosis group and 48% in the poor prognosis group (35).

Since then, the IGCCCG prognostic tool supports clinicians managing the treatment of metastasized TGCT patients (36). Beyer et al (2021) criticized that only 660 metastasized SGCT patients were included in the original study from the IGCCCG in 1997 and reevaluated the prognostic groups including a larger patient cohort. In 2021, Beyer et al performed a multi-center retrospective study including 2451

patients with metastatic SGCT treated with cisplatinum-based chemotherapy (37). They found out that LDH > 2.5 times upper limit of normal was another disadvantageous prognostic risk factor for overall survival and progression free survival in metastasized SGCT patients and recommended the inclusion of LDH > 2.5 times upper limit of normal to the IGCCCG prognosis tool. Patients in the good prognosis group having LDH > 2.5 times upper limit of normal had a significantly lower 3-year progression free survival and 3-year overall survival than patients with lower LDH (37). Furthermore, Beyer et al observed an improvement in 5-year overall survival and 5-year progression free survival in all three prognostic stage groups. (37).

In 2021, Gillessen et al reevaluated the IGCCCG classification of the prognostic groups for NSGCT patients. They performed a multicenter retrospective study, using data from 9728 metastasized NSGCT patients undergoing cisplatinum-based chemotherapy. They obtained similar results as the IGCCCG concerning the 5-years progression free survival in the good and intermediate prognostic group but observed increasement in the overall survival rate from 92% to 96%, from 80% to 89% and from 48% to 67% in the good, intermediate and poor prognosis group, respectively (36). They agreed to the validity of the IGCCCG classification but additionally elaborated that higher age, lung metastases and LDH > 2.5 times upper limit of normal were also disadvantageous risk factors in metastasized NSGCT patients (36).

Table 3 AJCC Classification for testicular germ cell tumors from the American joint committee on cancer (AJCC) cancer staging manual, 8th edition (2017), Springer int.

Stage	T	N	M	S
Stage 0	pTis	N0	M0	S0
Stage I	pT1-T4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
Stage IS	any pT/TX	N0	M0	S1 – S3
Stage II	any pT/TX	N1-N3	M0	SX
Stage IIA	any pT/TX	N1	M0	S0
	any pT/TX	N1	M0	S1
Stage IIB	any pT/TX	N2	M0	S0
	any pT/TX	N2	M0	S1
Stage IIC	any pT/Tx	N3	M0	S0
	any pT/TX	N3	M0	S1
Stage III	any pT/TX	any N	M1	SX
Stage IIIA	any pT/TX	any N	M1a	S0
	any pT/TX	any N	M1a	S1
Stage IIIB	any pT/TX	N1-3	M0	S2
	any pT/TX	any N	M1a	S2
Stage IIIC	any pT/TX	N1-3	M0	S3
	any pT/TX	any N	M1a	S3
	any pT/TX	any N	M1b	any S

Table 4 IGCCCG prognostic groups for metastatic germ cell cancer (24)

All tumor markers are measured after orchiectomy

Risk status	NSGCT	SGCT
GOOD RISK	Testicular or retroperitoneal primary tumor **and** No non-pulmonary visceral metastases **and** AFP < 1.000ng/ml HCG < 5.000iU/L LDH < 1.5 times upper limit of normal	Any primary site **and** No non-pulmonary visceral metastases **and** Normal AFP Normal HCG LDH either <2.5x ULN or LDH > 2.5x ULN
INTERMEDIATE RISK	Testicular or retroperitoneal primary tumor **and** No non-pulmonary visceral metastases **and** AFP 1.000 – 10.000ng/ml HCG 5.000 – 50.000IU/l LDH 1.5 – 10x upper limit of normal	Any primary site **and** Non-pulmonary visceral metastases **and** Normal AFP Any HCG Any LDH
POOR RISK	Mediastinal primary tumor **or** Non-pulmonary visceral metastases **or** AFP > 10.000ng/ml HCG > 50.000 IU/l LDH > 10x upper limit of normal	No patients with SGCT are classified as poor risk

1.2.4 Therapy

Before starting therapy, patients should have the possibility for sperm analysis and sperm cryopreservation because of the possible infertility risk (24). First-line therapy is the inguinal orchiectomy of the affected testicle followed by either active surveillance strategy, chemotherapy, radiotherapy or retroperitoneal lymph node dissection depending on type of tumor and tumor stage (24, 25).

Tumor markers in TGCT patients should be measured before and post orchiectomy, until normalization or until no further decrease is observed (24). When initiating chemotherapy, serum tumor markers should be measured immediately before starting the treatment (17).

Therapy of SGCT

SGCT in clinical stage I are preferably treated with active surveillance strategy after orchiectomy because of their extraordinary high survival rate of 99%. In case of risk factors for a possible occult metastatic spread (tumor size >4cm and rete testis infiltration), a singular adjuvant chemotherapy cycle with carboplatin 7 times area under the curve (AUC7) or an adjuvant radiation therapy of the retroperitoneum can be performed to reduce the risk of relapse (17, 24, 26, 30).

There exists no significant difference concerning the efficacy of an adjuvant therapy with carboplatin and an adjuvant radiation therapy of the retroperitoneum in SGCT clinical stage I. In 2005, Oliver et al published their results from a multi-center, randomized clinical trial regarding the efficacy of these two adjuvant therapies including 1477 SGCT patients in clinical stage I. They found out that one cycle of adjuvant carboplatin AUC7 and adjuvant radiotherapy of the retroperitoneum have similar relapse free survival rates of 94.8% (95% CI: 92.5 – 96.4) vs. 95.9% (95% CI: 94.4 – 97.1) after 3 years, respectively (30, 38).

Metastasized SGCT are treated according to the IGCCCG prognostic groups. Patients suffering from SGCT in the good prognosis group are treated with 3 cycles of bleomycin, etoposide and cisplatin (BEP). When Bleomycin is contraindicated, 4 cycles of etoposide and cisplatin (PE) are possible. In SGCT cs IIA, a radiotherapy of the retroperitoneum can alternatively be performed (24, 30).

Metastasized SGCT with intermediate prognosis are treated with 4 cycles of BEP or 4 cycles of fosfomycin, etoposide and cisplatin (VIP) when Bleomycin is contraindicated. No SGCT are allocated to the poor prognosis group (30).

Therapy of NSGCT

Patients with NSGCT and clinical stage I disease also have a superb survival rate of 98-100%. Stage I can be divided into a low-risk group and a high-risk group. The high-risk group is characterized by risk factors such as vascular and lymphatic invasion. The low-risk group is characterized by the absence of these risk factors. In the low-risk group, the metastasis rate is approximately 12% and therefore active surveillance is the preferred therapy. In the high-risk group, the metastasis rate is approximately 40-50%. There are two different treatment options in this group: either active surveillance or 1 cycle of adjuvant BEP chemotherapy. 1 cycle of adjuvant BEP can reduce the relapse risk from 50% to 3% but offers no advantage regarding the overall survival. Both treatment forms must be discussed with the patient and treatment strategy depends on his decision. In rare cases, when chemotherapy and active surveillance are contraindicated, a lymph node dissection of the retroperitoneum can also be taken into consideration (24, 30).

Metastasized NSGCT patients are handled according to the IGCCCG classification system for metastasized disease. Patients within the good prognosis group are either treated with 3 cycles of curative BEP or 4 cycles of curative PE when bleomycin is contraindicated. In a retrospective clinical trial from 2007, Culine et al compared 3 cycles of BEP with 4 cycles of PE regarding the overall survival and the event-free survival in 257 NSGCT patients within the good prognosis group. They found out that the 4-year event free survival in the BEP and the PE group was 91% and 86% (p=0,135), respectively. The overall survival was not statistically significant with 5 deaths in the BEP group and 12 deaths in the PE group (p=0,096) (30, 39).

NSGCT within the intermediate prognosis group should be treated with 4 cycles of BEP or 4 cycles of VIP when bleomycin is contraindicated (30). In comparison with BEP, the VIP schema has a higher risk for toxic bone marrow dysfunctions (30, 40).

NSGCT with poor prognosis should be treated with 4 cycles of BEP or 4 cycles of VIP, when bleomycin is contraindicated. In individual cases and a very poor

prognosis, an intensification of chemotherapy can be taken into consideration in form of a high-dosage chemotherapy with a subsequent autologous stem cell transplantation. Very disadvantageous characteristics in NSGCT patients in the poor prognosis group are a primary tumor in the mediastinum, an inappropriate decrease of the serum tumor markers after 1-2 cycles of cisplatinum-based chemotherapy or the presence of brain or bone metastases (30).

2 Patients and Methods

2.1 Patient Population

In this retrospective single-center cohort study we collected data from 1052 male patients with histologically verified TGCT treated at the Department of Oncology at the Medical University of Graz between January 2000 and December 2021. We retrospectively collected demographic and clinical data such as age, body mass index, smoking status, site of primary tumor, thromboembolic events, clinical stage, type of therapy, primary thromboprophylaxis and serum tumor marker levels (1).

After orchiectomy and histological verification of a TGCT, patients were staged. The staging consisted of computed tomography of the chest, abdomen and pelvis, and measurement of the post-orchiectomy serum tumor markers AFP, HCG and LDH. Post-orchiectomy tumor markers within normal limits and the absence of metastasis in the computed tomography were defined as clinical stage I according to the AJCC clinical guidelines. Patients suffering from metastasized disease were assigned to a risk group according to the IGCCCG classification (1).

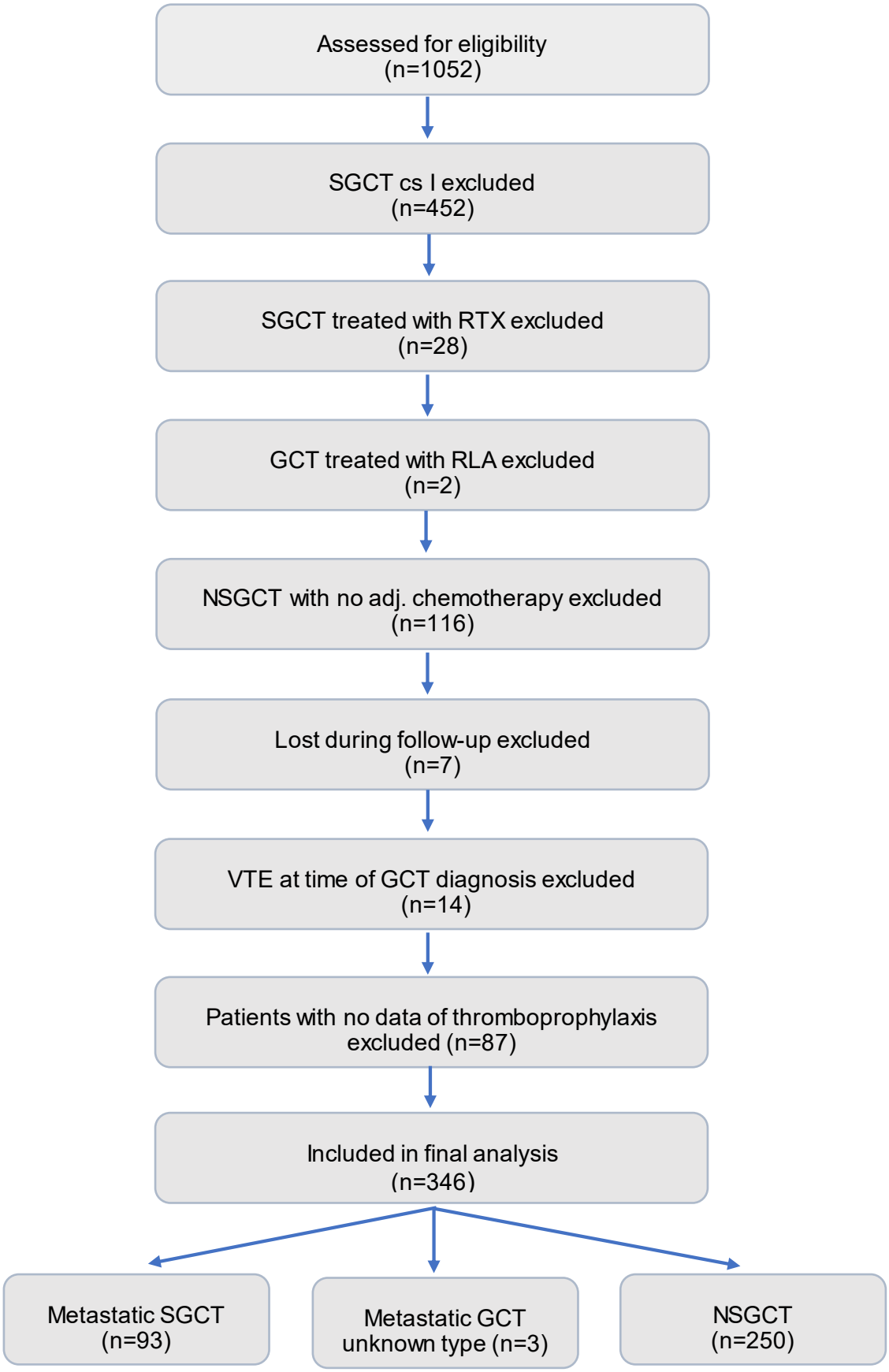
Patient documentations in electronic and paper form of all 1052 TGCT patients were retrospectively analyzed, and the occurrence of VTE were collected. VTE was defined as deep vein thrombosis (DVT), pulmonary embolism (PE) or visceral thrombosis (VT). The occurrence of VTE was detected with eligible diagnostic systems and diagnosed by independent, specialized experts. As diagnostic systems computed tomography, magnetic resonance tomography, doppler ultrasound, angiography and ventilation-perfusion scans were used (1).

Out of these 1052 male patients with TGCT, 346 patients were treated with a cisplatinum-based chemotherapy either as adjuvant or as curative treatment and were therefore included for further analysis (1).

The remaining 706 Patients were excluded from this study due to not meeting the inclusion criteria. 452 patients had a clinical stage I SGCT and were not treated with cisplatinum-based chemotherapy, 28 patients had a SGCT only treated with radiotherapy, 2 patients underwent retroperitoneal lymphadenectomy (RLA), 116 patients with NSGCT clinical stage I did not receive adjuvant chemotherapy, 7 patients were lost during follow up and 14 patients had a VTE prior to diagnosis (figure 1) (1).

We analyzed the risk of the 346 TGCT patients treated with cisplatinum-based chemotherapy for the occurrence of VTE and the application of primary thromboprophylaxis. This study was approved by the Institutional Review Board of the Medical University of Graz (No. 26-196 ex 13/1) (1).

Figure 1 Inclusion criteria (1)



2.2 Statistical Methods

Statistical analyses in this study were realized with Stata 17.0 (Windows version, Stata Corp., Houston, TX, USA). Continuous variables were declared as medians (25^{th} – 75^{th} percentile) and count data as absolute frequencies (%). The distribution of variables between two groups were compared either with rank-sum tests, X^2-tests or Fisher's exact tests, as appropriate. For time-to-VTE analyses, the date of chemotherapy initiation (either as adjuvant or as curative chemotherapy) was the baseline date. Risks of VTE were computed with 1-Kaplan-Meier estimators and competing risk cumulative incidence estimators, treating death-from-any-cause as the competing event. The comparisons of VTE risk between patients with and without primary thromboprophylaxis were performed with log-rank tests, log-rank tests stratified for clinical stage and adjusted Wald tests. VTE risk was modelled in the uni- and multivariable setting with Fine & Gray competing risk regression models. To gauge whether the association between primary thromboprophylaxis and VTE risk may be modified by clinical stage, interactions between thromboprophylaxis and clinical stage were fitted within a Fine & Gray model and cumulative VTE incidences by prophylaxis and clinical stage status directly predicted from this model. Missing data are reported in table 5 and a complete case analysis was performed (1).

3 Results

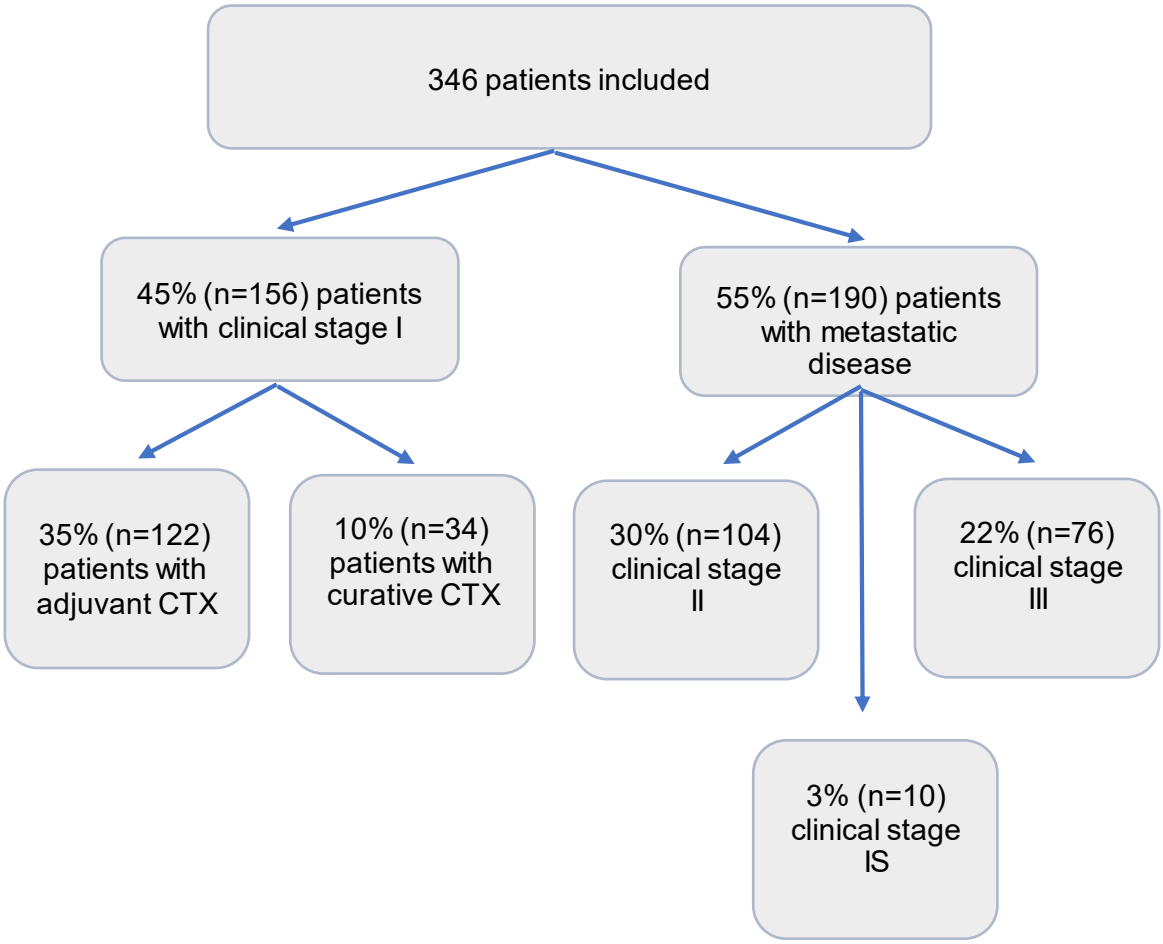
3.1 Baseline Characteristics

The cohort for the final analysis included 346 patients who were treated with cisplatinum-based chemotherapy. 122 patients (35%) were treated in the curative and 224 patients (65%) in the adjuvant setting. The cohort contained 93 patients with metastatic SGCT, 3 patients with TGCT of unknown type and 250 patients with NSGCT. 122 out of 156 (45%) patients who presented with clinical stage I were treated with adjuvant chemotherapy. 34 patients were initially handled with active surveillance strategy and then received curative chemotherapy because of disease relapse. 190 (55%) patients were initially treated with curative chemotherapy because of advanced disease. 104 patients presented with clinical stage II, 76 patients with clinical stage III and 10 patients with clinical stage IS. 57 patients (17%) presented with RPLN greater than 5cm in diameter (figure 2) (1).

Table 5 Baseline characteristics (1)

Variable	Number (%missing)	Overall (n=346)	No VTE during follow-up (n=297)	VTE during follow-up (n=49)	p*
Demographic characteristics					
Age	346 (0%)	35 [28-42]	35 [28-42]	34 [27-40]	0.508
BMI (kg/m²)	311 (10%)	25 [23-28]	25 [23-28]	25 [22-28]	0.754
Smoker or Ex-Smoker	239 (31%)	143 (60%)	128 (61%)	15 (54%)	0.472
Karnofsky Index <100%	286 (17%)	39 (14%)	31 (12%)	8 (22%)	0.129
Clinical variables					
Non-Seminomatous histology	343 (1%)	250 (73%)	213 (72%)	37 (77%)	0.481
Clinical tumor stage	344 (1%)	/	/	/	**0.012**
Stage IA-IB	/	156 (45%)	144 (49%)	12 (25%)	/
Stage IS	/	10 (3%)	9 (3%)	1 (2%)	/
Stage IIA–IIC	/	103 (30%)	85 (29%)	18 (38%)	/
Stage IIIA–IIIC	/	75 (22%)	58 (20%)	17 (35%)	/
RPLN(>5cm)	340 (1%)	57 (17%)	41 (14%)	16 (33%)	**0.001**
Primary metastatic disease	346 (0%)	190 (55%)	153 (52%)	37 (76%)	**0.002**
Initial treatment setting	346 (0%)	/	/	/	**0.004**
Active Surveillance	/	34 (10%)	30 (10%)	4 (8%)	/
Adjuvant treatment	/	122 (35%)	114 (38%)	8 (16%)	/
Curative treatment	/	190 (55%)	153 (52%)	37 (76%)	/
IGCCCG risk stratification**	190 (0%)	/	/	/	
Good risk	/	146 (77%)	121 (79%)	25 (68%)	/
Intermediate risk	/	20 (11%)	13 (9%)	7 (19%)	/
Poor risk	/	24 (13%)	19 (12%)	5 (14%)	/
Chemotherapy cycles given	346 (0%)	/	/	/	**0.004**
1 cycle	/	47 (14%)	45 (15%)	2 (4%)	/
2 cycles	/	70 (20%)	65 (22%)	5 (10%)	/
3 cycles	/	156 (45%)	132 (44%)	24 (49%)	/
≥4 cycles	/	73 (21%)	55 (19%)	18 (37%)	/

Figure 2 Included patients sorted by clinical stage (1)

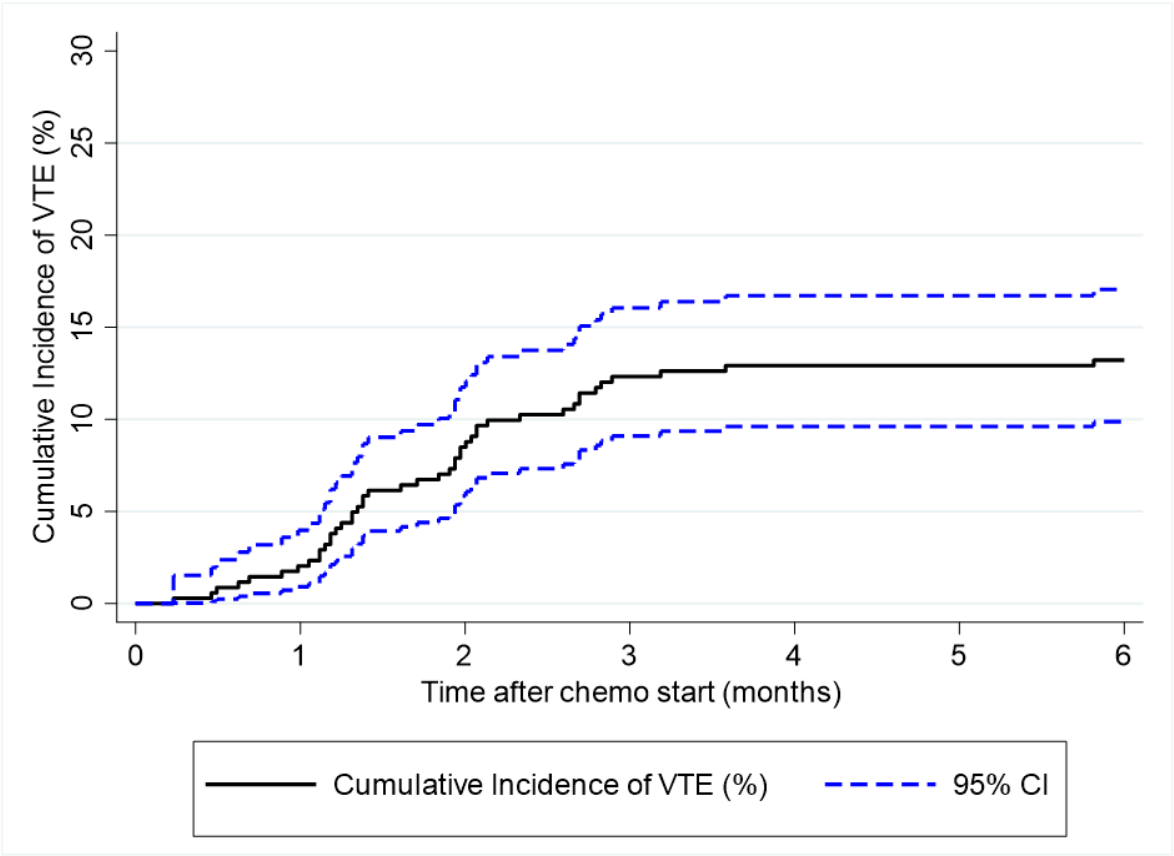


3.2 Risk of venous thromboembolic events

The average observation period was 50.6 months. 75% had an observation time of 31.1 months and 25% had observation times of 74.4 months. In the first six months after start of the chemotherapy, 49 patients (14%) developed VTE: 31 patients developed PE (63%), 6 patients developed DVT (12%), 8 patients developed PE and DVT (16%) and 4 patients developed other VTE (8%). This corresponded to a 1-month cumulative VTE incidence of 2.0% (95% CI: 0.9 – 4.0), a 2-month cumulative incidence of 8.4% (95% CI: 5.8 – 11.7), a 3-month cumulative incidence of 12.3% (95% CI: 9.1 – 16.1) and a 6-month cumulative incidence of 13.2% (95% CI: 9.9 – 17.1), respectively. The 1-, 2-, 3- and 6-month cumulative incidences for VTE are visualized in figure 3. Predictive factors for VTE were a higher clinical tumor stage, the presence of a RPLN and increasing cycles of cisplatinum-based chemotherapy (table 6). The risk of VTE did not change significantly during the inclusion period (p=0,267) (1).

In clinical stage I, 9% of all patients without thromboprophylaxis suffered from VTE whereas only 3% had a VTE despite of thromboprophylaxis. In clinical stage IIC 50% of all patients without thromboprophylaxis suffered from VTE compared to 15% with thromboprophylaxis. In clinical stage III, 30% of all patients not undergoing thromboprophylaxis developed a VTE whereas only 13% had VTE when undergoing primary thromboprophylaxis (1).

Figure 3 Cumulative VTE incidence in patients with TGCT undergoing cisplatinum-based chemotherapy. Curves were estimated with a competing risk cumulative incidence estimator, and the 95% confidence band of VTE risk is represented by the blue lines (1)



3.3 Primary thromboprophylaxis

In the patient cohort, 107 patients (31%) were treated with primary thromboprophylaxis. 106 patients (99%) received low molecular weight heparin and 1 patient received direct oral anticoagulants (DOAK) as primary thromboprophylaxis. In 87 patients the low molecular weight dose was prophylactic, in 11 patients semi-therapeutic and in 8 patients the dose was unknown (1). Prophylactic dose consisted of subcutaneous enoxaparin 40mg once daily. Therapeutical doses of low molecular heparin were weight adjusted and applied two times a day. Semi-therapeutic doses of low molecular weight heparin are doses between prophylactic and therapeutic doses.

Since Bezan et al published in 2017 that patients with higher clinical tumor stage and RPLN are more likely to suffer from VTE, the number of patients treated with primary thromboprophylaxis at the Department of Oncology at the Medical University of Graz strongly increased ($p<0.0001$). Since 2019, all patients in clinical stage IIC – III and 35% of all patients in clinical stage IA – IIB were treated with primary thromboprophylaxis (p for interaction 0.104) (figure 4) (1, 8).

As shown in table 6, patients who received primary thromboprophylaxis were more likely to have a Karnofsky Index less than 100%, a higher clinical tumor stage, suffered more often from primary metastatic disease and IGCCCG intermediate- to poor-risk disease and received more cycles of cisplatinum-based chemotherapy. (1).

Figure 4 Proportion of patients receiving primary thromboprophylaxis – Distribution by clinical stage (1)

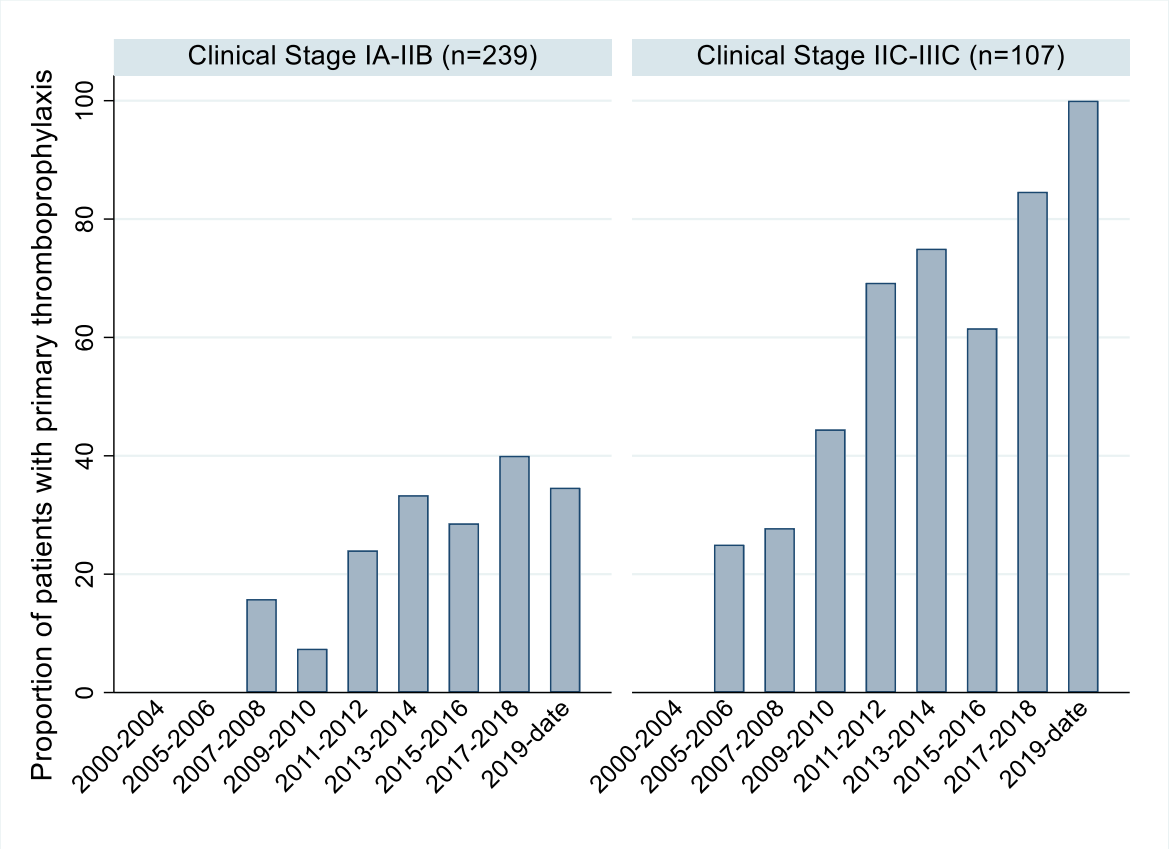


Table 6 Patient Characteristics - overall and distributed by primary thromboprophylaxis (1)

Variable	Number (%missing)	Overall (n=346)	No primary thrombo-prophylaxis (n=239)	Primary thrombo-prophylaxis (n=107)	p*
Demographic characteristics					
Age	346 (0%)	35 [28-42]	34 [28-41]	37 [28-45]	0.119
BMI (kg/m²)	311 (10%)	25 [23-28]	25 [23-28]	25 [23-28]	0.667
Smoker or Ex-Smoker	239 (31%)	143 (60%)	108 (61%)	35 (57%)	0.650
Karnofsky Index <100%	286 (17%)	39 (14%)	23 (11%)	16 (21%)	**0.033**
Clinical variables					
Non-Seminomatous histology	343 (1%)	250 (73%)	190 (80%)	60 (57%)	**<0.0001**
Clinical tumor stage	344 (1%)	/	/	/	**<0.0001**
Stage IA-IB	/	156 (45%)	125 (53%)	31 (29%)	/
Stage IS	/	10 (3%)	10 (4%)	0 (0%)	/
Stage IIA–IIC	/	103 (30%)	60 (25%)	43 (41%)	/
Stage IIIA–IIIC	/	75 (22%)	43 (18%)	32 (30%)	/
RPLN(>5cm)	340 (1%)	57 (17%)	23 (10%)	34 (33%)	**<0.0001**
Primary metastatic disease	346 (0%)	190 (55%)	114 (48%)	76 (71%)	**<0.0001**
Initial treatment setting	346 (0%)	/	/	/	**<0.0001**
Active Surveillance	/	34 (10%)	23 (10%)	11 (10%)	/
Adjuvant treatment	/	122 (35%)	102 (43%)	20 (19%)	/
Curative treatment	/	190 (55%)	114 (48%)	76 (71%)	/
IGCCCG risk stratification**	190 (0%)	/	/	/	**0.010**
Good risk	/	146 (77%)	96 (84%)	50 (66%)	/

Intermediate risk	/	20 (11%)	7 (6%)	13 (17%)	/
Poor risk	/	24 (13%)	11 (10%)	13 (17%)	/
Chemotherapy cycles in primary platinum-based treatment	346 (0%)	/	/	/	**<0.0001**
1 cycle	/	47 (14%)	39 (16%)	8 (7%)	/
2 cycles	/	70 (20%)	62 (26%)	8 (8%)	/
3 cycles	/	156 (45%)	106 (44%)	50 (47%)	/
≥4 cycles	/	73 (21%)	32 (13%)	41 (38%)	/

3.4 Predictors of venous thromboembolic events

The most significant predictor for developing a VTE was higher clinical tumor stage (table 7). Primary thromboprophylaxis was not associated with a higher risk of VTE in univariable analysis (subdistribution hazard ratio (SHR) = 0.68, 95% CI = 0.35 – 1.32, p=0.251). After adjusting for the confounding influence of a higher clinical tumor stage, primary thromboprophylaxis was strongly associated with a lower VTE risk (adjusted SHR = 0.48, 95% CI= 0.24-0.97; stage-stratified log-rank p=0.032 (figure 5), Wald-test p=0.042 (figure 6) (1).

The two most significant predictors for developing a VTE were higher clinical tumor stage and the presence of a RPLN greater than 5cm in diameter. As these two parameters are highly correlated with the use of primary thromboprophylaxis, we evaluated the association of VTE risk with primary thromboprophylaxis at first for patients with lower clinical tumor stages (cs I-IIB) and later for patients with higher clinical tumor stages (cs IIC-III) by performing an interaction analysis. In this analysis we did not obtain statistical evidence at the 5% level. The association between primary thromboprophylaxis and the reduction of VTE risk was not different between higher clinical stage disease (cs IIC -III) and lower clinical stage disease (cs IA - IIB) (p for interaction = 0.310). (1).

Table 7 Predictors of VTE – univariable competing risk regression (1)

Variable	SHR	95%CI	p
Main study exposure			
Primary thromboprophylaxis	**0.68**	**0.35 - 1.32**	**0.251**
Demographic characteristics			
Age (per 5 years increase)	0.97	0.85 - 1.12	0.725
BMI (per 5kg/m² increase)	0.96	0.70 - 1.32	0.821
Smoker/Ex-Smoker vs never smoker	0.60	0.27 - 1.31	0.200
Karnofsky Index <100%	1.84	0.79 - 4.28	0.156
Clinical variables			
Non-Seminomatous histology	1.30	0.65 - 2.62	0.460
Clinical stage IIC–IIIC	2.60	1.45 - 4.66	0.001
RPLN(>5cm)	2.36	1.27 - 4.40	0.007
Primary metastatic disease	2.24	1.15 - 4.37	0.018
IGCCCG risk stratification**			
Good risk	Ref.	Ref.	Ref.
---Intermediate risk and poor risk	1.45	0.70 - 2.99	0.322
Chemotherapy cycles in primary platinum-based treatment			
---1 cycle	Ref.	Ref.	Ref.
---2 cycles	1.61	0.30 - 8.59	0.576
---3 cycles	3.24	0.74 - 14.18	0.119
---≥4 cycles	5.03	1.13 - 22.45	0.034

Figure 5 Primary thromboprophylaxis and risk of VTE in patients with TGCT treated with cisplatinum-based chemotherapy. Data represent 1-Kaplan-Meier estimators and a log-rank test stratified by clinical tumor stage (IA-IIB vs. IIC -IIIC) (1)

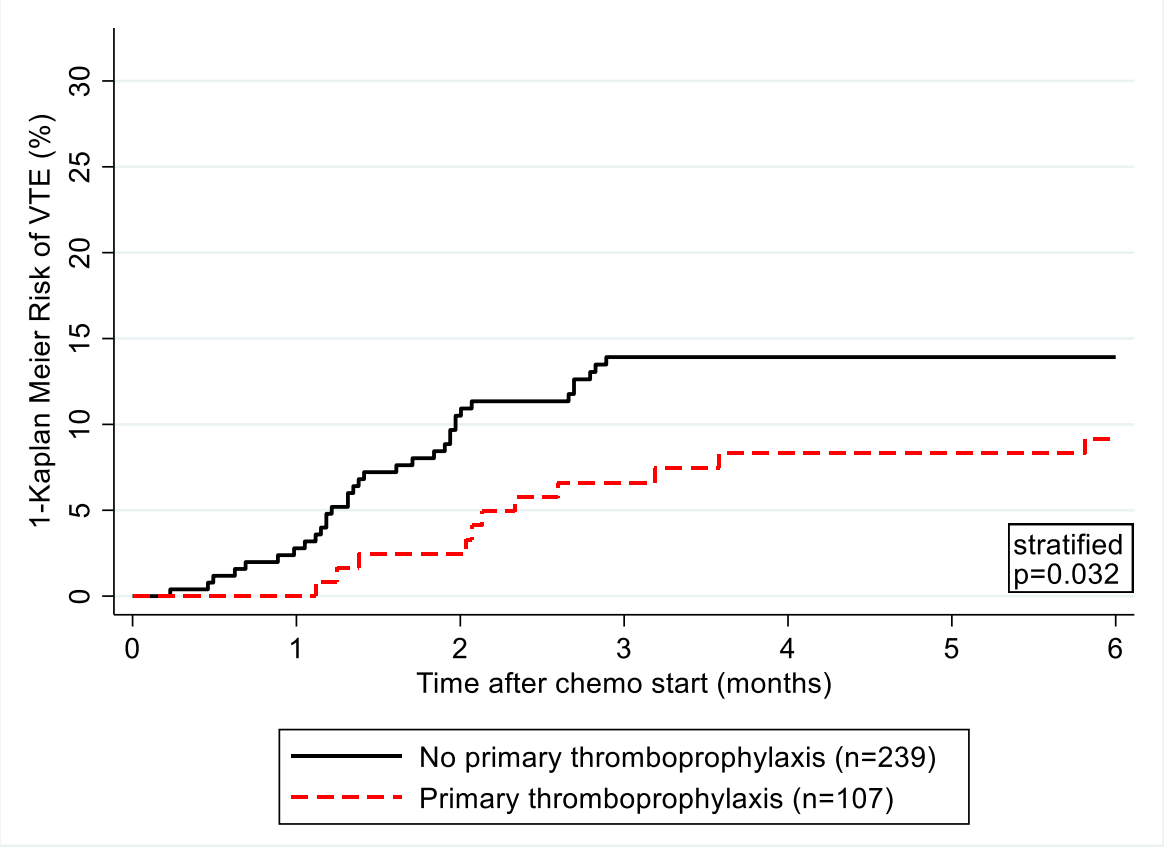
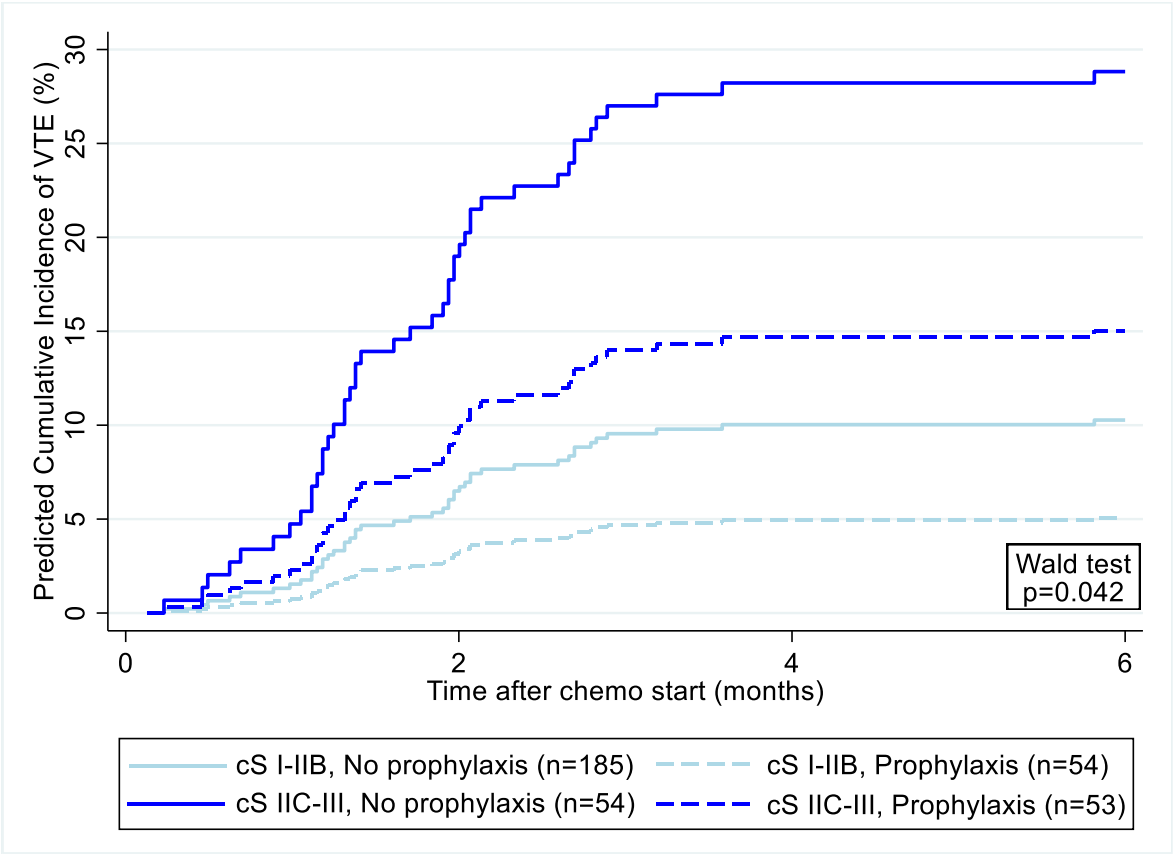


Figure 6 Predicted risk of VTE according to primary thromboprophylaxis and clinical stage in patients with TGCT treated with cisplatinum-based chemotherapy. Curves represent cumulative incidence functions that were predicted from a Fine & Gray competing risk regression model with two variables (primary prohpylaxis and clinical stage IA – IIB vs. IIC – IIIC). The Wald-test p-value represents the stage-adjusted p-value for thromboprophylaxis (overall model p-value= 0.001). This model constrains the relative risk reduction of thromboprohylaxis to be similar in patients with stage IA – IIB and stage IIC - IIIC disease (1)



4 Discussion

In this retrospective cohort study, we showed that the application of primary thromboprophylaxis in patients with TGCT undergoing cisplatinum-based chemotherapy reduced the relative risk for VTE in all clinical stages by 52%. This reduction is comparable with results of prospective clinical trials, in patients with other cancer types than TGCT (1, 5, 7, 41).

The two main predictors for VTE were a higher clinical tumor stage (cs IIC-III) and the presence of a large RPLN >5cm. Our results were similar to the results from Srikanthan et al and Bezan et al (1, 8, 9).

The main disadvantage of primary thromboprophylaxis is the increased risk for bleeding complications (1, 5, 7, 41). Fankhauser et al showed, that bleeding in TGCT patients undergoing primary thromboprophylaxis during chemotherapy occurred in 2.5% (95% CI 0.3 – 8.8%) whereas only 0.5% of the patients without anticoagulation had bleeding complications (95% CI 0.02 – 1.0%) (12). In the AVERT trial, Apixaban also resulted in a higher risk for bleeding than placebo but offered a significant advantage in VTE risk reduction in ambulatory cancer patients (5). Fankhauser concluded, that in absence of risk factors, the risk of bleeding is only slightly increased. The resulting benefit of preventing VTE would be much greater (12).

Possible risk factors for bleeding include chemotherapy induced thrombozytopenia, presence of histological fractions of chorioncarcinoma due to its great potential for neoangiogenesis, tumor invasion into surrounding organs and cerebral metastases (1, 12, 41, 42).

In absence of these risk factors, we therefore suggest, as already recommended by the German S3-guidelines for metastatic disease, application of primary thromboprophylaxis in TGCT patients undergoing cisplatinum-based chemotherapy (30).

In addition to the German S3-guidelines and in absence of any risk factors for bleeding, we have shown that it might also be useful to apply primary thromboprophylaxis to TGCT patients in clinical stage I disease receiving adjuvant cisplatinum-based chemotherapy. The duration of the primary thromboprophylaxis

should be limited to the time of chemotherapy as nearly no thromboembolic events occur after the treatment period (1, 41).

The major restriction of our study was its retrospective analysis. Further analyses with a bigger patient cohort in a prospective trial are needed to confirm our results.

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