Thesis

Cisplatin exposure and long-term kidney function trajectories in patients with testicular germ cell tumors

submitted by

Franziska Ruess

in partial fulfillment of the requirements for the degree of

Doktor(in) der gesamten Heilkunde

(Dr.(in) med. univ.)

at the

Medical University of Graz

Executed at the **University Department of Internal Medicine**

Division of Hematology

under the supervision of

Priv.-Doz. Dr.med.univ. Florian Posch MSc. PhD. and

Univ. FÄ Priv.-Doz. Dr.med.univ. Angelika Terbuch

Graz, 20.11.2024

Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Furthermore, I hereby declare that if artificial intelligence (AI) tools were used for the generation and/or correction of certain text passages in the creation of this work, such employment was conducted in compliance with ethical principles, academic integrity, and the regulations of my university. Additionally, it was ensured that this usage was transparently disclosed and appropriately attributed.

Graz, 20.11.2024 *Franziska Ruess m.p*

Danksagung

An dieser Stelle möchte ich die Gelegenheit nutzen, um all jenen zu danken, die mich auf meinem Weg zur Fertigstellung dieser Diplomarbeit begleitet und unterstützt haben.

Mein Dank gilt meinen Betreuern Dr. Florian Posch und Dr. Angelika Terbuch von der klinischen Abteilung für Hämatologie und Onkologie der Universitätsklinik Graz, die mich bei der Erstellung dieser Arbeit großartig unterstützt haben. Ihre Zeit, ihre Ratschläge und Expertise haben diese Arbeit überhaupt erst möglich gemacht. Bei meinem Mentor Dr. Florian Posch möchte ich mich bedanken für die vielen intensiven Arbeitsstunden, sein Engagement und sein Teaching. Meiner Zweitbetreuerin Dr. Angelika Terbuch möchte ich danken, für die zur Verfügungstellung der TGCT-Kohortendaten, für ihre Zeit und Mühe, die sie in diese Arbeit gesteckt hat.

Ein besonderer Dank gilt meinen Eltern, Silvia und Gerhard und meinem Bruder Michael, die mich immer unterstützt haben und mich motiviert haben, mein Bestes zu geben.

Meinem Partner Benjamin möchte ich von Herzen danken für seine Geduld, sein Verständnis und seine Ruhe in hektischen Zeiten.

Nicht zuletzt geht ein großes Dankeschön an meine Freunde und Familie, für die Unterstützung, Motivation und für immer gute Ratschläge.

Zusammenfassung

Hintergrund & Ziel: Die platinbasierte Chemotherapie ermöglicht die Heilung von Patienten mit Keimzelltumoren des Hodens (TGCT), kann jedoch mit Nierentoxizität einhergehen. Daher wollten wir in dieser Studie den Zusammenhang zwischen Art und Dosis der Platinexposition und den langfristigen Nierenfunktions-einschränkungen bei TGCT-Patienten quantifizieren.

Material & Methoden: Sechzehntausendneunhundertdreiundfünfzig longitudinale geschätzte glomeruläre Filtrationsraten (eGFR) von 777 TGCT-Patienten wurden mit einer time-to-event Regression und linear mixed models analysiert. Primäre Endpunkte waren die kumulative Inzidenz eines relativen eGFR-Rückgangs um 30% im Vergleich zur eGFR vor der Behandlung und die jährliche absolute Veränderung der eGFR (in ml/min/1,73 m²/Jahr).

Ergebnisse: Die eGFR vor der Behandlung betrug 96 ml/min/1,73 m². Die kumulativen 10-Jahres-Inzidenzen eines 30%-igen Rückgangs der eGFR betrugen 18% bei Patienten, die nie eine platinbasierte Therapie erhielten (Gruppe 1, n=335), 18% bei Patienten, die mit einer einmaligen adjuvanten Carboplatin-Dosis behandelt wurden (Gruppe 2, n=83), 17% bei Patienten, die 1-2 Zyklen adjuvantes Bleomycin/Etoposid/Cisplatin (BEP) erhielten (Gruppe 3, n=118), und 35% bei Patienten, die mit ≥3 Zyklen BEP behandelt wurden (Gruppe 4, n=241) (Gray-Test p<0,0001). Die zeitabhängigen Ereignisraten eines 30%-igen Rückgangs der eGFR dieser vier Gruppen waren jedoch nach 4 Jahren Follow-up sehr ähnlich. Die jährliche, durchschnittliche Veränderung der eGFR in absoluten Zahlen betrug -0,1 ml/min/1,73 m²/Jahr, 0,1 ml/min/1,73 m²/Jahr, -0,5 ml/min/1,73 m²/Jahr und -1,5 ml/min/1,73 m²/Jahr in den Gruppen 1-4. Das Risiko einer Hämodialyse nach Studieneinschluss betrug 0 %.

Conclusio: Im Vergleich zu TGCT-Patienten ohne Platinexposition hatten nur Patienten, die mit ≥3 Zyklen Cisplatin behandelt wurden, ein höheres Risiko eines längerfristigen Nierenfunktionsrückgangs.

Abstract

Background & Objective: Platinum-based chemotherapy induces cure in patients with testicular germ cell tumors (TGCT) but may come at the cost of kidney toxicity. In this study, we aimed to quantify the association of type and dose of platinum exposure with long-term kidney function trajectories in TGCT patients.

Methods: Sixteen-thousand-nine-hundred-fifty-three longitudinal estimated glomerular filtration rate (eGFR) measurements from 777 TGCT patients were analyzed with time-to-event regression and linear mixed models. Co-primary outcomes were the cumulative incidence of a 30% relative decline in eGFR from pre-treatment eGFR, and the longitudinal annualized absolute change in the eGFR (in ml/min/1.73m²/year).

Results: Pre-treatment eGFR was 96ml/min/1.73m². Cumulative 10-year incidences of a 30% decline in eGFR were 18% in patients who never received any platinum-based therapy (Group 1, n=335), 18% in patients treated with single-shot adjuvant carboplatin (Group 2, n=83), 17% in those treated with 1-2 cycles of adjuvant bleomycin/etoposide/cisplatin (BEP, Group 3, n=118), and 35% in those treated with ≥3 cycles of BEP (Group 4, n=241), respectively (Gray's test $p<0.0001$). However, time-dependent event rates of a 30% decline in eGFR of these 4 groups were highly similar after 4 years of follow-up. The annualized absolute average changes in eGFR were -0.1ml/min/1.73m²/year, 0.1ml/min/1.73m²/year, -0.5ml/min/1.73m²/year, and -1.5ml/min/1.73m²/year in groups 1-4, respectively. The risk of any haemodialysis after study inclusion was 0%.

Conclusion: As compared to TGCT patients without platinum exposure, only patients treated with ≥3 cycles of cisplatin experienced a higher risk of longer-term kidney function decline.

Publications and Presentations based on this Thesis

Ruess F, Odler B, Posch F, Terbuch A. Platinum exposure and 10-year kidney function trajectories in patients with testicular germ cell tumors. [in preparation]

Table of Content

Abbreviations

AdjBEP ..... *adjuvant BEP patient group*
AdjCBP ..... *adjuvant carboplatin AUC7 patient group*
ADPKD ..... *autosomal dominant polycystic kidney disease*
AFP ..... *alphafetoprotein*
AS ..... *active surveillance*, *active surveillance patient group*
AUC7 ..... *carboplatin chemotherapy*
BEP ..... *cisplatin, etopside and bleomycin chemotherapy*
BMI ..... *body mass index*
CAD ..... *coronary artery disease*
CKD ..... *chronic kidney disease*
CKD-EPI ..... *chronic kidney disease epidemiology collaboration*
CLL ..... *chronic lymphocytic leukemia*
COPD ..... *chronic obstructive pulmonary disease*
CS I ..... *clinial stage I*
CT ..... *computerised/computed tomography*, *chemotherapy*
CurBEP ..... *"curative" BEP/EP patient group*
DAMPS ..... *damage-associated molecular pattern molecules*
DNA ..... *deoxyribonucleic acid*
EC ..... *embryonal carcinoma*
EP ..... *etopside/cisplatin therapy*
ER ..... *endoplasmic reticulum*
ESRD ..... *end stage renal disease*
FDG-PET ..... *fluorodeoxyglucose-positron emission tomography*
GCNIS ..... *germ cell neoplasia in situ*
GCT ..... *germ cell tumor(s)*
GFR ..... *glomerular filtration rate*
GIP ..... *gemcitabine, ifosfamide, cisplatin salvage chemotherapy*
GR ..... *genital ridge*
HD ..... *high dose*
HD-CE ..... *high dose cisplatin and etoposide chemotherapy*
ICU ..... *intensive care unit*
IGCCCG ..... *International Germ Cell Cancer Collaborative Group*
IMI ..... *Department of Informatics,, Medical Statistics and Documentation*
LDH ..... *lactate dehydrogenase*
LVI ..... *lymphovascular invasion*
MDRD ..... *modified diet in renal disease*
miRNA ..... *micro ribonucleic acid*
MRI ..... *macnetic resonance imaging*
N/A ..... *not applicable*
NSGCT ..... *non-seminomatous germ cell tumor(s)*
OS ..... *overall survival*
p21 ..... *cyclin-dependent kinase inhibitor 1*
p53 ..... *tumor suppressor gen p53*
PFS ..... *progression-free survival*
PGC ..... *primordial germ cell(s)*
pT ..... *primary tumor*

PTEN.....*phosphatase and tensin homolog*
pTis.....*primary tumor in situ*
ROS.....*reactive oxygen species*
RPLND .....*retroperitoneal lymph node dissection*
RT.....*radiotherapy*
SGCT .....*seminoma germ cell tumor*
SHR.....*subdistribution hazard ratio*
SSC.....*spermatogonial stem cell(s)*
TGCT.....*testicular germ cell tumor(s)*
TIP.....*paclitaxel, ifosfamide, cisplatin salvage chemotherapy*
TLR.....*toll-like receptor(s)*
TNFα .....*tumor necrosis factor alpha*
UICC.....*Union International Contre Le Cancer, International Union Against Cancer*
VIP .....*etopside, cisplatin, ifosfamide chemotherapy*
β-hCG.....*beta subunit of chorionic gonadotropin*

Figures

Supplementary Figures

Tables

Supplementary Tables

1 Introduction

1.1 Testicular Germ Cell Tumors

Testicular germ cell tumors (TGCT) are the most frequent malignancies in young Caucasian men under the age of 50. The number of TGCT cases has been increasing over the past decades, notably in industrialized nations. (1–4)

TGCT are generally divided into pre-pubertal (unrelated to pre-invasive precursors) and post-pubertal TGCT, which are the focus of this thesis. Post-pubertal TGCT originate from pre-invasive precursors called germ cell neoplasia in situ (GCNIS), where defectively matured germ cells stay dormant until the onset of puberty. Histologically and clinically post-pubertal TGCT are divided into seminomas and non-seminomatous germ cell tumors (NSGCT). NSGCT are sub-divided into teratoma, embryonal carcinoma (EC), yolk sac tumor or choriocarcinoma. (5,6)

The peak incidence of NSGCT and mixed germ cell tumor (GCT) patients occurs in the third decade of life, while the highest incidence in seminoma patients occurs in the fourth decade. (7)

1.2 Pathophysiology

The fundamental mechanism underlying the development of TGCT is believed to be a malfunction in spermatogenesis during embryonic development. Regular spermatogenesis undergoes a complex and tightly regulated series of differentiation to ensure male fertility. (8) Starting point of spermatogenesis are primordial germ cells (PGC) that form during early embryonic development, migrate across the embryo to the genital ridge (GR) and form the functional gonads together with surrounding somatic cells. (9) Once the testicular cords are formed the germ cells present are referred to as “gonocytes”. Gonocytes undergo a maturation process, migrate towards the basement membrane of the seminiferous cords and differentiate into spermatogonial stem cells (SSC) or type A spermatogonia. Gonocytes are the stem cell reservoir and therefor maintain the potential of self-renewal to ensure life-long production of spermatozoa. Spermiogenesis then rests in a dormant stage until the onset of puberty, where proliferation of propagable spermatozoa is initiated. The spermatogenic cycle starts with a mitotic phase that takes place in SSC including differentiation of (type A- and type B-) spermatogonia

at different phases of maturation, followed by a meiotic phase with differentiation into primary spermatocytes, secondary spermatocytes and finally haploid spermatids, that then undergo spermiogenesis, resulting in haploid spermatozoa that complete maturation in the epididymis. (10) Within this complex process pathological errors can occur in different phases of differentiation. Key incident in the development of TGCT seems to be a defective differentiation of gonocytes, which is suspected to lead to the formation of GCNIS during early germline development. (8,10,11)

On a molecular level regular developed germ cells go through a thorough eradication and reestablishment of DNA-methylation, whereas DNA in GCNIS cells appears to remain demethylated, which could contribute to malignant degradation. (12) Gain and loss of chromosomal regions such as loss of PTEN (a tumor suppressor gene encoding for inhibition of cellular proliferation), loss of p21 (a cyclin-dependent kinase inhibitor regulated by p53 intervening in the cell cycle), a gain of function mutation of mdm-2 (a ubiquitin ligase regulating the tumor suppressor gene p53) or an increase of chromosome arm 12p material, seem to contribute to the neoplastic transformation from GCNIS to invasive TGCT. (13–15)

1.3 Risk Factors

Epidemiological risk factors for the development of TGCT are cryptorchidism, hypospadias, infertility, gonadal dysgenesis, familial predisposition and contralateral TGCT. (16–24) Recent genome-wide association studies were able to detect susceptibility loci associated with an increased risk of TGCT. (25)

1.4 Diagnosis

The diagnosis of TGCT is based on a combination of the patient’s clinical presentation, imaging and serum tumor marker elevation.

A testicular enlargement, sometimes concomitant with pain, can be found during physical examination. In advanced stages back pain, dyspnea, weight loss, headaches, gynecomastia and hyperthyroidism can also be present. (26,27)

First line imaging is the scrotal ultrasonography of both testes, that confirms intra- or extra-testicular tissue growth, identifies location and size of the tumor and allows an assessment of the contralateral testis. (27)

Serum tumor markers are determined pre-orchiectomy providing diagnostic and histological information and post-orchiectomy providing staging, prognostic and therapeutic information. (27–29) Elevation patterns of α-fetoprotein (AFP), beta subunit of human chorionic gonadotropin (β-hCG) and lactate dehydrogenase (LDH) pre-orchiectomy may be indicative of tumor subtypes, notably NSGCT. (29) Marker elevation is integrated into standardized patient risk grouping (see Table 3), which is utilized to guide therapeutic management. Post-orchiectomy serum tumor markers correlate with prognosis, with a slow marker decline potentially indicating metastatic disease. (28,29) In disseminated TGCT marker decline is utilized to assess treatment response following chemotherapy. Therefore, serum tumor markers play a critical role in the diagnosis, prognosis, and therapeutic management of TGCT. (29) However, limitations include a low specificity and sensitivity as tumor markers are only elevated in less than 50% of cases. (30)

Computed tomography (CT) imaging is utilized for staging and the identification of metastases in the thoracic, abdominal, and pelvic regions. (26,31) Brain imaging is reserved for patients exhibiting neurological symptoms, significant elevation in serum tumor markers, the presence of multiple pulmonary metastases, or in cases of TGCT recurrence. (26) In comparison to contrast enhanced CT, magnetic resonance imaging (MRI) is more precise in detecting metastases located in the central nervous system. (31) Remaining a second line diagnostic device, MRI is recommended only in cases of non-specific sonography, specific preoperative staging, differentiation of extra- or intratesticular growth and distinction of some TGCT subtypes. (32) Fluorodeoxyglucose-positron emission tomography (FDG-PET) is not recommended in first line diagnosis and staging. (33,34)

Cryopreservation of semen should be offered and undertaken prior to orchiectomy, chemotherapy (CT) and radiotherapy (RT) to preserve fertility as it can be negatively impacted by these treatment measures. (35–37)

Research currently focuses on micro RNA (miRNA) as potential tumor biomarkers for clinical applications in terms of primary diagnosis, treatment, monitoring and

disease recurrence. (27,38) Particularly miR-371a-3p seems to be exclusively expressed by GCT and could therefor differentiate germ cell and non-germ cell neoplasia. (39) Data also suggests that miR-371a-3p could potentially serve as an early relapse marker in GCT. (40)

1.5 Tumor Staging

The classification to assess the extent of testicular neoplastic growth is based on the 2016 TNM-classification of the International Union Against Cancer (UICC) according to EAU guidelines on testicular cancer and is shown in Table 1. (27)

Table 1: TNM classification for testicular cancer (adapted from UICC 2016, 8th edn.) (27,41)

pT – primary tumor	
pTX	Primary tumor cannot be assessed[1]
pT0	No evidence of primary tumor (e.g. histological scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma in situ)[2]
pT1	Tumor limited to testis and epididymis without vascular/lymphatic invasion; tumor may invade tunica albuginea but not tunica vaginalis[3]
pT2	Tumor limited to testis and epididymis with vascular/lymphatic invasion, or tumor extending through tunica albuginea with involvement of tunica vaginalis[4]
pT3	Tumor invades spermatic cord with or without vascular/lymphatic invasion[5]
pT4	Tumor invades scrotum with or without vascular/lymphatic invasion
N – regional lymph nodes (clinical)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive,

[1] Except for pTis and pT4, where radical orchiectomy is not always required for classification purposes, the assessment of the primary tumor's extent is conducted in the radical orchiectomy specimen and classified as pT0-4, TX is used if no radical orchiectomy has been performed
[2] "Carcinoma in situ" nomenclature is replaced by GCNIS (125)
[3] *AJCC 8th edition subdivides T1 Seminoma by T1a (size not greater than 3 cm in greatest dimension) and T1b (size greater than 3 cm in greatest dimension)* (126)
4 *AJCC 8th edition categorizes the hilar soft tissue invasion and epididymal invasion as pT2 while the discontinuous involvement of the spermatic cord is classified as pM1* (126)

	none more than 5 cm; or evidence of extranodal extension of tumor		
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
pN – regional lymph nodes (pathological)			
pNX	Regional lymph nodes cannot be assessed		
pN0	No regional lymph node metastasis		
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension		
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extra-nodal extension of tumor		
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
M – distant metastasis			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis[4]		
M1a	Non-regional lymph node(s) or lung metastasis		
M1b	Distant metastasis other than non-regional lymph nodes and lung		
S – serum tumor markers (pre-chemotherapy)			
SX	Serum marker studies not available or not performed		
S0	Serum marker study levels within normal limits		
	LDH (U/l)	β-hCG (mIU/ml)	AFP (ng/ml)
S1	<1,5 × N^6 and	< 5,000 and	< 1,000
S2	1.5-10 x N^5 or	5,000-50,000 or	1,000-10,000
S3	> 10 x N^5 or	> 50,000 or	> 10,000

In accordance with the 2016 TNM classification of testicular tumors, prognostic groups are formed by the UICC according to EAU guidelines on testicular cancer as shown in Table 2. (27)

Table 2: Prognostic groups for testicular cancer (UICC, 2016, 8th edn.) (27,41)

Stage	P	T	M	S
Stage 0	pTis	N0	M0	S0

Stage I	pT1-pT4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2-pT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-3
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	M1a	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1-N3	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

In Stage IA the primary tumor is limited to testis and epididymis showing no signs of vascular or lymphatic invasion or metastasis. In Stage IB the primary tumor growth is increasingly invasive, with vascular and/or lymphatic infiltration but no distant metastasis. Serum tumor marker levels after the orchiectomy stay within normal range. In Stage IS the serum tumor markers post-orchiectomy stay continuously elevated or increase suggesting the presence of subclinical metastatic growth. Stage II is characterized by lymph node metastasis, further divided into IIA, IIB and IIC according to the lymph node size. In stage III distant metastasis are present. (27,41)

1.6 Prognosis

In 1997 the International Germ Cell Cancer Collaborative Group (IGCCCG) established a prognostic system for metastatic GCT identifying clinically

independent adverse factors. (28) This prognostic risk-factor system was updated in 2021 by the IGCCCG Update Consortium and is shown in Table 3. (42)

Table 3: Prognostic risk-factor system for metastatic germ cell tumors (IGCCCG) (28,42)[5]

Good-prognosis group		**Prognosis**
Non-seminoma	All of the following criteria: • Testis/retro-peritoneal primary • No non-pulmonary visceral metastases • AFP < 1,000 ng/mL • hCG < 5,000 IU/L (1,000 ng/mL) • LDH < 1.5 x ULN	5-year PFS 90% 5-year survival 96%
Seminoma	All of the following criteria: • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any β-hCG and any LDH	5-year PFS 89% 5-year survival 95%
Intermediate-prognosis group		
Non-seminoma	• Testis/retro-peritoneal primary • No non-pulmonary visceral metastases And any of the following criteria: • AFP 1,000 - 10,000 ng/mL or • β-hCG 5,000 - 50,000 IU/L or • LDH 1.5 - 10 x ULN	5-year PFS 78% 5-year survival 89%
Seminoma	All of the following criteria: • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any β-hCG and any LDH	5-year PFS 79% 5-year survival 88%
Poor-prognosis group		
Non-seminoma	Any of the following criteria: • Mediastinal primary • Non-pulmonary visceral metastases • AFP > 10,000 ng/mL or • β-hCG > 50,000 IU/L (10,000 ng/mL) or LDH > 10 x ULN	5-year PFS 54% 5-year survival 67%
Seminoma	No patients classified as “poor-prognosis”	

Caption:

PFS: Progression-free survival

The updated IGCCCG prognostic model shows an increase of the overall survival (OS)[6] in patients within the intermediate prognostic group from 80% to 89%. An increase of the PFS from 41% to 54% as well as an increase of the OS from 48% to 67% was found in patients with poor prognosis. (42)

[5] Assessment of tumor markers should take place immediately before initiation of chemotherapy (on the same day) (42)

[6] OS defined from start of chemotherapy to death of any cause (42)

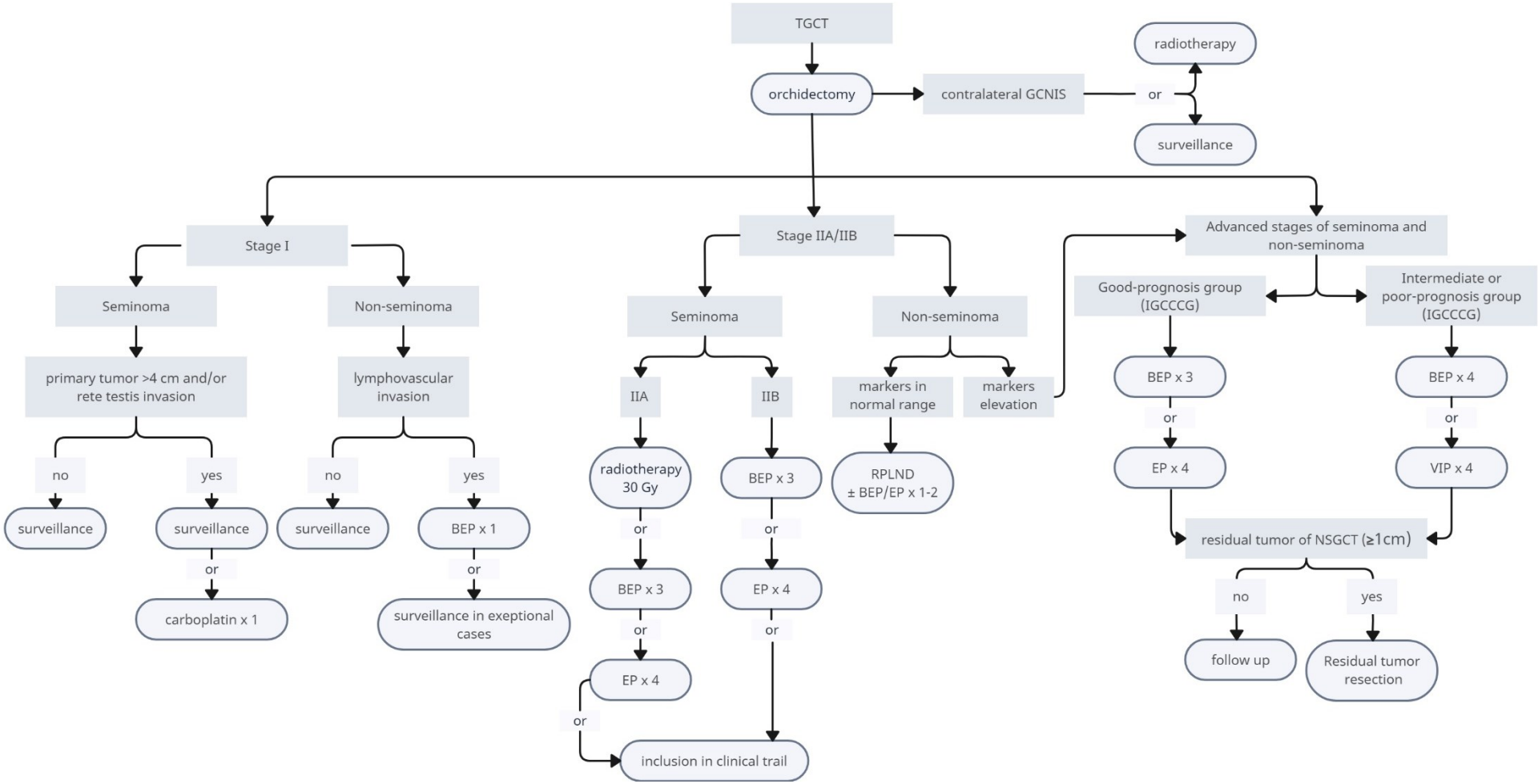
Prognosis on metastatic recurrence in clinical stage I seminoma seems predominantly dependent on two risk factors: primary testicular tumor size and rete testis invasion. (43) The risk of relapse in the absence of these two risk factors is considered low (6%). (44) However systematic reviews indicate that the value of these two risk factors in metastatic relapse prognosis has significant limitations. (45,46)

In clinical stage I NSGCT lymphovascular invasion (LVI) of the primary tumor mass is considered a prognostic factor of metastatic relapse. The lack of a standardized definition however limits its application. (47,48)

1.7 Therapy

The first-line therapy algorithm of TGCT according to Onkopedia guidelines is shown in the following Figure 1. (26)

Figure 1: First-line therapy algorithm of TGCT (26)



Caption:
"marker(s)" refer to AFP, β-hCG and LDH (26)
BEP - cisplatin, etoposide, bleomycin chemotherapy; the number refers to number of cycles (27)
EP - etoposide, cisplatin chemotherapy (27)
RPLND - retroperitoneal lymph node dissection (27)
VIP - etoposide, cisplatin, ifosfamide chemotherapy (27)
Good, intermediate and poor-prognosis group see Table 3 (28,42)

1.7.1 Orchiectomy – primary treatment

Orchiectomy of the affected testis is the first-line treatment of TGCT. Consideration of an organ-preserving approach for small, isolated tumors of <30% of the testicular volume is advised. In case of highly progressed tumor stage or acute life-threatening disease, immediate initiation of chemotherapy without prior orchiectomy is considered as primary treatment option. (49)

1.7.2 Seminoma clinical stage I

Overall, seminomatous germ cell tumor (SGCT) patients in clinical stage I (CS I) have a low risk of relapse. (27) Therapy management can be adjusted to individual risk factors such as primary tumor size (>4 cm) or rete testis invasion (see 1.6 Prognosis). (26,50) After first-line orchiectomy “active surveillance” (AS) including habitual cross-section imaging, tumor marker monitoring and clinical assessments, represents a treatment option for all SGCT patients irrespective of individual risk factors. The cause-specific survival of AS is close to 100%, whilst toxicity associated with other adjuvant therapies is minimized. (27,51,52) Patients with one or more risk factors may alternatively receive one cycle of adjuvant carboplatin chemotherapy (AUC7) after careful evaluation of individual circumstances, potential benefits and risks. (26,27,50)

1.7.3 Non-seminomatous germ cell tumor clinical stage I

The most important prognostic factor in NSGCT is the presence or absence of LVI in orchiectomy specimen. About 70% of CS I NSGCT patients are cured with orchiectomy alone. In patients with the high-risk feature of LVI, relapse occurs in up to 50% of cases, compared to 15% in patients without LVI. (27) The majority of relapses in LVI positive as well as LVI negative NSGCT patients occur within two years after orchiectomy. A late relapse of disease-free patients 3 years or later post-orchiectomy is extremely rare. (53) Therefore, AS[7] is an appropriate therapy option to avoid overtreatment in patients without LVI. (27,53,54). In contrast, LVI positive patients benefit from a risk adapted treatment approach considering their higher risk of relapse. One cycle of adjuvant BEP chemotherapy (see Table 4) is advised in LVI positive patients, resulting in very low relapse rates of 2-3%. (55,56) However

[7] habitual cross-sectional imaging, tumor marker monitoring and clinical assessments (27)

treatment decisions should be individually discussed to meet the patient's needs. (27)

1.7.4 Seminoma clinical stage IIA/B

In seminoma patients with isolated retroperitoneal lymph nodes ≤ 2 cm in greatest diameter without tumor marker elevation (CS IIA), re-assessment imaging (CT or MRI) after 6-8 weeks should be performed to differentiate reactive lymph node enlargement and actual metastatic disease. (26,42,57)

After re-staging, standard treatment involves initiating either chemotherapy or radiotherapy. In stage IIA seminoma, both treatment options yield comparable outcomes. (58) Radiotherapy requires radiation doses of 30 Gy (in CS IIA) with the standard field encompassing the para-aortic and ipsilateral iliac lymph nodes. (59,60) In stage IIB seminoma a meta-analysis of 13 high-quality studies comparing efficacy and toxicity of radiotherapy and chemotherapy demonstrated a non-significant trend indicating greater efficacy of chemotherapy. (61) The standard chemotherapy regimen for both CS IIA and IIB seminoma is BEP x 3 or EP x 4 in case of contraindication to bleomycin. (62) Cisplatin-based chemotherapy is preferred to treat larger lymph nodes, invasion of multiple lymph nodes and to evade second malignancy and long term effects of RT. Radiation therapy is preferred in stage IIA disease in case of advanced age and/or physical frailty with lower tolerance to chemotherapy. (26,27)

1.7.5 Non-seminomatous tumor clinical stage IIA/B

NSGCT patients with normal tumor marker levels and equivocal lymph nodes < 2 cm may be considered for initial surveillance to differentiate reactive lymph node enlargement and actual metastatic disease, followed by early re-evaluation at six weeks. If the lesions persist or progress, patients should be classified and treated as CS II. (27) In case of non-elevated markers but persisting suspect retroperitoneal lymph nodes, primary retroperitoneal lymph node dissection (RPLND) by an experienced surgeon in a specialized centre is the recommended single-modality treatment. (26,63,64) In case of vital cancer after RPLND, the administration of adjuvant chemotherapy should be discussed to reduce the risk of relapse. The standard regimen is BEP or EP for a maximum of 2 cycles. However, the risk of

overtreatment, the need for close follow-up and the potential side effects of chemotherapy must be carefully considered. (65,66)

Patients with elevated tumor markers in stage IIA/B NSGCT are treated according to the IGCCCG classification (see Table 3) analogously to the treatment algorithm (see Figure 1) for advanced tumor stages. (26)

1.7.6 GCT clinical stage IIC and III

Treatment of GCT clinical stage IIC and onwards (including CS II NSGCT with tumor marker elevation) are managed according to the IGCCCG risk classification (see Table 3). (26) Patients in the good-prognosis group receive a standardized cisplatin-based regimen of 3 cycles, each consisting of 21 days of BEP according to the European organization for research and treatment of cancer genitourinary tract cancer cooperative group and the IGCCCG (see Table 4). Alternatively 4 cycles of EP may be considered if bleomycin is contraindicated. (67,68)

The standard regimen for patients in the intermediate and poor-prognosis group (advanced disseminated GCT) is 4 cycles of BEP. (69) Alternatively 4 cycles of VIP[8] are an option for patients with contraindications to bleomycin. However under VIP treatment myelotoxicity occurs more frequently. (70) The administration of high-dose chemotherapy as first-line treatment in the poor-prognosis group is controversial. (71,72) A treatment strategy is to initiate a standard regimen and escalate chemotherapy intensity if tumor markers insufficiently decline during treatment. (72,73)

Table 4: BEP regimen (interval 21 days) (28,67)

Drug	Dosage	Duration of cycles
Cisplatin	20 mg/m^2	Days 1-5*
Etoposide	100 mg/m^2	Days 1-5
Bleomycin	30 mg	Days 1, 8, 15

**Plus, hydration*

1.7.7 Residual tumor resection

[8] etoposide, cisplatin, ifosfamide (71,72)

About 30% of TGCT patients with metastatic disease require residual tumor surgery or salvage therapy. (26)

In SGCT patients with tumor residuals post-chemotherapy < 3 cm, initial monitoring is preferred. A residual tumor resection is not indicated. FDG-PET is advised for residuals > 3 cm to predict viable tumor masses. (26,74)

In NSGCT patients residual tumor resection is indicated if the residual mass remains > 1 cm after the last cycle of chemotherapy. (75,76)

1.7.8 Systemic salvage chemotherapy

Salvage chemotherapy, an intensified treatment regimen, remains an option for patients with metastatic disease responding poorly to first-line chemotherapy, failing to achieve complete remission through first-line chemotherapy or relapsing from complete remission. (26) Standard VIP, TIP[9] and GIP[10] salvage chemotherapy regimen are described in Table 5 according to the EAU guidelines on testicular cancer. (27,77) Sequential high-dose (HD) chemotherapy (HD-carboplatin and HD-etoposide = HD-CE) combined with autologous stem cell support in GCT relapse is an established salvage treatment option. Even as third-line or later therapy, HD-CE can achieve effective long-term survival. (78–80)

Table 5: Standard VIP, TIP and GIP salvage chemotherapy (interval 21 days) (27,77)

Regimen	Drugs	Dosage	Duration of cycles
VIP	Cisplatin	20 mg/m2	Days 1-5
	Etoposide	75-100 mg/m2	Days 1-5
	Ifosfamide	1.2 g/m2	Days 1-5
TIP	Paclitaxel	250 mg/m2	24h continuous infusion day 1
	Ifosfamide	1.5 g/ m2	Days 2-5
	Cisplatin	25 mg/m2	Days 2-5
	Alternative schedule		
	Paclitaxel	175 mg/m2	3-hour infusion day 1
	Ifosfamide	1.2 g/m2	Days 1-5
	Cisplatin	20 mg/m2	Days 1-5
GIP	Gemcitabine	1000 mg/m2	Day 1, 5
	Ifosfamide	1200 mg/m2	Days 1-5
	Cisplatin	20 mg/m2	Days 1-5

1.7.9 Late relapse

[9] Paclitaxel, ifosfamide, cisplatin salvage chemotherapy
[10] Gemcitabine, ifosfamide, cisplatin salvage chemotherapy

Late relapse is defined as relapse occurring 2 years or later after completion of successful first-line treatment including chemotherapy. (81) In comparison to primary metastatic TGCT, late relapses show a reduced chemosensitivity. Due to the insufficient chemotherapy response, surgical resection remains the recommended course of action, aiming at complete resection of the viable tumor mass, if feasible. (82–85) In nonresectable, multisite disease, dose-intense or high-dose chemotherapy should be considered. (86) In general late relapse is more frequent in NSGCT (incidence of 1.4% vs. 3.5% in seminoma vs. non-seminoma patients, respectively). (87) However, the overall cure rate in late relapse is low at around 50%, which emphasizes the importance of adequate first-line therapy. (85)

1.7.10 Follow-up

The objective of follow-up after curative primary care within the subsequent 5 years is early diagnosis of relapse, improvement of recovery and prolongation of the overall survival. (26) Follow-up schemes are based on tumor staging, initial treatment and individual risk factors of relapse. Recommendations suggest minimal follow-up over a cycle of 5 years with routinely monitoring of tumor markers, clinical assessment, chest X-ray, abdominopelvic MRI or CT and thorax CT depending on the individual risk profile. Relapse-free patients after a 5-year follow-up period are further managed according to survivorship care plans, aiming to detect late side-effects of treatment rather than rare late relapse. (88)

1.8 Quality of Life and long-term Toxicity after Cure of TGCT

Testicular cancer is highly curable with a 5-year survival rate of 97% and a 10-year survival rate of more than 95%. (89,90) The success is largely attributed to the introduction of cisplatin-based chemotherapy. (91) In addition to effective treatment regimens, the young average age at diagnosis can extend the life expectancy of TC patients by several decades. Therefore, it became increasingly important to focus on long-term effects of cisplatin-based treatment regimens including, among others, second primary malignancies, cardiovascular diseases, metabolic syndrome, gonadal toxicity, neurotoxicity, nephrotoxicity, pulmonary toxicity, decreased fertility, and psychological disorders. (90–93) Consequently clinical research is required to expand into long-term treatment-associated side effects in TGCT patients. (90)

1.9 Nephrotoxicity of Cisplatin

Nephrotoxic effects following cisplatin administration were reported early on during initial clinical trials. (94) Nephrotoxicity clinically manifests as decreased glomerular filtration rate (GFR), elevated serum creatinine, and reduced serum magnesium and potassium levels. (95,96) Acute nephrotoxicity is a well-recognized adverse effect, experienced by up to one third of GCT patients treated with cisplatin. (97) The cytotoxic agent has been shown to persist in the body of TGCT patients for decades after treatment administration, potentially impacting regular renal function. (98) However longer-term nephrotoxicity is incompletely understood. The existing literature presents conflicting findings, with cross-sectional studies indicating a high proportion of patients with reduced kidney function post-treatment, while a prospective study shows a rebound to mostly normal levels. (99,100)

To comprehend acute and longer-term effects of cisplatin, it is crucial to gain insight into the mode of action of the widely used cytotoxic drug. (90)

1.9.1 Mode of action of cisplatin

Many biological processes within human cells rely on essential metals to ensure proper function. Cisplatin contains metallic-platinum, which is thought to disrupt numerous intracellular signal transduction pathways, ultimately leading to the initiation of apoptosis. Several intracellular mechanisms have been identified contributing to the cytotoxic effects of cisplatin: DNA intercalation, interference in cytoplasmatic organelle function, induction of caspase-dependent and death-receptor mediated apoptosis, formation of oxidative stress via reactive oxygen species (ROS) and induction of inflammation through tumor necrosis factor alpha (TNFα) and other chemokines. (101,102) The exposure of tubular cells to these complex cisplatin-induced cellular and molecular mechanisms leads to a loss of renal function through tubular cell injury or tubular cell death. (103)

1.9.2 DNA interaction of cisplatin

Anti-neoplastic effects of cisplatin are, among others, induced by DNA damage. By entering the cell, cisplatin undergoes complex interactions with cellular components leading to a positively charged electrophile with high affinity to the DNA. (104) DNA cross links are formed, preventing DNA synthesis and replication hence causing cell cycle arrest. (105)

1.9.3 Cytoplasmatic organelle dysfunction

Apart from DNA interaction, cisplatin appears to exert its cytotoxic effects on a cellular level through the endoplasmic reticulum (ER) and mitochondria. After cisplatin application, an upregulation in caspase-12 activity, localized and regulated in the ER, is shown and seems to trigger an ER-specific apoptosis pathway. (106,107) The other cellular target of cisplatin is the mitochondria, where mitochondria-associated apoptosis is induced. (101,108) Mitochondrial density is highest in the proximal tubule cells, which is where cisplatin-induced damage is also frequently found. (101)

1.9.4 Apoptosis

Cisplatin promotes apoptotic (and necrotic) cell death through the interruption of signaling pathways, contributing to tubular cell injury and death. Several apoptotic pathways have been found to be implicated in this cytotoxic process (103): Intrinsic apoptotic pathways through ER or mitochondrial damage (as described in chapter 1.9.3), extrinsic apoptotic pathways through the production of TNFα, apoptosis triggered by p53 (a tumor suppressor protein) and apoptosis triggered by ROS. (101,109,110)

1.9.5 Oxidative stress

Cisplatin treatment increases free reactive oxygen radicals in renal tubular cells, which seems to contribute to its nephrotoxic effects. Three mechanisms have been proposed to play a critical role: Firstly, cisplatin interacts with glutathione, shifting the cellular redox status and leading to an accumulation of ROS. Secondly, cisplatin interferes with the mitochondrial respiratory chain leading to a greater production of ROS. Lastly, cisplatin induces ROS production in the microsomes through the cytochrome P450 system. (103,111)

1.9.6 Inflammation

Cisplatin causes renal intracellular damage, which seems to provoke the release of damage-associated molecular pattern molecules (DAMPS). DAMPS can bind to toll-like receptors (TLR) that cause the release of proinflammatory chemokines and cytokines through the activation of multiple signaling pathways. TLR-mediated local inflammation could impact renal tissue damage. (101,112,113)

1.10 Aim of this Thesis

Cisplatin is a potent antineoplastic agent. (103) It is the mainstay of treatment in TGCT patients, achieving contemporary cure rates exceeding 90% for most. While these excellent tumor-specific treatment outcomes are consistent with cure from TGCT for the vast majority of patients, they have also shifted the focus of TGCT clinical research toward the longer-term side effects of the therapy. (90) Cisplatin can persist in the body for decades, potentially leading to various acute and chronic complications. Acute kidney injury is a well-documented immediate side effect of cisplatin treatment. (90–93,98) However, there is currently insufficient data on the longer-term impact of cisplatin on kidney function in TGCT survivors. (99,100,114) This diploma thesis aims to quantify the longer-term renal function trajectories and the risk of chronic kidney disease in TGCT survivors, with the aim of enhancing the understanding of cisplatin's safety in these patients.

2 Methods

2.1 Study Cohort and Kidney Function Measurements

Our cohort includes all adult (i.e. ≥ 18 years) males with TGCT referred to the Division of Oncology, Medical University of Graz, Austria since December 21st, 1993. Patients are referred to us either as secondary referrals after orchiectomy from urologic facilities in our area, or as primary referrals in case of metastatic disease. As we are the only medical oncology centre in Southern Austria for TGCT our cohort includes the whole TGCT population in this area. After referral and respective treatment (active surveillance, adjuvant therapy, curative therapy), patients undergo structured follow-up including laboratory analyses over a period of at least 10 years. For the present analysis, we use a data cut-off on January 17th, 2022 (n=1,239) and merged the clinical cohort data with the routinely obtained estimated glomerular filtration rate (eGFR) data extracted from our electronic health record system "openMEDOCS" data as described in Supplementary Paragraph 1. Due to the advent of our local electronic health record system in 2003 and consequently unavailable electronic eGFR data capture before this time, patients with histology dates prior January 1st, 2004 were excluded as described in Supplementary Paragraph 2.

2.2 Exposure

To examine the association of platinum exposure with patients' eGFR trajectories, we categorized our study cohort into 4 groups with different baseline dates for the longitudinal analysis: Group #1 ("AS"): patients who never received any platinum-based therapy and were always on active surveillance (baseline date: date of testicular cancer histology); Group #2 ("AdjCBP"): patients who were treated with adjuvant carboplatin AUC7 "single shot" and never relapsed or received any TGCT-specific systemic therapy thereafter (baseline date: day of carboplatin administration); Group #3 ("AdjBEP"): patients who were treated with 1-2 cycles of adjuvant bleomycin/etoposide/cisplatin and never relapsed or received any TGCT-specific systemic therapy thereafter (BEP, baseline date: first day of BEP adminstration); Group #4 ("CurBEP"): patients who were treated with "curative" BEP, i.e. at least 3 cycles BEP or 4 cycles EP and potential further lines of therapy in case of relapse/refractory courses of disease (baseline date: first day of BEP

administration). Consequently, some smaller patient subgroups not relevant to this study's question or with a potential confounding effect on kidney function (e.g. adjuvant or curative radiotherapy) were excluded a priori as described in Supplementary Paragraph 2.

2.3 Outcomes

The co-primary outcomes of the present study are (1) the cumulative incidence of a 30% relative decline in eGFR from baseline eGFR, and (2) the longitudinal annualized absolute change in the eGFR (in ml/min/1.73m²/year). The rationale for selecting a 30% decline in eGFR as a co-primary outcome of this study is that this is an established and recommended outcome for kidney disease trials and an established surrogate outcome for progression of chronic kidney disease. (115,116) The rationale for selecting the second co-primary outcome was that this will provide a more granular representation of the longitudinal change in kidney function in our study population. (117)

2.4 Statistical Methods

All statistical analyses were performed with Stata (Windows version 18, Stata Corp., Houston, TX, USA). Continuous variables were reported as medians [25th-75th percentile] and count data as absolute frequencies (column %). Median follow-up was estimated with the reverse Kaplan-Meier method. Follow-up for the first co-primary outcome analysis was truncated at 10 years after inspection of our data showed a "25% follow-up" of at least 9.8 years. Follow-up for the second co-primary outcome analysis was left unconstrained to the last eGFR measurement 18.6 years after baseline. The first co-primary outcome was analyzed with a competing risk cumulative incidence estimator, treating death-from-any-cause as the competing event of interest, Gray's test, as well as uni- and multivariable Fine & Gray competing risk regression. The second co-primary endpoint was analyzed with a linear mixed model with patient-level random intercepts and random slopes for eGFR. Technical details on the linear mixed model building/selection process are described in Supplementary Paragraph 3. For both outcomes, we pre-specified a multivariable analysis adjusting for age, baseline eGFR, and select comorbidities with a known adverse effect on kidney function and its trajectory (Diabetes mellitus,

heart failure, hypertension, cardiovascular diseases). However, as the analysis demonstrated the prevalence of these comorbidities to be extremely low, we only performed multivariable adjustment for age and baseline eGFR. In sensitivity analysis, a flexible parametric model with time-varying effects of study group was fitted to explore the dynamics of developing a 30% decline in eGFR during follow-up.

3 Results

3.1 Cohort Description and longitudinal Kidney Function Trajectory

We analyzed 777 patients and 16,953 eGFR measurements (Table 6). The median number of eGFR measurements per patient was 19 [25th-75th percentile: 14-25] and ranged from 1 to 290 measurements. The baseline prevalence of comorbidities with an established negative impact on kidney function, such as diabetes mellitus and hypertension, were very low (Table 6). Median follow-up of the cohort was 6.1 years, with 75% and 25% of the cohort being followed-up for at least 3.9 and 9.8 years, respectively. The 1-, 3-, 5-, and 10-year competing risk cumulative incidence estimates of developing a 30% decline in eGFR in the overall cohort were 7% (95%CI: 6-9), 16% (13-19), 20% (17-23), and 23% (20-27), respectively (Supplementary Figure 1). In linear mixed modelling allowing for a non-linear change in the eGFR over time, overall baseline eGFR was 96ml/min/1.73m² and did not materially decline over time (Supplementary Figure 2). Assuming a linear decline in eGFR over time, eGFR declined by 0.6ml/min/1.73m²/year.

3.2 Long-term Kidney Function Trajectory according to Platinum Exposure

Among our cohort of 777 patients, 335 (43%) were always on active surveillance (Group 1 – AS), 83 (11%) received one cycle of adjuvant carboplatin and did not recur thereafter (Group 2 – AdjCBP), 118 (15%) received one or two cycles of adjuvant BEP and did not recur thereafter (Group 3 – AdjBEP), and 241 (31%) received at least three cycles of curative platinum-based chemotherapy for advanced disease (Group 4 -CurBEP). Some small differences in the distribution of baseline variables between these four study groups were observed. For example, Group 3 was slightly younger than the other groups while Group 1 had a slightly lower baseline eGFR (Table 6). The competing risk cumulative 10-year incidence estimates of a 30% decline in eGFR were 18%, 18%, 17%, and 35% in the AS, AdjCBP, AdjBEP, and CurBEP group, respectively (Figure 2). In univariable competing risk regression, the risks of a 30% decline in eGFR did not differ between AS, AdjCBP, and AdjBEP, but were significantly higher in patients in the CurBEP group (Table 7). These results prevailed after the pre-specified multivariable

adjustment for age and baseline eGFR (Table 7), as well as after adjusting for other variables that were significantly associated with GFR decline in univariable analysis (Supplementary Table 1). In flexible parametric modeling, the time-dependent event rates of a 30% decline in eGFR of the 4 groups approached each other after around 4 years of follow-up (Supplementary Figure 3). In exploratory analysis, the cumulative incidences of a 30% decline in eGFR did not significantly differ between patients in “Group 2 - AdjBEP” treated with one or two cycles of platinum-based chemotherapy (Gray’s test p=0.311, Supplementary Figure 4).

In linear mixed modelling of the second co-primary outcome, the annualized absolute average changes in eGFR were -0.1ml/min/1.73m²/year, 0.1ml/min/1.73m²/year, -0.5ml/min/1.73m²/year, and -1.5ml/min/1.73m²/year in the AS, AdjCBP, AdjBEP, and CurBEP groups, respectively (Model #1 in Table 8). Notably, annualized declines did not significantly differ between the AS, AdjCBP, and AdjBEP groups (all p≥0.10), whereas the annualized eGFR decline was significantly higher in the CurBEP group as compared to all other three groups (all p<0.0001). These results prevailed after multivariable adjustment for age and baseline eGFR (Model #2 in Table 8). However, over 10 years of follow-up, these absolute average eGFR changes and their differences between the four platinum exposure groups remained relatively small. (Figure 3Figure 3). We therefore queried our dataset for eGFR measurements <15ml/min/1.73m², which identified 4 patients who had at least once an eGFR measurement below this threshold. Individual analysis of these four patients found no meaningful association of these eGFR measurements with platinum exposure, and a risk of any haemodialysis in our study cohort after platinum exposure of 0% (Table 9).

4 Discussion

In this study, we aimed to quantify the association between platinum exposure and longer-term kidney function changes in patients with TGCT. To achieve this aim, we analyzed a large eGFR dataset from an ongoing single-centre TGCT study with highly granular patient-level data quality and completeness. This allowed us to model eGFR trajectories over time in four clinically relevant subgroups of patients treated (1) without any platinum-based therapy, (2) with single-shot adjuvant carboplatin, (3) with 1-2 cycles of BEP, and (4) with ≥ 3 cycles of BEP. We found that declines in kidney function occurred more often only in the group of TGCT patients exposed to ≥ 3 cycles of BEP (CurBEP). The absolute magnitude of this excess risk when modelling absolute annualized changes in eGFR appeared to be relatively small. The other three groups (AS, AdjCBP, AdjBEP) had similar eGFR decline risks and similarly stable kidney function trajectories. Overall, no patient needed new haemodialysis after the study inclusion date. Collectively, these results do not suggest that clinically significant chronic kidney morbidity is a common problem of TGCT survivors 10 years after treatment.

Our findings are highly consistent with an elegant prospective study by Lauritsen and colleagues, who observed in a population of advanced TGCT receiving standard BEP an association between a higher number of BEP cycles and a higher decline in kidney function. (100) The study by Lauritsen also investigated potential associations of kidney function change with cardiovascular morbidity and death, which was not done in our study, while our study also includes patients with early TGCT not exposed to cisplatin to better delineate the contribution of cisplatin to kidney outcomes. Both the Lauritsen study and our study found that the declines in kidney function attributable to platinum exposure, while statistically significant, are rather small in absolute magnitude.

Importantly, we did not observe a meaningful difference in kidney function decline between patients exposed to single-shot adjuvant carboplatin and those exposed to 1-2 cycles of adjuvant BEP. This supports the hypotheses that (1) the adverse impact of platinum on kidney function appears to manifest itself only at cumulative cisplatin doses higher than 200mg/m², and (2) one cycle of adjuvant BEP appears to be safe in terms of longer-term kidney outcomes.

Of note is that we observed an unadjusted and adjusted association with higher baseline eGFR and a higher risk of a 30% decline in eGFR. This is counterintuitive, but we are confident that this association is spurious and attributable to (1) nearly all patients in our sample having eGFR measurements within the normal or near-normal range, and (2) the known non-linearity between kidney function and eGFR particularly in subjects with normal kidney function.

As with all analyses on retrospective data, issues surrounding patient selection, outcome data collection, informative censoring, and local practice patterns may induce difficult-to-quantify biases and may limit external generalizability. Nonetheless, we believe that our analysis, despite its retrospectivity, is robust against these important limitations as it based on an all-comer population with high prospective retention at the treating centre, with patients undergoing consistent treatment and follow-up as enforced by local institutional policy in accordance with internationally accepted treatment standards. Our previous work on this cohort has yielded results which were highly in line with findings from other cohorts in the field of TGCT outcomes and survivorship research, further supporting the external validity of our population. (118–124) Nonetheless, one major and one minor limitation of our study need to be clearly addressed. First, despite the large sample size, our follow-up duration (25th percentile of follow-up at ~10 years) may be too short to capture incident chronic kidney disease in a TGCT survivor population with relatively uncompromised life expectancy. Our follow-up duration could have been increased by not excluding patients from the early 2000s, but this would have come at the cost of a significantly lower data completeness regarding eGFR measurements originating from an era of “paper charts.” Thus, we have refrained from interpreting our results as “long-term” kidney outcomes, and rather use “10-year” terminology to highlight this major limitation with follow-up duration. Defining truly long-term kidney disease outcomes over a horizon of 30-50 years after TGCT diagnosis thus remains an important goal for future research, with a linkage analysis of kidney disease and TGCT diagnosis codes in large population-based claims registries may be the most optimal design for addressing this question. Second, the presence of CKD in our study population was extremely low and the vast majority of patients had normal baseline eGFR. This leads to the minor limitation that our study does not provide comprehensive data on kidney outcomes and platinum-

exposure in the small patient subset with pre-existing CKD. We would like to refer to the study by Lauritsen and colleagues, who captured a subpopulation of TGCT patients with pre-existing CKD, and provide specific results for this small population. (100)

5 Conclusion

Our data are consistent with the concept that only TGCT patients treated with a cumulative dose of ≥3 cycles of cisplatin experienced a higher risk of longer-term kidney function decline over a 10-year horizon. However the absolute magnitude of this risk appears to be rather small.

6 References

1. Park JS, Kim J, Elghiaty A, Ham WS. Recent global trends in testicular cancer incidence and mortality. Medicine. September 2018;97(37):e12390.

2. Ghazarian AA, Kelly SP, Altekruse SF, Philip SR, Mcglynn KA. Future of testicular germ cell tumor incidence in the United States: Forecast through 2026. Cancer [Internet]. September 2017;123(12). Verfügbar unter: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b58g008c.han.medunigraz.at/28241106/?dopt=Abstract

3. Trabert B, Chen J, Devesa S, Bray F, McGlynn K. International patterns and trends in testicular cancer incidence, overall and by histologic subtype, 1973-2007. Andrology [Internet]. Januar 2015;3(1). Verfügbar unter: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b58g008c.han.medunigraz.at/25331326/?dopt=Abstract

4. Huyghe E, Matsuda T, Thonneau P. Increasing Incidence of Testicular Cancer Worldwide: A Review. Journal of Urology. Juli 2003;170(1):5–11.

5. Vasdev N, Moon A, Thorpe AC. Classification, epidemiology and therapies for testicular germ cell tumours. Int J Dev Biol. 2013;57(2–4):133–9.

6. Looijenga LHJ, Van der Kwast TH, Grignon D, Egevad L, Kristiansen G, Kao CS, u. a. Report From the International Society of Urological Pathology (ISUP) Consultation Conference on Molecular Pathology of Urogenital Cancers. American Journal of Surgical Pathology. Juli 2020;44(7):e66–79.

7. Oosterhuis JW, Looijenga LHJ. Testicular germ-cell tumours in a broader perspective. Nat Rev Cancer. März 2005;5(3):210–22.

8. Batool A, Karimi N, Wu XN, Chen SR, Liu YX. Testicular germ cell tumor: a comprehensive review. Cell Mol Life Sci. September 2019;76(9):1713–27.

9. Chen SR, Zheng QS, Zhang Y, Gao F, Liu YX. Disruption of genital ridge development causes aberrant primordial germ cell proliferation but does not affect their directional migration. BMC Biol. 5. Dezember 2013;11(1):22.

10. Manku G, Culty M. Mammalian gonocyte and spermatogonia differentiation: recent advances and remaining challenges. REPRODUCTION. März 2015;149(3):R139–57.

11. Skakkebaek NE, Berthelsen JG, Giwercman A, Muller J. Carcinoma-in-situ of the testis: possible origin from gonocytes and precursor of all types of germ cell tumours except spermatocytoma. Int J Androl. 28. Februar 1987;10(1):19–28.

12. Kristensen DG, Nielsen JE, Jørgensen A, Skakkebæk NE, Meyts ERD, Almstrup K. Evidence that active demethylation mechanisms maintain the genome of carcinoma in situ cells hypomethylated in the adult testis. Br J Cancer. September 2014;110(3):668–78.

13. Vizio D Di, Cito L, Boccia A, Chieffi P, Insabato L, Pettinato G, u. a. Loss of the tumor suppressor gene PTEN marks the transition from intratubular germ cell neoplasias (ITGCN) to invasive germ cell tumors. Oncogene. September 2005;24(11):1882–94.

14. Datta MW, Macri E, Signoretti S, Renshaw AA, Loda M. Transition from in situ to invasive testicular germ cell neoplasia is associated with the loss of p21 and gain of mdm-2 expression. Mod Pathol. September 2001;14(5):437–42.

15. Ottesen AM, Skakkebaek NE, Lundsteen C, Leffers H, Larsen J, Meyts ERD. High-resolution comparative genomic hybridization detects extra chromosome arm 12p material in most cases of carcinoma in situ adjacent to overt germ cell tumors, but not before the invasive tumor development. Genes Chromosomes Cancer. September 2003;38(2):117–25.

16. Jørgensen N, Meyts ER, Main KM, Skakkebæk NE. Testicular dysgenesis syndrome comprises some but not all cases of hypospadias and impaired spermatogenesis. Int J Androl. 14. April 2010;33(2):298–303.

17. Del Giudice F, Kasman AM, De Berardinis E, Busetto GM, Belladelli F, Eisenberg ML. Association between male infertility and male-specific malignancies: systematic review and meta-analysis of population-based retrospective cohort studies. Fertil Steril. November 2020;114(5):984–96.

18. Lip SZL, Murchison LED, Cullis PS, Govan L, Carachi R. A meta-analysis of the risk of boys with isolated cryptorchidism developing testicular cancer in later life. Arch Dis Child. Januar 2013;98(1):20–6.

19. Slowikowska-Hilczer J, Szarras-Czapnik M, Duranteau L, Rapp M, Walczak-Jedrzejowska R, Marchlewska K, u. a. Risk of gonadal neoplasia in patients with disorders/differences of sex development. Cancer Epidemiol. Dezember 2020;69:101800.

20. Peng X, Zeng X, Peng S, Deng D, Zhang J. The Association Risk of Male Subfertility and Testicular Cancer: A Systematic Review. PLoS One. 18. Mai 2009;4(5):e5591.

21. Kharazmi E, Hemminki K, Pukkala E, Sundquist K, Tryggvadottir L, Tretli S, u. a. Cancer Risk in Relatives of Testicular Cancer Patients by Histology Type and Age at Diagnosis: A Joint Study from Five Nordic Countries. Eur Urol. August 2015;68(2):283–9.

22. Holzik MFL, Rapley E, Hoekstra H, Sleijfer D, Nolte I, Sijmons R. Genetic predisposition to testicular germ-cell tumours. Lancet Oncol. Juni 2004;5(6):363–71.

23. Greene MH, Kratz CP, Mai PL, Mueller C, Peters JA, Bratslavsky G, u. a. Familial testicular germ cell tumors in adults: 2010 summary of genetic risk factors and clinical phenotype. Endocr Relat Cancer. Juni 2010;17(2):R109–21.

24. Schaapveld M, van den Belt-Dusebout AW, Gietema JA, de Wit R, Horenblas S, Witjes JA, u. a. Risk and prognostic significance of metachronous contralateral testicular germ cell tumours. Br J Cancer. 11. Oktober 2012;107(9):1637–43.

25. Pluta J, Pyle LC, Nead KT, Wilf R, Li M, Mitra N, u. a. Identification of 22 susceptibility loci associated with testicular germ cell tumors. Nat Commun. 23. Juli 2021;12(1):4487.

26. Lorch A, Albers P, Beyer J, Cathomas R, Oing C, Souchon R, u. a. Keimzelltumoren des Mannes [Internet]. 2020 [zitiert 12. September 2023]. Verfügbar unter:

https://www.onkopedia.com/de/onkopedia/guidelines/keimzelltumoren-des-mannes/@@guideline/html/index.html

27. Nicol. D., Berney D, Boormans JL, Di Nardo D, Frankhauser CD, Fischer S, u. a. EAU Guidelines on Testicular Cancer. 2023.

28. Mead GM, Stenning SP. The International Germ Cell Consensus Classification: a new prognostic factor-based staging classification for metastatic germ cell tumours. Clin Oncol (R Coll Radiol). 1997;9(4):207–9.

29. Barlow LJ, Badalato GM, McKiernan JM. Serum tumor markers in the evaluation of male germ cell tumors. Nat Rev Urol. September 2010;7(11):610–7.

30. Dieckmann KP, Simonsen-Richter H, Kulejewski M, Anheuser P, Zecha H, Isbarn H, u. a. Serum Tumour Markers in Testicular Germ Cell Tumours: Frequencies of Elevated Levels and Extents of Marker Elevation Are Significantly Associated with Clinical Parameters and with Response to Treatment. Biomed Res Int. 2019;2019:5030349.

31. Shaw J. Diagnosis and treatment of testicular cancer. Am Fam Physician. September 2008;77(4):469–74.

32. Tsili AC, Argyropoulou MI, Dolciami M, Ercolani G, Catalano C, Manganaro L. When to ask for an MRI of the scrotum. Andrology. September 2021;9(5):1395–409.

33. Huddart RA, O'Doherty MJ, Padhani A, Rustin GJS, Mead GM, Joffe JK, u. a. 18fluorodeoxyglucose positron emission tomography in the prediction of relapse in patients with high-risk, clinical stage I nonseminomatous germ cell tumors: preliminary report of MRC Trial TE22–the NCRI Testis Tumour Clinical Study Group. J Clin Oncol. September 2007;25(21):3090–5.

34. Oechsle K, Hartmann M, Brenner W, Venz S, Weissbach L, Franzius C, u. a. [18F]Fluorodeoxyglucose positron emission tomography in nonseminomatous germ cell tumors after chemotherapy: the German multicenter positron emission tomography study group. J Clin Oncol. September 2008;26(36):5930–5.

35. Petersen PM, Skakkebaek NE, Rørth M, Giwercman A. Semen quality and reproductive hormones before and after orchiectomy in men with testicular cancer. J Urol. September 1999;161(3):822–6.

36. Brydøy M, Fosså SD, Klepp O, Bremnes RM, Wist EA, Wentzel-Larsen T, u. a. Paternity and testicular function among testicular cancer survivors treated with two to four cycles of cisplatin-based chemotherapy. Eur Urol. September 2010;58(1):134–40.

37. Brydøy M, Fosså SD, Klepp O, Bremnes RM, Wist EA, Bjøro T, u. a. Sperm counts and endocrinological markers of spermatogenesis in long-term survivors of testicular cancer. Br J Cancer. September 2012;107(11):1833–9.

38. Leão R, Albersen M, Looijenga LHJ, Tandstad T, Kollmannsberger C, Murray MJ, u. a. Circulating MicroRNAs, the Next-Generation Serum Biomarkers in Testicular Germ Cell Tumours: A Systematic Review. Eur Urol. September 2021;80(4):456–66.

39. Belge G, Grobelny F, Radtke A, Bodes J, Matthies C, Wülfing C, u. a. Serum levels of microRNA-371a-3p are not elevated in testicular tumours of non-germ cell origin. J Cancer Res Clin Oncol. September 2021;147(2):435–43.

40. Lobo J, Leão R, Gillis AJM, van den Berg A, Anson-Cartwright L, Atenafu EG, u. a. Utility of Serum miR-371a-3p in Predicting Relapse on Surveillance in Patients with Clinical Stage I Testicular Germ Cell Cancer. Eur Urol Oncol. September 2021;4(3):483–91.

41. Brierley JD, Gospodarowicz MK, Wittekind C. TNM Classification of Malignant Tumours [Internet]. 8th Edition. Brierley JD, Gospodarowicz MK, Wittekind C, Herausgeber. Wiley-Blackwell; 2016. Verfügbar unter: https://www.wiley.com/en-gb/TNM+Classification+of+Malignant+Tumours%2C+8th+Edition-p-9781119263579

42. Gillessen S, Sauvé N, Collette L, Daugaard G, de Wit R, Albany C, u. a. Predicting Outcomes in Men With Metastatic Nonseminomatous Germ Cell Tumors (NSGCT): Results From the IGCCCG Update Consortium. J Clin Oncol. September 2021;39(14):1563–74.

43. Warde P, Specht L, Horwich A, Oliver T, Panzarella T, Gospodarowicz M, u. a. Prognostic factors for relapse in stage I seminoma managed by surveillance: A pooled analysis. Journal of Clinical Oncology. 15. November 2002;20(22):4448–52.

44. Aparicio J, Germà JR, Del Muro XG, Maroto P, Arranz JA, Sáenz A, u. a. Risk-adapted management for patients with clinical stage I seminoma: the Second Spanish Germ Cell Cancer Cooperative Group study. J Clin Oncol [Internet]. 2005 [zitiert 13. September 2023];23(34):8717–23. Verfügbar unter: https://pubmed.ncbi.nlm.nih.gov/16260698/

45. Boormans JL, Mayor de Castro J, Marconi L, Yuan Y, Laguna Pes MP, Bokemeyer C, u. a. Testicular Tumour Size and Rete Testis Invasion as Prognostic Factors for the Risk of Relapse of Clinical Stage I Seminoma Testis Patients Under Surveillance: a Systematic Review by the Testicular Cancer Guidelines Panel. Eur Urol. 1. März 2018;73(3):394–405.

46. Zengerling F, Kunath F, Jensen K, Ruf C, Schmidt S, Spek A. Prognostic factors for tumor recurrence in patients with clinical stage I seminoma undergoing surveillance—A systematic review. Urologic Oncology: Seminars and Original Investigations. 1. Oktober 2018;36(10):448–58.

47. Albers P, Siener R, Kliesch S, Weissbach L, Krege S, Sparwasser C, u. a. Risk factors for relapse in clinical stage I nonseminomatous testicular germ cell tumors: Results of the German Testicular Cancer Study Group Trial. Journal of Clinical Oncology. 15. April 2003;21(8):1505–12.

48. Blok JM, Pluim I, Daugaard G, Wagner T, Jóźwiak K, Wilthagen EA, u. a. Lymphovascular invasion and presence of embryonal carcinoma as risk factors for occult metastatic disease in clinical stage I nonseminomatous germ cell tumour: a systematic review and meta-analysis. BJU Int [Internet]. 1. März 2020 [zitiert 14. September 2023];125(3):355–68. Verfügbar unter: https://onlinelibrary.wiley.com/doi/full/10.1111/bju.14967

49. Beyer J, Albers P, Altena R, Aparicio J, Bokemeyer C, Busch J, u. a. Maintaining success, reducing treatment burden, focusing on survivorship: highlights from the third European consensus conference on diagnosis and

treatment of germ-cell cancer. Annals of Oncology [Internet]. 1. April 2013 [zitiert 15. September 2023];24(4):878–88. Verfügbar unter: http://www.annalsofoncology.org/article/S0923753419371935/fulltext

50. Tandstad T, Ståhl O, Dahl O, Haugnes HS, Håkansson U, Karlsdottir A, u. a. Treatment of stage I seminoma, with one course of adjuvant carboplatin or surveillance, risk-adapted recommendations implementing patient autonomy: A report from the Swedish and Norwegian Testicular Cancer Group (SWENOTECA). Annals of Oncology [Internet]. 1. Juli 2016 [zitiert 18. September 2023];27(7):1299–304. Verfügbar unter: http://www.annalsofoncology.org/article/S0923753419356923/fulltext

51. Groll RJ, Warde P, Jewett MAS. A comprehensive systematic review of testicular germ cell tumor surveillance. Crit Rev Oncol Hematol. 1. Dezember 2007;64(3):182–97.

52. Chung P, Mayhew LA, Warde P, Winquist E, Lukka H, Genitourinary Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Management of stage I seminomatous testicular cancer: a systematic review. Clin Oncol (R Coll Radiol). Februar 2010;22(1):6–16.

53. Kollmannsberger C, Tandstad T, Bedard PL, Cohn-Cedermark G, Chung PW, Jewett MA, u. a. Patterns of relapse in patients with clinical stage I testicular cancer managed with active surveillance. Journal of Clinical Oncology. 1. Januar 2015;33(1):51–7.

54. Kollmannsberger C, Moore C, Chi KN, Murray N, Daneshmand S, Gleave M, u. a. Non-risk-adapted surveillance for patients with stage I nonseminomatous testicular germ-cell tumors: diminishing treatment-related morbidity while maintaining efficacy. Ann Oncol. Juni 2010;21(6):1296–301.

55. Tandstad T, Dahl O, Cohn-Cedermark G, Cavallin-Stahl E, Stierner U, Solberg A, u. a. Risk-adapted treatment in clinical stage I nonseminomatous germ cell testicular cancer: The SWENOTECA management program. Journal of Clinical Oncology. 1. Mai 2009;27(13):2122–8.

56. Tandstad T, Ståhl O, Håkansson U, Dahl O, Haugnes HS, Klepp OH, u. a. One course of adjuvant BEP in clinical stage I nonseminoma mature and

expanded results from the SWENOTECA group. Annals of Oncology. 2014;25:2167–72.

57. Aparicio J, Sánchez-Muñoz A, Ochenduszko S, Gumà J, Fernández-Aramburo A, García del Muro X, u. a. Treatment and Outcome of Patients with Stage IS Testicular Cancer: A Retrospective Study from the Spanish Germ Cell Cancer Group. J Urol [Internet]. 1. Oktober 2019 [zitiert 19. September 2023];202(4):742–7. Verfügbar unter: https://www.auajournals.org/doi/10.1097/JU.0000000000000366

58. Heinzelbecker J, Schmidt S, Lackner J, Busch J, Bokemeyer C, Classen J, u. a. Therapy of clinical stage IIA and IIB seminoma: a systematic review. World J Urol. 15. November 2021;40(12):2829–41.

59. Chung PWM, Gospodarowicz MK, Panzarella T, Jewett MAS, Sturgeon JFG, Tew-George B, u. a. Stage II testicular seminoma: patterns of recurrence and outcome of treatment. Eur Urol. Juni 2004;45(6):754–9; discussion 759-60.

60. Classen J, Schmidberger H, Meisner C, Souchon R, Sautter-Bihl ML, Sauer R, u. a. Radiotherapy for stages IIA/B testicular seminoma: Final report of a prospective multicenter clinical trial. Journal of Clinical Oncology. 15. März 2003;21(6):1101–6.

61. Giannatempo P, Greco T, Mariani L, Nicolai N, Tana S, Farè E, u. a. Radiotherapy or chemotherapy for clinical stage IIA and IIB seminoma: A systematic review and meta-analysis of patient outcomes. Annals of Oncology [Internet]. 1. April 2015 [zitiert 19. September 2023];26(4):657–68. Verfügbar unter: http://www.annalsofoncology.org/article/S0923753419314413/fulltext

62. Culine S, Kerbrat P, Kramar A, Théodore C, Chevreau C, Geoffrois L, u. a. Refining the optimal chemotherapy regimen for good-risk metastatic nonseminomatous germ-cell tumors: a randomized trial of the Genito-Urinary Group of the French Federation of Cancer Centers (GETUG T93BP). Annals of Oncology. Mai 2007;18(5):917–24.

63. Nicolai N, Nazzani S, Tesone A, Macchi A, Piva L, Salvioni R, u. a. Retroperitoneal lymph-node dissection (RPLND) as upfront management in

stage II germ-cell tumours: Evaluation of safety and efficacy. Tumori Journal. 1. August 2023;109(4):379–86.

64. Hamilton RJ, Nayan M, Anson-Cartwright L, Atenafu EG, Bedard PL, Hansen A, u. a. Treatment of relapse of clinical stage i nonseminomatous germ cell tumors on surveillance. Journal of Clinical Oncology. 1. August 2019;37(22):1919–26.

65. McHugh DJ, Funt SA, Silber D, Knezevic A, Patil S, O'Donnell D, u. a. Adjuvant chemotherapy with etoposide plus cisplatin for patients with pathologic stage II nonseminomatous germ cell tumors. Journal of Clinical Oncology. 20. April 2020;38(12):1332–7.

66. Neuenschwander A, Lonati C, Antonelli L, Papachristofilou A, Cathomas R, Rothermundt C, u. a. Treatment Outcomes for Men with Clinical Stage II Nonseminomatous Germ Cell Tumours Treated with Primary Retroperitoneal Lymph Node Dissection: A Systematic Review. Eur Urol Focus. Mai 2023;9(3):541–6.

67. de Wit R, Stoter G, Kaye SB, Sleijfer DT, Jones WG, ten Bokkel Huinink WW, u. a. Importance of bleomycin in combination chemotherapy for good-prognosis testicular nonseminoma: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group. Journal of Clinical Oncology. Mai 1997;15(5):1837–43.

68. Bokemeyer C, Kollmannsberger C, Stenning S, Hartmann JT, Horwich A, Clemm C, u. a. Metastatic seminoma treated with either single agent carboplatin or cisplatin-based combination chemotherapy: a pooled analysis of two randomised trials. Br J Cancer. 13. August 2004;91(4):683–7.

69. de Wit R, Stoter G, Sleijfer Dt, Neijt J, ten Bokkel Huinink W, de Prijck L, u. a. Four cycles of BEP vs four cycles of VIP in patients with intermediate-prognosis metastatic testicular non-seminoma: a randomized study of the EORTC Genitourinary Tract Cancer Cooperative Group. Br J Cancer. September 1998;78(6):828–32.

70. Nichols CR, Catalano PJ, Crawford ED, Vogelzang NJ, Einhorn LH, Loehrer PJ. Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. Journal of Clinical Oncology. April 1998;16(4):1287–93.

71. Daugaard G, Skoneczna I, Aass N, De Wit R, De Santis M, Dumez H, u. a. A randomized phase III study comparing standard dose BEP with sequential high-dose cisplatin, etoposide, and ifosfamide (VIP) plus stem-cell support in males with poor-prognosis germ-cell cancer. An intergroup study of EORTC, GTCSG, and Grupo Germinal (EORTC 30974). Annals of Oncology. Mai 2011;22(5):1054–61.

72. Motzer RJ, Nichols CJ, Margolin KA, Bacik J, Richardson PG, Vogelzang NJ, u. a. Phase III Randomized Trial of Conventional-Dose Chemotherapy With or Without High-Dose Chemotherapy and Autologous Hematopoietic Stem-Cell Rescue As First-Line Treatment for Patients With Poor-Prognosis Metastatic Germ Cell Tumors. Journal of Clinical Oncology. 20. Januar 2007;25(3):247–56.

73. Fizazi K, Pagliaro L, Laplanche A, Fléchon A, Mardiak J, Geoffrois L, u. a. Personalised chemotherapy based on tumour marker decline in poor prognosis germ-cell tumours (GETUG 13): A phase 3, multicentre, randomised trial. Lancet Oncol [Internet]. 1. Dezember 2014 [zitiert 20. September 2023];15(13):1442–50. Verfügbar unter: http://www.thelancet.com/article/S1470204514704905/fulltext

74. De Santis M, Bokemeyer C, Becherer A, Stoiber F, Oechsle K, Kletter K, u. a. Predictive Impact of 2- ^{18} Fluoro-2-Deoxy- <scp>d</scp> -Glucose Positron Emission Tomography for Residual Postchemotherapy Masses in Patients With Bulky Seminoma. Journal of Clinical Oncology. 1. September 2001;19(17):3740–4.

75. Hendry WF, Norman AR, Dearnaley DP, Fisher C, Nicholls J, Huddart RA, u. a. Metastatic nonseminomatous germ cell tumors of the testis. Cancer. 15. März 2002;94(6):1668–76.

76. Sheinfeld J. The role of adjunctive postchemotherapy surgery for nonseminomatous germ-cell tumors: Current concepts and controversies. Semin Urol Oncol. November 2002;20(4):asuro0200262.

77. Mead GM, Cullen MH, Huddart R, Harper P, Rustin GJS, Cook PA, u. a. A phase II trial of TIP (paclitaxel, ifosfamide and cisplatin) given as second-line (post-BEP) salvage chemotherapy for patients with metastatic germ cell cancer: a medical research council trial. Br J Cancer. 5. Juli 2005;93(2):178–84.

78. Einhorn LH, Williams SD, Chamness A, Brames MJ, Perkins SM, Abonour R. High-Dose Chemotherapy and Stem-Cell Rescue for Metastatic Germ-Cell Tumors. New England Journal of Medicine. 26. Juli 2007;357(4):340–8.

79. Feldman DR, Sheinfeld J, Bajorin DF, Fischer P, Turkula S, Ishill N, u. a. TI-CE High-Dose Chemotherapy for Patients With Previously Treated Germ Cell Tumors: Results and Prognostic Factor Analysis. Journal of Clinical Oncology. 1. April 2010;28(10):1706–13.

80. Lorch A, Kleinhans A, Kramar A, Kollmannsberger CK, Hartmann JT, Bokemeyer C, u. a. Sequential Versus Single High-Dose Chemotherapy in Patients With Relapsed or Refractory Germ Cell Tumors: Long-Term Results of a Prospective Randomized Trial. Journal of Clinical Oncology. 10. März 2012;30(8):800–5.

81. Beyer J, Albers P, Altena R, Aparicio J, Bokemeyer C, Busch J, u. a. Maintaining success, reducing treatment burden, focusing on survivorship: highlights from the third European consensus conference on diagnosis and treatment of germ-cell cancer. Annals of Oncology. April 2013;24(4):878–88.

82. Che Y, Lusch A, Winter C, Große Siemer R, Buddensieck C, Albers P, u. a. Late relapsing germ cell tumors with elevated tumor markers. World J Urol. 13. Februar 2022;40(2):363–71.

83. Moore JA, Slack RS, Lehner MJ, Campbell MT, Shah AY, Zhang M, u. a. Very Late Recurrence in Germ Cell Tumor of the Testis: Lessons and Implications. Cancers (Basel). 23. Februar 2022;14(5):1127.

84. Richardson NH, Althouse SK, Ashkar R, Cary C, Masterson T, Foster RS, u. a. Late Relapse of Germ Cell Tumors After Prior Chemotherapy or Surgery-only. Clin Genitourin Cancer. August 2023;21(4):467–74.

85. Lipphardt ME, Albers P. Late relapse of testicular cancer. World J Urol. 1. April 2004;22(1):47–54.

86. Alifrangis C, Lucas O, Benafif S, Ansell W, Greenwood M, Smith S, u. a. Management of Late Relapses After Chemotherapy in Testicular Cancer: Optimal Outcomes with Dose-intense Salvage Chemotherapy and Surgery. Eur Urol Focus. Juli 2021;7(4):835–42.

87. Oldenburg J, Martin JM, Fosså SD. Late Relapses of Germ Cell Malignancies: Incidence, Management, and Prognosis. Journal of Clinical Oncology. 10. Dezember 2006;24(35):5503–11.

88. Honecker F, Aparicio J, Berney D, Beyer J, Bokemeyer C, Cathomas R, u. a. ESMO Consensus Conference on testicular germ cell cancer: diagnosis, treatment and follow-up. Annals of Oncology. August 2018;29(8):1658–86.

89. Verdecchia A, Francisci S, Brenner H, Gatta G, Micheli A, Mangone L, u. a. Recent cancer survival in Europe: a 2000–02 period analysis of EUROCARE-4 data. Lancet Oncol. September 2007;8(9):784–96.

90. Travis LB, Beard C, Allan JM, Dahl AA, Feldman DR, Oldenburg J, u. a. Testicular Cancer Survivorship: Research Strategies and Recommendations. JNCI Journal of the National Cancer Institute. 4. August 2010;102(15):1114–30.

91. Gospodarowicz M. Testicular Cancer Patients: Considerations in Long-Term Follow-Up. Hematol Oncol Clin North Am. April 2008;22(2):245–55.

92. van den Belt-Dusebout AW, de Wit R, Gietema JA, Horenblas S, Louwman MWJ, Ribot JG, u. a. Treatment-Specific Risks of Second Malignancies and Cardiovascular Disease in 5-Year Survivors of Testicular Cancer. Journal of Clinical Oncology. 1. Oktober 2007;25(28):4370–8.

93. Terbuch A, Posch F, Annerer LM, Bauernhofer T, Pichler M, Szkandera J, u. a. Long-term cardiovascular complications in stage I seminoma patients. Clinical and Translational Oncology. 29. November 2017;19(11):1400–8.

94. Hill JM, Speer RJ. Organo-platinum complexes as antitumor agents (review). Anticancer Res. 1982;2(3):173–86.

95. Gonzales-Vitale JC, Hayes DM, Cvitkovic E, Sternberg SS. The renal pathology in clinical trials of cis-platinum (II) diamminedichloride. Cancer. April 1977;39(4):1362–71.

96. Gomez Campdera FJ, Gonzalez P, Carrillo A, Estelles MC, Rengel M. Cisplatin nephrotoxicity: symptomatic hypomagnesemia and renal failure. Int J Pediatr Nephrol. 1986;7(3):151–2.

97. Beyer J, Rick O, Weinknecht S, Kingreen D, Lenz K, Siegert W. Nephrotoxicity after high-dose carboplatin, etoposide and ifosfamide in germ-cell tumors: incidence and implications for hematologic recovery and clinical outcome. Bone Marrow Transplant. 1. November 1997;20(10):813–9.

98. Gietema J, Meinardi M, Messerschmidt J, Gelevert T, Alt F, Uges D, u. a. Circulating plasma platinum more than 10 years after cisplatin treatment for testicular cancer. The Lancet. März 2000;355(9209):1075–6.

99. Fosså SD, Aass N, Winderen M, Börmer OP, Olsen DR. Long-term renal function after treatment for malignant germ-cell tumours. Annals of Oncology. Februar 2002;13(2):222–8.

100. Lauritsen J, Mortensen MS, Kier MGG, Christensen IJ, Agerbaek M, Gupta R, u. a. Renal impairment and late toxicity in germ-cell cancer survivors. Ann Oncol. Januar 2015;26(1):173–8.

101. Manohar S, Leung N. Cisplatin nephrotoxicity: a review of the literature. J Nephrol. 5. Februar 2018;31(1):15–25.

102. Florea AM, Büsselberg D. Cisplatin as an Anti-Tumor Drug: Cellular Mechanisms of Activity, Drug Resistance and Induced Side Effects. Cancers (Basel). 15. März 2011;3(1):1351–71.

103. Pabla N, Dong Z. Cisplatin nephrotoxicity: Mechanisms and renoprotective strategies. Kidney Int. Mai 2008;73(9):994–1007.

104. Wang D, Lippard SJ. Cellular processing of platinum anticancer drugs. Nat Rev Drug Discov. 24. April 2005;4(4):307–20.

105. Jamieson ER, Lippard SJ. Structure, Recognition, and Processing of Cisplatin−DNA Adducts. Chem Rev. 8. September 1999;99(9):2467–98.

106. Mandic A, Hansson J, Linder S, Shoshan MC. Cisplatin Induces Endoplasmic Reticulum Stress and Nucleus-independent Apoptotic Signaling. Journal of Biological Chemistry. März 2003;278(11):9100–6.

107. Nakagawa T, Zhu H, Morishima N, Li E, Xu J, Yankner BA, u. a. Caspase-12 mediates endoplasmic-reticulum-specific apoptosis and cytotoxicity by amyloid-β. Nature. Januar 2000;403(6765):98–103.

108. Hirama M, Isonishi S, Yasuda M, Ishikawa H. Characterization of mitochondria in cisplatin-resistant human ovarian carcinoma cells. Oncol Rep. November 2006;16(5):997–1002.

109. Manfredi JJ. p53 and Apoptosis: It's Not Just in the Nucleus Anymore. Mol Cell. März 2003;11(3):552–4.

110. Wei Q, Dong G, Yang T, Megyesi J, Price PM, Dong Z. Activation and involvement of p53 in cisplatin-induced nephrotoxicity. American Journal of Physiology-Renal Physiology. Oktober 2007;293(4):F1282–91.

111. Chirino YI, Pedraza-Chaverri J. Role of oxidative and nitrosative stress in cisplatin-induced nephrotoxicity. Experimental and Toxicologic Pathology. Mai 2009;61(3):223–42.

112. Gluba A, Banach M, Hannam S, Mikhailidis DP, Sakowicz A, Rysz J. The role of Toll-like receptors in renal diseases. Nat Rev Nephrol. 23. April 2010;6(4):224–35.

113. Kono H, Rock KL. How dying cells alert the immune system to danger. Nat Rev Immunol. 14. April 2008;8(4):279–89.

114. Brilleta G, Demya G, Jacquiauda C, Mignotb L, Bunkera D, Meilletc D, u. a. Long-Term Renal Effect of Cisplatin in Man. Am J Nephrol. 1994;14(2):81–4.

115. Levey AS, Inker LA, Matsushita K, Greene T, Willis K, Lewis E, u. a. GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. Am J Kidney Dis. Dezember 2014;64(6):821–35.

116. Coresh J, Turin TC, Matsushita K, Sang Y, Ballew SH, Appel LJ, u. a. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA. 25. Juni 2014;311(24):2518–31.

117. Posch F, Ay C, Stöger H, Kreutz R, Beyer-Westendorf J. Exposure to vitamin k antagonists and kidney function decline in patients with atrial fibrillation and chronic kidney disease. Res Pract Thromb Haemost. April 2019;3(2):207–16.

118. Terbuch A, Posch F, Annerer LM, Bauernhofer T, Pichler M, Szkandera J, u. a. Long-term cardiovascular complications in stage I seminoma patients. Clin Transl Oncol. November 2017;19(11):1400–8.

119. Klöckl MC, Kasparek AK, Riedl JM, Moik F, Mollnar S, Stotz M, u. a. Estimation versus measurement of the glomerular filtration rate for kidney function assessment in patients with cancer undergoing cisplatin-based chemotherapy. Sci Rep. 8. Juli 2020;10(1):11219.

120. Terbuch A, Posch F, Bauernhofer T, Jost PJ, Partl R, Stranzl-Lawatsch H, u. a. Patterns of Disease Progression and Outcome of Patients With Testicular Seminoma Who Relapse After Adjuvant or Curative Radiation Therapy. Int J Radiat Oncol Biol Phys. 15. Juli 2022;113(4):825–32.

121. Terbuch A, Posch F, Bauernhofer T, Pichler M, Peinsith H, Szkandera J, u. a. Age as a Predictor of Treatment Outcome in Metastatic Testicular Germ Cell Tumors. Anticancer Res. Oktober 2019;39(10):5589–96.

122. Terbuch A, Posch F, Partl R, Zurl B, Bauernhofer T, Pichler M, u. a. Risk stratification for febrile neutropenia in patients with testicular germ cell tumors. Cancer Med. Februar 2018;7(2):508–14.

123. Terbuch A, Walser G, Stotz M, Gerger A, Posch F, Bauernhofer T. Primary Thromboprophylaxis and the Risk of Venous Thromboembolic Events in Patients With Testicular Germ Cell Tumors Treated With Cisplatinum-Based Chemotherapy. Clin Genitourin Cancer. Februar 2023;21(1):24–31.

124. Bezan A, Posch F, Ploner F, Bauernhofer T, Pichler M, Szkandera J, u. a. Risk stratification for venous thromboembolism in patients with testicular germ cell tumors. PLoS One. 2017;12(4):e0176283.

125. Berney DM, Looijenga LHJ, Idrees M, Oosterhuis JW, Meyts ERD, Ulbright TM, u. a. Germ cell neoplasia in situ (GCNIS): evolution of the current nomenclature for testicular pre-invasive germ cell malignancy. Histopathology. September 2016;69(1):7–10.

126. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, u. a. AJCC Cancer Staging Manual. 8. Aufl. Springer Cham; 2017. 727 S.

The following tool was used for the sole purpose of optimization of language and phrasing in accordance with the applicable standards for good scientific practice of the Medical University of Graz:

- Name and version of the tool: ChatGPT (GPT-4)
- Provider: OpenAI
- Date of content generation: September 2024
- Address: https://chat.openai.com

7 Tables

Table 6: Baseline characteristics of the study cohort – Distribution overall and by treatment group (n=777)

Variable	n (% miss.)*	Overall (n=777)	Group 1 – AS (n=335)	Group 2 – AdjCBP (n=83)	Group 3 – AdjBEP (n=118)	Group 4 – CurBEP (n=241)	p**
Demographic characteristics							
Age (years)	777 (0%)	37 [29-45]	38 [31-47]	38 [32-48]	32 [28-38]	37 [28-44]	0.0001
BMI (kg/m²)	664 (15%)	25 [23-28]	25 [23-28]	25 [23-28]	25 [23-27]	25 [23-28]	0.865
Smoker or Ex-Smoker	516 (34%)	282 (55%)	100 (47%)	33 (65%)	60 (72%)	89 (53%)	<0.0001
Karnofsky Index <100%	630 (19%)	64 (10%)	19 (7%)	6 (9%)	4 (4%)	35 (18%)	<0.0001
Clinical variables							
Non-Seminomatous histology	768 (1%)ǂ	350 (46%)	90 (27%)	1 (1%)ǂǂ	117 (99%)ǂǂ	142 (60%)	<0.0001
Initial clinical stage IS-IIIC	777 (0%)	192 (25%)	0 (0%)	0 (0%)	0 (0%)	195 (81%)	<0.0001
IGCCCG risk stratification***	194 (<1%)	/	/	/	/	/	N/A
---Good risk	N/A	N/A	N/A	N/A	N/A	148 (76%)	/
---Intermediate risk	/	/	/	/	/	20 (10%)	/
---Poor risk	/	/	/	/	/	26 (13%)	/
Type of primary group-defining treatment	777 (0%)	/	/	/	/	/	<0.0001
---No chemotherapy	/	335 (43%)	335 (100%)	0 (0%)	0 (0%)	0 (0%)	/
---Carboplatin	/	83 (11%)	0 (0%)	83 (100%)	0 (0%)	0 (0%)	/
---BEP	/	328 (42%)	0 (0%)	0 (0%)	117 (99%)	211 (88%)	/
---EP	/	24 (3%)	0 (0%)	0 (0%)	1 (1%)	23 (10%)	/
---PEI	/	4 (<1%)	0 (0%)	0 (0%)	0 (0%)	4 (2%)	/
---Other	/	3 (<1%)	0 (0%)	0 (0%)	0 (0%)	3 (1%)	/
Comorbidities at baseline with potential							

impact on kidney function							
Diabetes mellitus	516 (36%)	8 (2%)	3 (2%)	1 (2%)	2 (2%)	2 (1%)	0.611
Hypertension	569 (27%)	48 (8%)	13 (7%)	5 (8%)	9 (9%)	21 (10%)	0.718
Heart failure	567 (27%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	N/A
CAD	570 (27%)	2 (<1%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)	0.745
Laboratory variables							
Baseline eGFR (ml/min/1.73m²)	777 (0%)	94 [81-108]	90 [80-103]	96 [81-106]	98 [88-111]	98 [84-109]	0.0001

Table 7: Uni- and multivariable competing risk regression models of time-to-30%-decline-in-eGFR

		Univariable models			**Multivariable model**	
Variable		SHR	95%CI (p)		SHR	95%CI (p)
Study group						
---Group 1 - AS		Ref.	Ref.		Ref.	Ref.
---Group 2 - AdjCBP		1.05	0.56-1.98, p=0.870		0.95	0.50-1.80, p=0.881
---Group 3 - AdjBEP		0.97	0.55-1.71, p=0.923		0.98	0.55-1.74, p=0.951
---Group 4 - CurBEP		2.40	1.70-3.45, **p<0.0001**		2.40	1.65-3.50, **p<0.0001**
Age (per 5 years increase)		1.08	1.00-1.15, **p=0.042**		1.23	1.13-1.33, **p<0.0001**
BMI (per 5 kg/m² increase)		0.98	0.80-1.19, p=0.810			/
Smoker or Ex-Smoker		0.97	0.67-1.41, p=0.868			/
Karnofsky Index <100%		1.95	1.21-3.16, **p=0.006**			/
Nonseminoma		1.55	1.12-2.14, **p=0.009**			/
Diabetes mellitus		0.51	0.08-3.29, p=0.477			/
Hypertension		1.35	0.79-2.30, p=0.271			/
Baseline eGFR (per 10 ml/min/1.73m² increase)		1.35	1.23-1.48, **p<0.0001**		1.43	1.30-1.58, **p<0.0001**

Table 8: Random intercept and slope models for modelling the change in eGFR over time

Model	Dependent variable	Independent variables	Coefficient (Absolute difference)	95%CI	p
Model #1	eGFR	Follow-up time (per year)	-0.06	-0.32-0.20	0.640
		Group 1 - AS	Ref.	Ref.	Ref.
		Group 2 - AdjCBP	1.83	-2.02-5.68	0.351
		Group 3 - AdjBEP	8.12	4.79-11.44	**<0.0001**
		Group 4 - CurBEP	5.89	3.29-8.49	**<0.0001**
		Group 1 – AS # Follow-up time	Ref.	Ref.	Ref.
		Group 2 – AdjCBP # Follow-up time	0.20	-0.40-0.80	0.514
		Group 3 – AdjBEP # Follow-up time	-0.42	-0.92-0.08	0.100
		Group 4 – CurBEP # Follow-up time	-1.46	-1.84-(-1.09)	**<0.0001**
		INTERCEPT	90.43	88.72-92.14	**<0.0001**
Model #2	eGFR	Follow-up time (per year)	0.10	-0.16-0.36	0.453
		Group 1 - AS	Ref.	Ref.	Ref.
		Group 2 - AdjCBP	-0.04	-2.37-2.30	0.974
		Group 3 - AdjBEP	1.05	-0.97-3.08	0.308
		Group 4 - CurBEP	1.73	0.19-3.27	**0.028**
		Age (per 1 year increase above 35 years)	-0.29	-0.36-(-0.23)	**<0.0001**
		Baseline eGFR (per 1ml/min/1.73m² increase above 90min/min/1.73m²)	-0.64	-0.68-(-0.60)	**<0.0001**
		Group 1 – AS # Follow-up time	Ref.	Ref.	Ref.
		Group 2 – AdjCBP # Follow-up time	0.27	-0.31-0.85	0.359
		Group 3 – AdjBEP # Follow-up time	-0.40	-0.89-0.10	0.115
		Group 4 – CurBEP # Follow-up time	-1.37	-1.74-(-1.00)	**<0.0001**
		Age # Follow-up time	-0.03	-0-05-(-0.02)	**<0.0001**

				Baseline eGFR # Follow-up time	0.03	0.02-0.04	**<0.0001**
				INTERCEPT	90.88	98.80-91.97	**<0.0001**

Table 9: Clinical annotation of the four patients who had at least one eGFR <15ml/min/1.73m² at any time during the study

Clinical item		Patient #1	Patient #2	Patient #3	Patient #4
Demographics and testicular cancer		43-year-old male NSGCT CS IIIA IGCCCG: Good prognosis	50-year-old male SGCT pT1	41-year-old male SGCT IIC IGCCCG: Good prognosis	54-year-old male NSGCT CS ≥IIC IGCCCG: Poor prognosis
Study group		Group 3 – Curative BEP	Group 1 – Active surveillance	Group 3 – Curative BEP	Group 3 – Curative BEP
Pre-existing CKD		Yes (ADPKD on chronic hemodialysis)	No	No	Yes (non-functional left kidney following hydronephrosis due to NSGCT retroperitoneal lymph node bulk)
Other clinical context		Multiple comorbidities, legal guardian due to mental retardation	Child's C liver cirrhosis due to chronic alcohol abuse, COPD	Sarcoidosis	None
Time and type of platinum exposure		Individualized treatment with 3xPEI (due to ESRD) and daily dialysis during chemo	No platinum exposure	3xBEP	Individualized treatment with 4xPEI (due to CKD)
Time of eGFR<15ml/min/1.73m²		always	9 years after SGCT diagnosis	1 week before platinum exposure	12 years after platinum exposure
Clinical context / Outcome		Died from neutropenic sepsis during the 3rd PEI cycle	eGFR<15ml/min/1.73m² occurred within an ICU stay due to hepatorenal syndrome caused by terminal liver disease, large-volume ascites paracentesis and pre-renal kidney failure due	eGFR<15ml/min/1.73m² occurred due to extensive retroperitoneal bulk causing grade III hydronephrosis, fully resolved after Double J ureteral stenting,	eGFR<15ml/min/1.73m² occurred due to heart failure and pulmonary edema following myocardial infarction, patient still alive, no current eGFR

			to diuretics; died from liver failure	patient died ~ 4 months after 3rd BEP cycle due to generalized staphylococcal abscesses / sepsis	measurements available
Presumed relationship between platinum exposure and eGFR<15ml/min/1.73m²		None	None	None	Possible

Supplementary Table 1: Uni- and multivariable competing risk regression models of time-to-30%-decline-in-eGFR

		Univariable models			Multivariable model	
Variable		SHR	95%CI (p)		SHR	95%CI (p)
Study group						
---Group 1 - AS		Ref.	Ref.		Ref.	Ref.
---Group 2 - AdjCBP		1.05	0.56-1.98, p=0.870		1.34	0.68-2.63, p=0.392
---Group 3 - AdjBEP		0.97	0.55-1.71, p=0.923		0.73	0.36-1.47, p=0.382
---Group 4 - CurBEP		2.40	1.67-3.45, **p<0.0001**		2.21	1.43-3.40, **p<0.0001**
Age (per 5 years increase)		1.08	1.00-1.15, **p=0.042**		1.28	1.17-1.40, **p<0.0001**
BMI (per 5 kg/m² increase)		0.98	0.80-1.19, p=0.810		/	/
Smoker or Ex-Smoker		0.97	0.67-1.41, p=0.868		/	/
Karnofsky Index <100%		1.95	1.21-3.16, **p=0.006**		1.14	0.62-2.10, p=0.665
Nonseminoma		1.55	1.12-2.14, **p=0.009**		1.45	0.93-2.27, p=0.105
Diabetes mellitus		0.51	0.08-3.29, p=0.477		/	/
Hypertension		1.35	0.79-2.30, p=0.271		/	/
Baseline eGFR (per 10 ml/min/1.73m² increase)		1.35	1.23-1.48, **p<0.0001**		1.39	1.23-1.56, **p<0.0001**

8 Table and Supplementary Table Legends

8.1 Table 6

Baseline characteristics of the study cohort – Distribution overall and by treatment group (n=777):

Reported data are medians [25th-75th percentile] for continuous variables and absolute frequencies (column %) for count data. * n (%miss.) indicates the number of patients with observed variable (% missing). ** p-values are from Kruskal-Wallis tests, χ2-tests, and Fisher's exact tests, as appropriate. ǂ These histologies are truly missing as the histology report indicates a fully necrotic tumor. ǂǂ One patient with non-seminoma (95% seminoma, 5% yolk sac tumor) received adjuvant carboplatin as an individualised decision, one patient with seminoma (9cm bulk, fully resected with clear margins as a so-called whoops procedure, no evidence of further residual tumor on imaging or in laboratory analysis) received one cycle of "pseudo-adjuvant" BEP as an individualized decision. ***Only reported for primary metastatic disease.

Abbreviations: AS – Active Surveillance without any further metastasis or TGCT-specific treatment, AdjCBP – adjuvant carboplatin AUC 7 single shot without any further metastasis or TGCT-specific treatment, AdjBEP – adjuvant bleomycin/etoposide/cisplatin without any further metastasis or TGCT-specific treatment, CurBEP – curative treatment with at least three cycles bleomycin/etoposide/cisplatin (indicated in Table 6 if other therapy than BEP), BMI – Body mass index, IGCCCG - International germ cell cancer collaborative group, BEP – bleomycin/etoposide/cisplatin, EP – etoposide/cisplatin, PEI – cisplatin/etoposide/ifosfamide, CAD – Coronary artery disease, N/A – not applicable, eGFR – Estimated glomerular filtration rate.

8.2 Table 7

Uni- and multivariable competing risk regression models of time-to-30%-decline-in-eGFR:

Abbreviations: SHR – Subdistribution hazard ratio, 95%CI (p) – 95% confidence interval (p-value), AS – Active Surveillance without any further metastasis or TGCT-specific treatment, Ref. – Reference group, AdjCBP – adjuvant carboplatin AUC 7

single shot without any further metastasis or TGCT-specific treatment, AdjBEP – adjuvant bleomycin/etoposide/cisplatin without any further metastasis or TGCT-specific treatment, CurBEP – curative treatment with at least three cycles bleomycin/etoposide/cisplatin (indicated in Table 6) if other therapy than BEP), BMI – Body mass index, eGFR – Estimated glomerular filtration rate.

8.3 Table 8

Random intercept and slope models for modelling the change in eGFR over time:

The coefficients are absolute differences in eGFR for the respective variables. In model #2, age and baseline eGFR are centered at 35 years and 90ml/min/1.73m². The intercept is the eGFR at baseline as estimated by the model.

Abbreviations: 95%CI – 95% confidence interval, p – p-value, Ref. – Reference category, AS – Active Surveillance without any further metastasis or TGCT-specific treatment, AdjCBP – adjuvant carboplatin AUC 7 single shot without any further metastasis or TGCT-specific treatment, AdjBEP – adjuvant bleomycin/etoposide/cisplatin without any further metastasis or TGCT-specific treatment, CurBEP – curative treatment with at least three cycles bleomycin/etoposide/cisplatin (indicated in Table 6 if other therapy than BEP), # - interaction time (i.e. the change in eGFR per year for the respective variable), eGFR – Estimated glomerular filtration rate.

8.4 Table 9

Clinical annotation of the four patients who had at least one eGFR <15ml/min/1.73m² at any time during the study:

Abbreviations: (N)SGCGT – (Non-)Seminomatous germ cell tumor, CS – Clinical stage, IGCCCG – International germ cell cancer collaborative group, BEP – bleomycin/etoposide/cisplatin, CKD – Chronic kidney disease, ADPKD – Autosomal dominant polycystic kidney disease, COPD – Chronic obstructive pulmonary disease, PEI – cisplatin/etoposide/ifosfamide, ESRD – End-stage renal disease, eGFR – Estimated glomerular filtration rate, ICU – Intensive care unit.

8.5 Supplementary Table 1

Uni- and multivariable competing risk regression models of time-to-30%-decline-in-eGFR:

Abbreviations: SHR – Subdistribution hazard ratio, 95%CI (p) – 95% confidence interval (p-value), AS – Active Surveillance without any further metastasis or TGCT-specific treatment, Ref. – Reference group, AdjCBP – adjuvant carboplatin AUC 7 single shot without any further metastasis or TGCT-specific treatment, AdjBEP – adjuvant bleomycin/etoposide/cisplatin without any further metastasis or TGCT-specific treatment, CurBEP – curative treatment with at least three cycles bleomycin/etoposide/cisplatin (indicated in Table 6 if other therapy than BEP), BMI – Body mass index, eGFR – Estimated glomerular filtration rate.

9 Figures

Figure 2: Cumulative incidence of a 30% decline in eGFR according to study group (n=777)

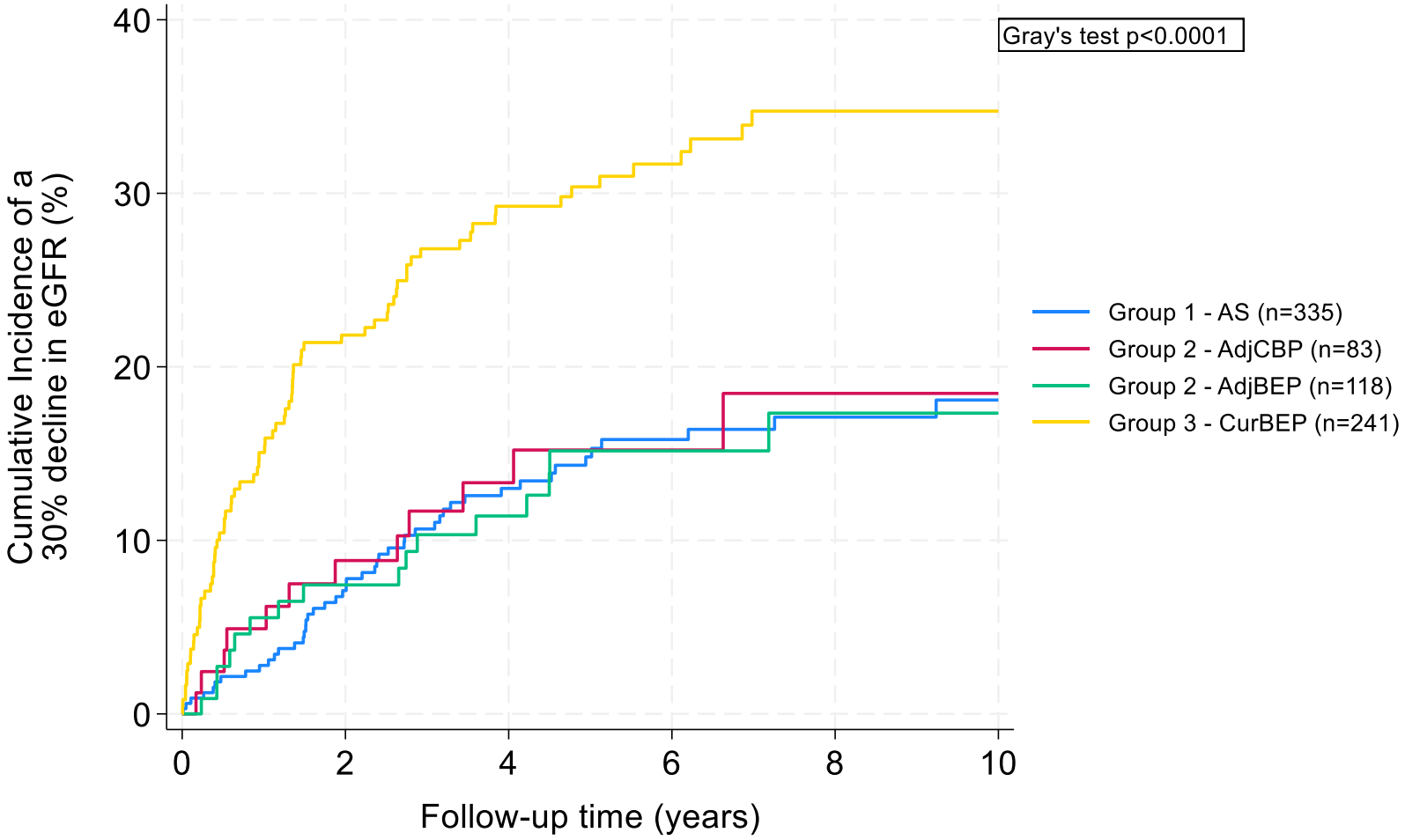
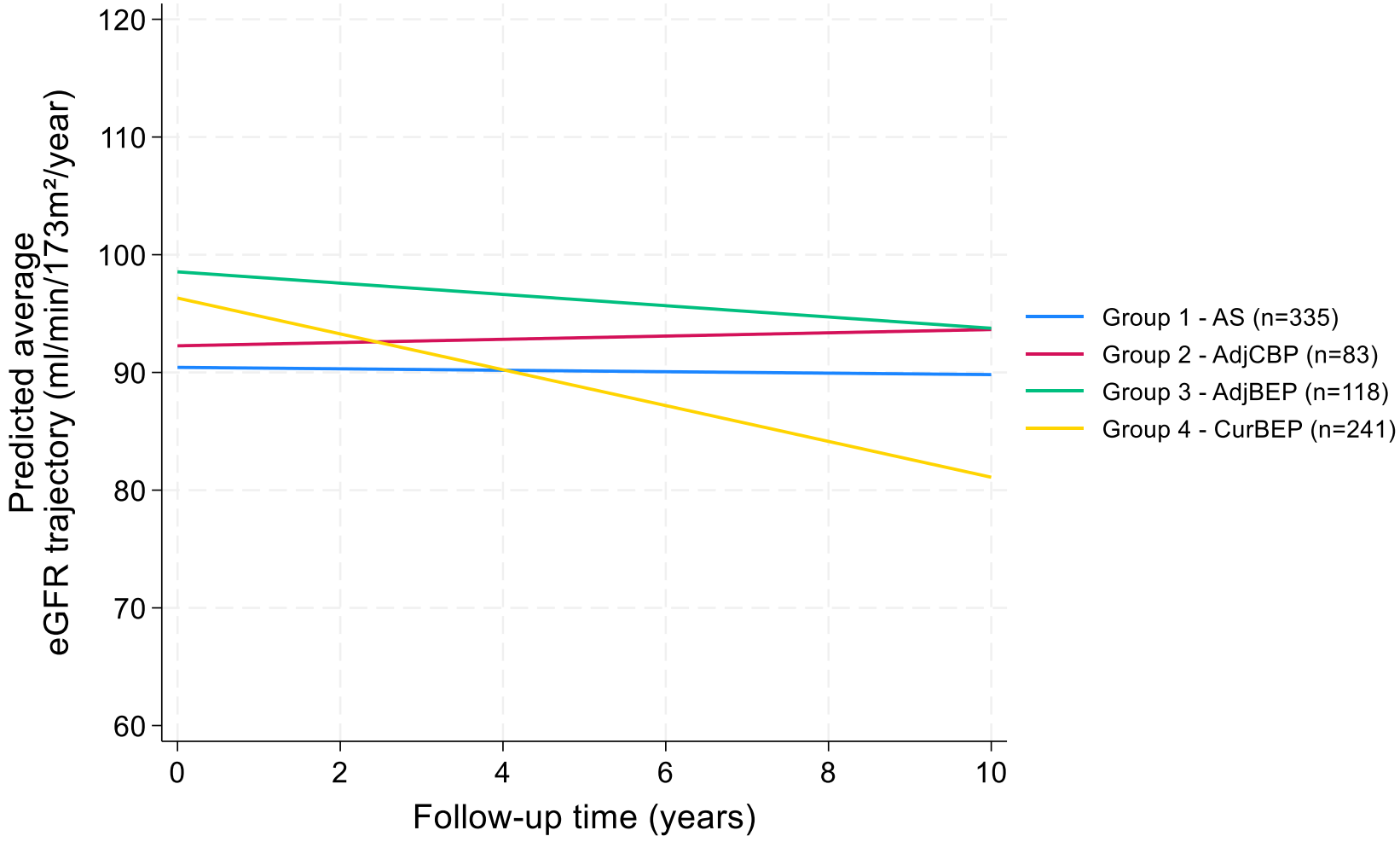
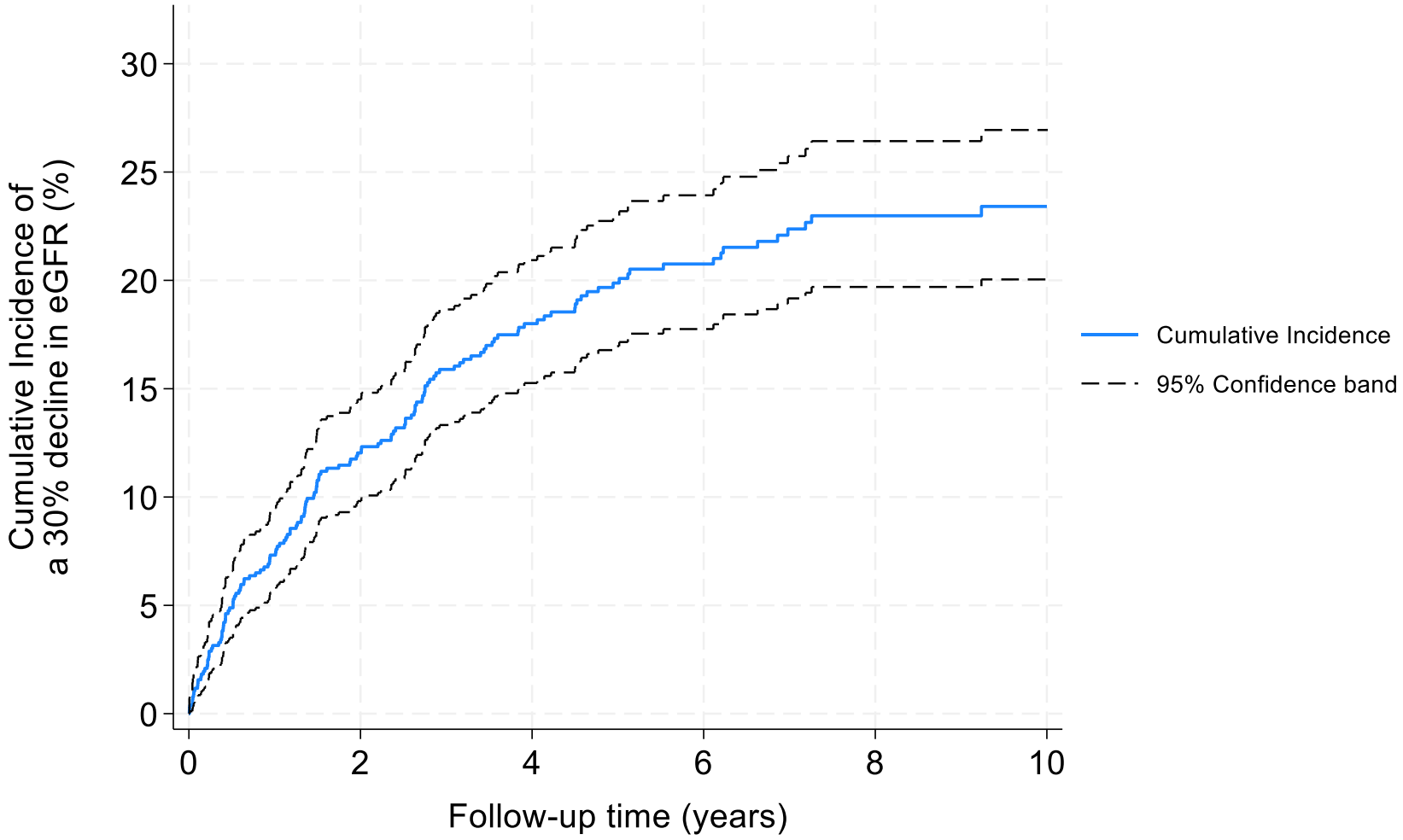


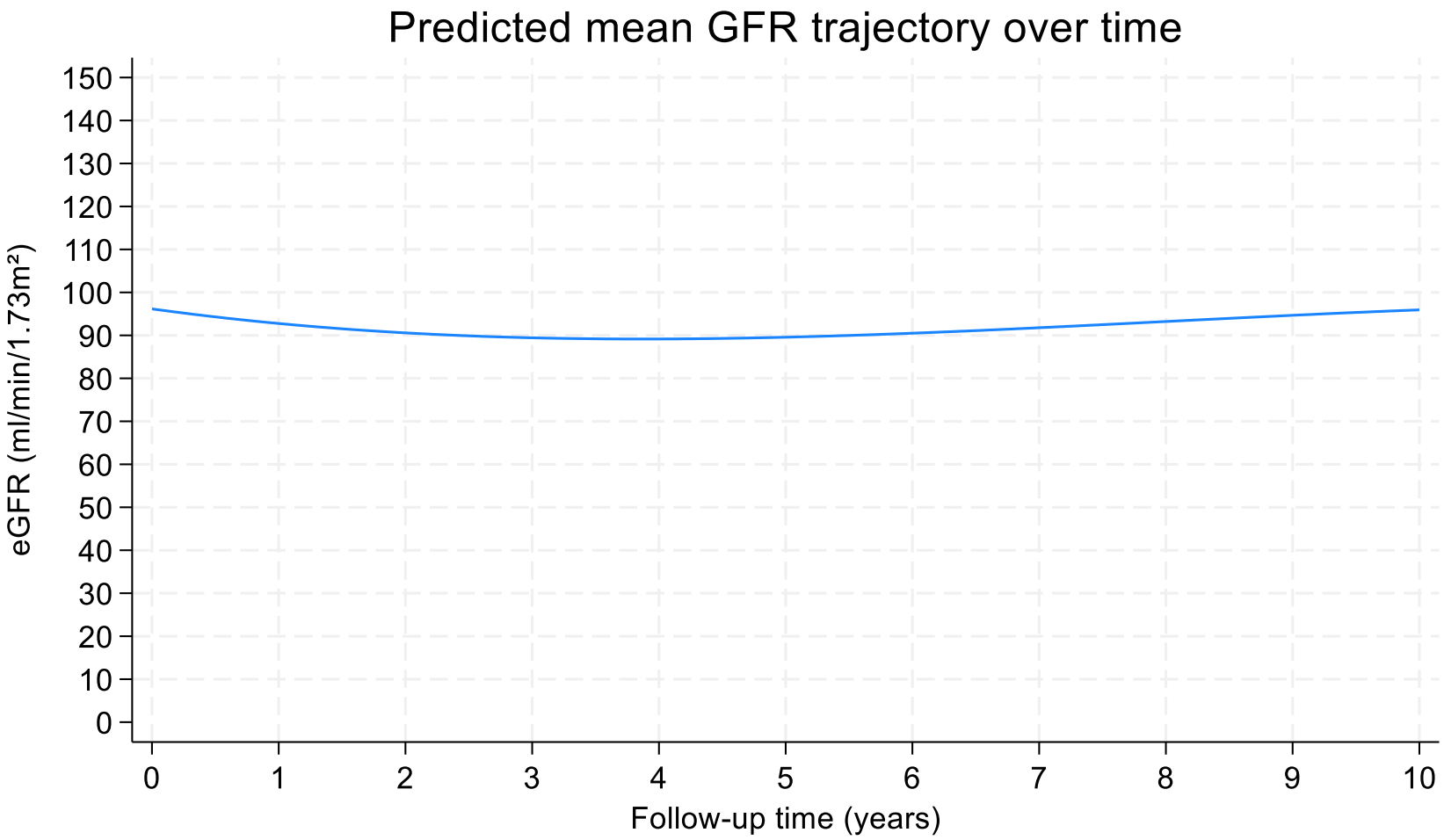
Figure 3: Predicted longitudinal eGFR trajectories according to study group (n=777)



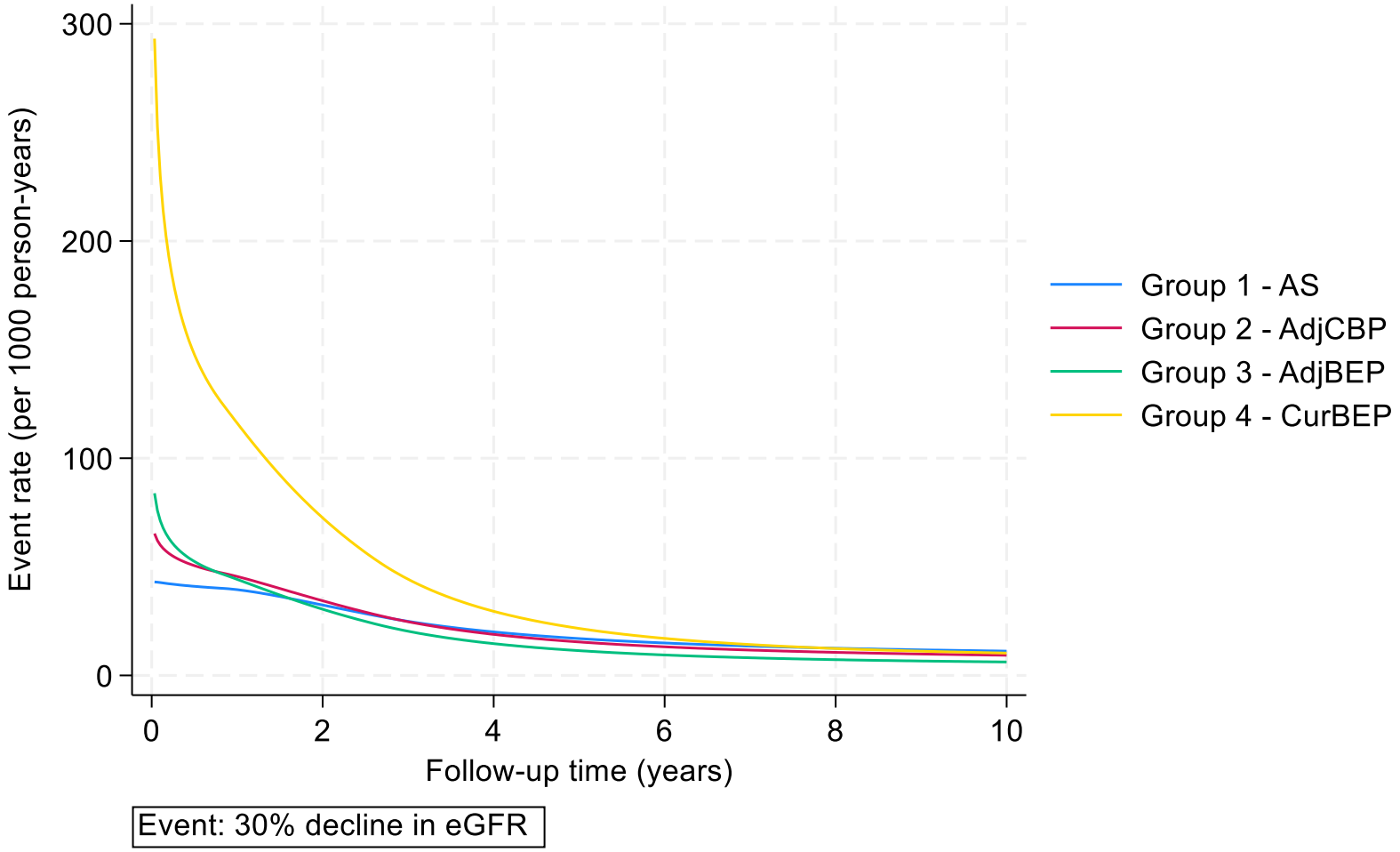
Supplementary Figure 1: Cumulative incidence of a 30% decline in eGFR in the overall cohort (n=777)



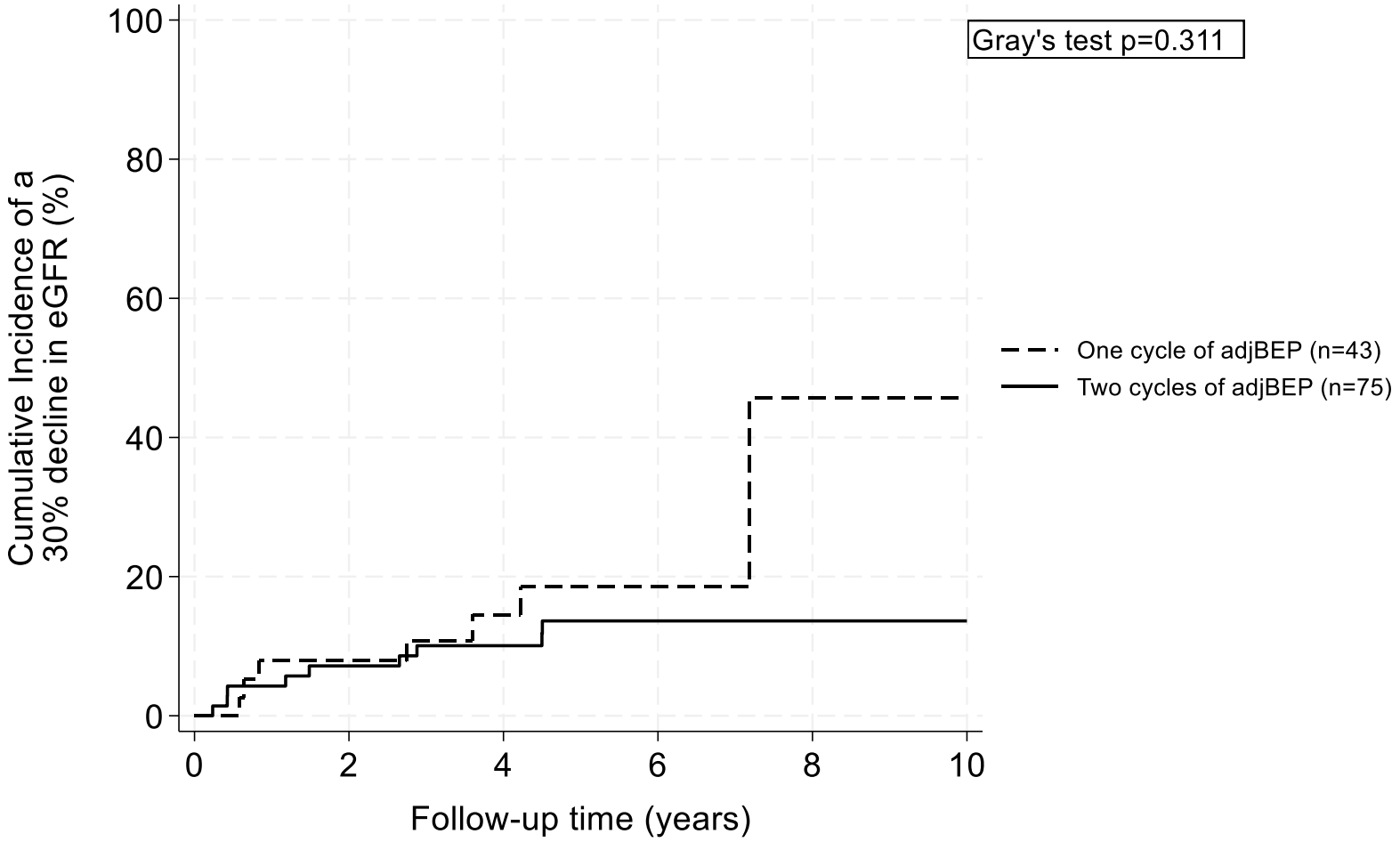
Supplementary Figure 2: Predicted longitudinal eGFR trajectory in the overall cohort (n=777)



Supplementary Figure 3: Time-dependent event rates of a 30% decline in eGFR according to study group (n=777)



Supplementary Figure 4: Cumulative incidences of a 30% decline in eGFR in group 2 – AdjBEP according to whether one or two cycles of adjuvant platinum-based therapy was administered (n=118)



10 Figure and Supplementary Figure Legends

10.1 Figure 2

Cumulative incidence of a 30% decline in eGFR according to study group (n=777):

Curves were estimated with a competing risk cumulative incidence estimator, treating death-from-any-cause as the competing event of interest.

Abbreviations: AS – Active Surveillance without any further metastasis or TGCT-specific treatment, AdjCBP – adjuvant carboplatin AUC 7 single shot without any further metastasis or TGCT-specific treatment, AdjBEP – adjuvant bleomycin/etoposide/cisplatin without any further metastasis or TGCT-specific treatment (indicated in Table 6 if other therapy than BEP), CurBEP – curative treatment with at least three cycles bleomycin/etoposide/cisplatin (indicated in Table 6 if other therapy than BEP), eGFR – Estimated glomerular filtration rate.

10.2 Figure 3

Predicted longitudinal eGFR trajectories according to study group (n=777):

Curves were estimated with a random intercept and slope model on n=16,953 eGFR measurements, with model choice described in Supplementary Paragraph 3.

Abbreviations: AS – Active Surveillance without any further metastasis or TGCT-specific treatment, AdjCBP – adjuvant carboplatin AUC 7 single shot without any further metastasis or TGCT-specific treatment, AdjBEP – adjuvant bleomycin/etoposide/cisplatin without any further metastasis or TGCT-specific treatment (indicated in Table 6 if other therapy than BEP), CurBEP – curative treatment with at least three cycles bleomycin/etoposide/cisplatin (indicated in Table 6 if other therapy than BEP), eGFR – Estimated glomerular filtration rate.

10.3 Supplementary Figure 1

Cumulative incidence of a 30% decline in eGFR in the overall cohort (n=777):

The cumulative incidence curve (blue solid line) and its 95% confidence bands (black dashed lines) were estimated with a competing risk cumulative incidence estimator, treating death-from-any-cause as the competing event of interest.

Abbreviations: eGFR – Estimated glomerular filtration rate.

10.4 Supplementary Figure 2

Predicted longitudinal eGFR trajectory in the overall cohort (n=777):

The curve was predicted from a random intercept and slope model on n=16,953 eGFR measurements with fixed effects for quadratic and cubic follow-up time. The slight U-shape of the curve informed our final model choice as described in Supplementary Paragraph 3.

Abbreviations: eGFR – Estimated glomerular filtration rate.

10.5 Supplementary Figure 3

Time-dependent event rates of a 30% decline in eGFR according to study group (n=777):

Curves were predicted from a flexible parametric regression model (Stata routine stpm2) allowing for a time-varying effect of treatment group on the rate of a 30% decline in eGFR.

Abbreviations: AS – Active Surveillance without any further metastasis or TGCT-specific treatment, AdjCBP – adjuvant carboplatin AUC 7 single shot without any further metastasis or TGCT-specific treatment, AdjBEP – adjuvant bleomycin/etoposide/cisplatin without any further metastasis or TGCT-specific treatment (indicated in Table 6 if other therapy than BEP), CurBEP – curative treatment with at least three cycles bleomycin/etoposide/cisplatin (indicated in Table 6 if other therapy than BEP), eGFR – Estimated glomerular filtration rate.

10.6 Supplementary Figure 4

Cumulative incidences of a 30% decline in eGFR in group 2 – AdjBEP according to whether one or two cycles of adjuvant platinum-based therapy was administered (n=118):

The cumulative incidence curves (black dashed line for patients with one cycle, black solid line for patients with two cycles) were estimated with a competing risk

cumulative incidence estimator, treating death-from-any-cause as the competing event of interest.

Abbreviations: AdjBEP – adjuvant bleomycin/etoposide/cisplatin without any further metastasis or TGCT-specific treatment (indicated in Table 6 if other therapy than BEP), eGFR – Estimated glomerular filtration rate.

11 Supplementary Paragraph 1

Kidney function data was extracted with support of our local Department of Informatics, Medical Statistics, and Documentation (IMI) from the local electronic health records system "openMEDOCS." The process of how we arrived at one final kidney function measurement per each day per patient is described in detail in this paragraph:

We provided IMI with a list of n=1,324 testicular cancers from n=1,313 individual patients from our Graz testicular cancer cohort, and extracted all creatinine and glomerular filtration rate (GFR) data from two weeks prior to these patients' testicular cancer histology date until May 5th, 2023. At least one kidney function measurement was available for n=1,239 (94%) of these testicular cancers, and we obtained a total of n=51,980 laboratory measurements of kidney function. There were n=13,585 (26%) estimated GFR (eGFR) measurements according to the chronic kidney disease epidemiology collaboration (CKD-EPI) formula, n=12 GFR (0.02%) measurements by Cystatin Clearance, n=11,912 (23%) eGFR measurements according to the modified diet in renal disease (MDRD) formula, and n=26,471 (51%) measurements of creatinine. Creatinine measurements were from serum (n=26,435), whole blood (n=28), capillary blood (n=7), and from an operating theatre point-of-care device (n=1). Creatinine measurements (n=26,471, all patients were men of white ethnicity) were transformed into eGFR values according to the CKD-EPI formula as follows:

$$eGFR = 142 * \min\left(\frac{Scr}{0.9}, 1\right)^{-0.302} * \max\left(\frac{Scr}{0.9}, 1\right)^{-1.200} * 0.9938^{Age}$$

The median number of GFR measurements per patient were n=35 [25th-75th percentile: 22-48] and ranged from n=1 to n=719 measurements per patient. From the overall n=51,980 measurements, n=51,063 (98%) were from the same day (i.e., both a creatinine and eGFR readout or more readouts), and readings were from n=26,016 individual days. We then deleted all creatinine values for days where a concurrent GFR measurement or estimate was available (n=25,500 deletions). This led to a median number of GFR measurements per patient of n=18 [25th-75th percentile: 11-25]. GFR measurements ranged from n=1 to n=370 measurements per patient and came from n=26,016 individual days. On these individual-patient

days, n=25,581 days (98%) had only one GFR measurements, n=409 days (2%) had two GFR measurements, n=23 days (0.09%) had 3 GFR measurements, and n=3 days (0.01%) had 4 GFR measurements, respectively. Individual inspection of these days with multiple GFR measurements was not indicative of double entry, e.g., a patient with 4 GFR measurements in a single day had them measured as part of a venetoclax ramp-up for chronic lymphocytic leukemia (CLL) within a study protocol. We therefore took the average of the measurements within a day to obtain a single GFR measurement per day. Finally, to remove duplicates within the first record of the n=11 patients with two histology dates (i.e., patients with a contralateral testicular cancer which was removed), we deleted n=127 GFR measurements beyond the second tumor histology date for these patients. Thus, a final n=25,889 GFR readings from n=1,239 testicular cancers from n=1,313 individual patients were obtained, of whom n=24,947 (96%) were direct GFR results from the laboratory reports and n=942 (4%) were eGFR estimates based on creatinine readouts. We then merged these data with the full dataset of the n=1,324 testicular cancers in our Graz testicular cancer cohort. Here, n=85 testicular cancers were not matched due to not having any GFR data available, resulting in a pre-final dataset of n=1,239 testicular cancers from n=1,228 patients with n=25,889 GFR readings.

12 Supplementary Paragraph 2

The electronic health record system “openMEDOCS” was introduced at our institution in 2003. Consequently, GFR data are available electronically only from this time on. This leads to patients with TGCT histology dates prior 2003 lacking full coverage of their longitudinal kidney function trajectory from diagnosis onwards, rendering their incomplete data of little use for the present analysis. We therefore excluded testicular cancers with a histology date prior Jan 1st, 2004, leading to a cohort of n=857 testicular cancers from n=847 patients with n=19,100 GFR measurements. Next, to simplify hierarchical statistical modelling and avoiding GFR duplicates within a patient, we then excluded testicular cancers who were second testicular cancers, leading to a dataset with n=850 testicular cancers from n=850 patients and n=18,991 GFR measurements. Next, we excluded patients treated with adjuvant radiotherapy and no subsequent metastasis/chemotherapy, and patients with primary metastatic disease treated with curative radiotherapy and no subsequent metastasis/chemotherapy, or patients treated with adjuvant/curative retroperitoneal lymphadenectomy (RPLND) without subsequent metastasis/chemotherapy, resulting in a dataset with n=792 patients and n=17,381 GFR measurements. We then excluded one patient who turned out to have benign histology upon review, and further 7 patients who were referred to us ≥1 year for routine follow-up after tumor diagnosis due to resettlement into Southern Austria or delayed referral due to COVID-19 lockdowns, resulting in a population of n=784 patients and n=17,328 GFR measurements. Finally, we excluded n=7 patients who did not have an eGFR measurement within the 6 weeks preceding their baseline date, resulting in a final study cohort for analysis of n=777 patients with 16,953 GFR measurements.

13 Supplementary Paragraph 3

We started with a fixed-effects linear growth model with eGFR as the dependent variable and follow-up time in years as the explanatory variable. We then fitted a corresponding random-intercept model, which provided a significantly better fit to the data (likelihood ratio $\chi 2$ (1 d.f.) comparing the two models=12150, $p<0.0001$). Next, we fitted an additional random effect for follow-up time ("random intercept and slope model"). This model again provided a better fit to the data than the random intercept and slope model (likelihood ratio $\chi 2$ (1 d.f.) comparing the two models=860, $p<0.0001$). We then fitted a model with quadratic and cubic fixed-effects terms for follow-up time ("non-linear growth model"), which provided a better fit to the data than the previous random intercept and slope model (likelihood ratio $\chi 2$ (1 d.f.) comparing the two models=373, $p<0.0001$). However, eGFR trajectory predictions from this model yielded minimally U-shaped eGFR trajectory curves with a minimal increase in eGFR over time beyond 5 years of follow-up Supplementary Figure 2). We considered this U-shape to be related to potential informative censoring of eGFR follow-up data, with the cohort potentially getting progressively enriched with "lower kidney disease risk" over time and fewer eGFR observations, rather than having a clear biologic mechanism (assuming/knowing that the eGFR on average will decline rather than increase over the lifetime of an average person). Therefore, we selected the random intercept and slope model as the final model for comparing eGFR trajectories between the four studies groups, as this model appeared for the reasons described above to have the best trade-off between statistical fit to the data and biologic/clinical plausibility.