Diploma thesis

# TREATMENT-RELATED MORBIDITY IN PATIENTS WITH TESTICULAR CANCER


submitted by

**Lisa Marie Annerer**


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under supervision of

**Assoz. Prof. Priv.-Doz. Dr.med.univ. et scient.med. Armin Gerger, MBA**

**Dr.in med.univ. Angelika Terbuch**

Wels, 8th of October, 2017

## Statutory Declaration

I hereby declare that I have authored the following diploma thesis independently, that I have not used other than the declared sources, and that I have explicitly marked all material, which has been quoted either literally or by content from the used sources.

Wels, 8th of October, 2017 Lisa Marie Annerer eh

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## Abstract

Purpose: Testicular germ cell tumours (TGCT) represent the most common solid malignancies among men aged 20 to 40 years. If detected in early stage disease, the cure rates lie between 90-100%, regardless of the treatment strategy. Therefore, we shifted the focus of our research towards the prevention of treatment-related complications and tried to investigate differences between the available treatment modalities. In our study, we focused on the adjuvant treatment of patients with stage I seminoma and the occurrence of cardiovascular complications.

Methods: The retrospective cohort study included 406 patients with histologically confirmed clinical stage I seminoma, who presented to the Division of Oncology at the Medical University of Graz between 1994 and 2013. Their medical records were retrospectively reviewed and cardiovascular events (CVE), preliminarily defined as myocardial infarction, cerebrovascular event, coronary heart disease and peripheral arterial disease, were documented. The primary endpoint of the study was the CVE rate.

Results: In our study population of 406 patients, 23 CVEs were observed during a median follow up of 8.6 years (10-year CVE risk: 5.6% (95%CI: 3.2 -8.8)). A univariable competing risk analysis revealed a significant association between higher age, positive smoking status, history of diabetes, hypertension and the occurrence of cardiovascular events. Further, new onset of diabetes, hypertension and hyperlipidemia during follow-up proofed to be predictive of an excessively increased CVE risk in our multi-state analysis. Our results also showed that patients receiving adjuvant radiotherapy had a significantly higher probability of cardiovascular events than patients being treated with adjuvant carboplatin (16% vs. 0%; risk difference (RD)=16%, 95%CI: 6-25%, p=0,001).

Conclusion: We identified multiple baseline risk factors and predictors of cardiovascular events in patients with stage I seminoma. Those may be useful for the management of comorbidities. We also discovered an association between adjuvant radiotherapy and higher risk of cardiovascular events, which warrants further investigation.

## Zusammenfassung

Zielsetzung: Der Keimzelltumor des Hodens repräsentiert die häufigste solide Malignität der 20- bis 40-jährigen Männer. Wenn der Tumor noch im Frühstadium entdeckt wird, liegt die Heilungsrate zwischen 90-100%, unabhängig von der gewählten Therapie. Daher haben wir den Fokus unserer Forschungen auf die Prävention von Therapie-bedingten Komplikationen verschoben und versucht, Unterschiede zwischen den verwendeten Therapiemöglichkeiten zu erforschen. In unserer Studie haben wir uns auf die adjuvante Therapie von Patienten mit Seminomen im Stadium I und das Auftreten von kardiovaskulären Ereignissen (KVE) konzentriert.

Methoden: Die retrospektive Kohortenstudie umfasste 406 Patienten mit histologisch bestätigtem Seminom im klinischen Stadium I, welche zwischen 1994 und 2013 auf der Abteilung für Onkologie auf der Medizinischen Universität Graz vorstellig wurden. Die medizinischen Aufzeichnungen wurden retrospektiv aufgearbeitet und kardiovaskuläre Ereignisse, welche zuvor als Myokardinfarkt, zerebrovaskuläres Ereignis, koronare Herzerkrankung und periphere arterielle Gefäßerkrankung definiert wurden, dokumentiert. Der primäre Endpunkt der Studie war die Rate an KVE.

Resultate: Unter den 406 Patienten unserer Studie wurden 23 kardiovaskuläre Ereignisse während einer durchschnittlichen Nachverfolgung von 8.6 Jahren beobachtet. Eine einzelvariablenbasierte „competing risk“-Analyse zeigte signifikante Assoziationen zwischen höherem Alter, positivem Raucher-Status, vorbekanntem Diabetes, Hypertonus und dem Auftreten von kardiovaskulären Ereignissen. Weiters zeigten sich das Neuauftreten von Diabetes, Hypertonus und Hyperlipidämie während der Nachkontrollen als prädiktiv für ein übermäßig erhöhtes Risiko für kardiovaskuläre Ereignisse in „multi-state“-Analysen. Unsere Resultate zeigten auch, dass Patienten, die mit adjuvanter Radiotherapie behandelt wurden, eine signifikant höhere Wahrscheinlichkeit für ein kardiovaskuläres Ereignis hatten als Patienten, die mit adjuvantem Carboplatin behandelt wurden (16% vs. 0%; risk difference (RD)=16%, 95%CI: 6-25%, p=0,001).

Schlussfolgerung: Wir haben mehrere primäre Risikofaktoren und Prädiktoren für kardiovaskuläre Ereignisse bei Patienten mit Seminomen im Stadium I identifiziert,

welche für das Management von Komorbiditäten nützlich sein könnten. Des Weiteren haben wir auch eine Verbindung zwischen adjuvanter Radiotherapie und einem höheren Risiko für kardiovaskuläre Ereignisse entdeckt, welche weiterer Untersuchung bedarf.

# *Table of contents*

Statutory Declaration ..... ii
Acknowledgement ..... iii
Abstract ..... iv
Zusammenfassung ..... v
Table of contents ..... vii
Abbreviations ..... x
Tables ..... xii
Figures ..... xii
1. INTRODUCTION ..... 1
2. EPIDEMIOLOGY ..... 2
3. INCIDENCE ..... 2
4. RISK FACTORS ..... 3
4.1. Cryptorchidism ..... 3
4.2. Testicular cancer in the contralateral testis ..... 3
4.3. Testicular microlithiasis ..... 4
4.4. Family history ..... 4
4.5. Other factors ..... 4
5. HYPOTHESIS OF TGCT DEVELOPMENT ..... 4
6. CIS – CARCINOMA IS SITU ..... 5
7. WHO CLASSIFICATION OF GERM CELL TUMOURS ..... 6
7.1. Seminoma ..... 7
7.2. Nonseminoma ..... 8
7.2.1. Embryonal carcinoma ..... 8
7.2.2. Yolk sac tumour ..... 9
7.2.3. Choriocarcinoma ..... 9
7.2.4. Teratoma ..... 10
8. TNM CLASSIFICATION ..... 11
9. STAGING ..... 12
10. PRESENTATION ..... 13
11. DIAGNOSTIC ..... 14
12. TUMOUR MARKER ..... 15
12.1. AFP ..... 15

12.2. hCG ..... 15
12.3. LDH ..... 15
13. IMAGING ..... 16
14. PROGNOSIS ..... 17
15. THERAPY ..... 18
15.1. Surgical Therapy ..... 19
15.1.1. Orchiectomy ..... 19
15.1.2. Organ-preserving surgery ..... 19
15.2. Chemotherapy ..... 19
15.3. Radiotherapy ..... 21
15.4. Active surveillance ..... 21
16. TREATMENT GUIDELINES FOR CLINICAL PRACTICE ..... 22
16.1. SEMINOMA ..... 22
16.1.1. Stage I Seminoma ..... 23
16.1.2. Stage IIA Seminoma ..... 23
16.1.3. Stage IIB/IIC Seminoma ..... 23
16.1.4. Stage III Seminoma ..... 24
16.1.5. Post-chemotherapy management ..... 24
16.2. NONSEMINOMA ..... 25
16.2.1. Stage I Nonseminoma ..... 25
16.2.2. Low-risk Stage I Nonseminoma ..... 26
16.2.3. High-risk Stage I Nonseminoma ..... 26
16.2.4. Stage IIA (IIB) Nonseminoma, marker negative ..... 26
16.2.5. Stage IS/II/III Nonseminoma ..... 27
16.2.6. Post-chemotherapy management ..... 27
17. TREATMENT-RELATED TOXICITY ..... 28
17.1. Fertility ..... 28
17.2. Hypogonadism ..... 28
17.3. Complications of the RPLND ..... 28
17.4. Secondary malignancies ..... 29
17.5. Pulmonary toxicity ..... 29
17.6. Nephrotoxicity ..... 30
17.7. Neurotoxicity ..... 31
17.8. Cardiovascular toxicity ..... 31

18. OUR STUDY “LONG-TERM CARDIOVASCULAR COMPLICATIONS IN STAGE I SEMINOMA PATIENTS” ..... 33
18.1. INTRODUCTION ..... 33
18.2. MATERIAL AND METHODS ..... 34
18.2.1. Patient Population ..... 34
18.2.2. Statistical Analysis ..... 35
18.3. RESULTS ..... 37
18.3.1. Analysis at baseline ..... 37
18.3.2. Analysis of arterial cardiovascular complications at baseline ..... 39
18.3.3. Predictors of cardiovascular events ..... 39
18.3.4. Adjuvant therapy and CVE risk ..... 41
18.4. DISCUSSION ..... 43
19. REFERENCES ..... 45

**ABBREVIATIONS**

| | |
|---|---|
| AA | Arachidonic Acid |
| AFP | Alpha Fetoprotein |
| AJCC | American Joint Committee on Cancer |
| AUC | Area under the Curve |
| BEP | Bleomycin/Etoposide/Cisplatin |
| BIP | Bleomycin-Induced Pneumonia |
| CC | Choriocarcinoma |
| CE | Carboplatin/Etoposide |
| CIS | Carcinoma In Situ |
| CS | Clinical Stage |
| CT | Computed Tomography |
| CVD | Cardiovascular Disease |
| CVE | Cardiovascular Event |
| EC | Embryonal Carcinoma |
| EGCCCG | European Germ-Cell Cancer Consensus Group |
| EP | Etoposide/Cisplatin |
| FDG-PET | Fluorodeoxyglucose-Positron Emission Tomography |
| GCT | Germ Cell Tumour |
| GFR | Glomerular Filtration Rate |
| Gy | Grey |
| hCG | human Chorionic Gonadotropin |
| hsCRP | high sensitive C-Reactive Protein |
| IGCCCG | International Germ Cell Cancer Collaborative Group |
| IGCN | Intratubular Germ Cell Neoplasia |
| IU/L | International Unit |
| LDH | Lactate Dehydrogenase |
| LI | Lymphatic Invasion |
| MRI | Magnetic Resonance Imaging |
| MS | Metabolic Syndrome |
| NL | Normal Limit |
| NS | Nonseminoma |

| | |
|---|---|
| PAI-1 | Plasminogen Activator Inhibitor-1 |
| PET | Positron Emission Tomography |
| RPLND | Retroperitoneal Lymph Node Dissection |
| RR | Relative Risk |
| SDIHD | Sudden Death Ischemic Heart Disease |
| SGCT | Seminomatous Germ Cell Tumour |
| SMN | Second Malignant Neoplasia |
| SMR | Standardized Mortality Ratio |
| TC | Testicular Cancer |
| TGCT | Testicular Germ Cell Tumour |
| TI-CE | Paclitaxel/Ifosfamide-Carboplatin/Etoposide |
| TIN | Testicular Intraepithelial Neoplasia |
| TIP | Paclitaxel/Ifosfamide/Cisplatin |
| TM | Testicular Microlithiasis |
| TNF | Tumour Necrosis Factor |
| TNM | Tumour-Nodes-Metastasis |
| t-PA | tissue-Plasminogen Activator |
| UICC | Union for International Cancer Control |
| UK | United Kingdom |
| ULN | Upper Limit of Normal |
| VeIP | Vinblastine/Ifosfamide/Cisplatin |
| VI | Vascular Invasion |
| VIP/PEI | Cisplatin/Etoposide/Ifosfamide |
| vWF | von Willebrand Factor |
| WHO | World Health Organization |
| YST | Yolk Sac Tumour |

## TABLES

Table 1: “Primary Tumour”.....11
Table 2: “Regional Lymph Nodes” .....11
Table 3: “Distant Metastasis” .....12
Table 4: “Post-orchiectomy staging of metastatic seminoma and non-seminoma according to AJCC/UICC and IGCCCG classification” .....13
Table 5: “Prognostic classification of the IGCCCG - International Germ Cell Collaborative Group” .....17
Table 6: “Expected Survival for Disseminated Disease” .....18
Table 7: “Chemotherapy regimens in metastatic seminoma and non-seminoma” .....20
Table 8: “Standard treatment strategies for seminoma” .....22
Table 9: “Standard treatment strategies for nonseminoma”.....25
Table 10: Baseline characteristics of the patient population .....36
Table 11: Baseline characteristics – Distribution overall and by treatment modality..38
Table 12: Overall Incidence of cardiovascular events .....39
Table 13: Predictors of cardiovascular event risk in TGCT patients .....40

## FIGURES

Figure 1: “Incidence of Testicular Cancer in Males by Race/Ethnicity”.....3
Figure 2: “Tumourigenic model for germ cell tumours of the testis” .....5
Figure 3: “Cumulative-cardiovascular-event-risk during follow-up of testicular cancer patients”.....42
Figure 4: “Cumulative-cardiovascular-event-risk during follow-up of testicular cancer patients depending on adjuvant therapy”.....42

# TREATMENT-RELATED MORBIDITY IN PATIENTS WITH TESTICULAR CANCER

## 1. INTRODUCTION

Testicular germ cell tumours (TGCT) represent the most common solid malignancies among men aged 20 to 40 years. If detected in early-stage disease, cure rates lie between 90 - 100%, so the recent focus of clinical research has shifted towards the prevention of treatment-related complications. Especially in stage I seminoma, there is a debate whether patients profit from adjuvant therapy after orchiectomy to prevent relapse or if it is wise to keep them under active surveillance to reduce acute and long-term treatment-related complications. We therefore focused on the adjuvant treatment options in stage I seminoma and looked for differences regarding cardiovascular complications.

## 2. EPIDEMIOLOGY

Testicular cancer (TC) is the most common malignancy in men aged 20-40 [1]. While only 1% of all cancers occurring in 10-14-year-old boys are testicular cancers, they represent approximately 21,8% of all diagnosed tumours in 25-29-year-old men [2]. Bilateral occurrence is observed in only 1-2% of the cases [1][3].

## 3. INCIDENCE

A clear trend of increasing incidence in the majority of industrialized countries [4] as well as apparently a doubling of the whole global incidence has been observed over the last 30 years [5]. The Austrian incidence increased as well, with 161 cases of testicular cancer back in 1983 and 344 cases in 2012 [6].
According to the American Cancer Society 2016, the lifetime chance to develop testicular cancer is about 1 in 263, the risk of dying from it about 1 in 5.000 [7]. Studies have shown that geographical and ethnical differences have an impact on the incidence of testicular cancer [8]. The age-standardized incidence has massively increased in European countries in contrast to Asia. While there are 15.2 new diagnoses per 100.000 men in Scandinavian countries every year, Japan only reports 0.8 per 100.000. Even within the same countries, there are differences noted, e.g. in the US between Caucasian men with an incidence of 5.4 and African America with only 1.3 per 100.000 [9]. Including all adolescent and adults over the time period from 1975-2000, the highest incidence of testicular cancer has been observed in “Whites, non-Hispanic”, while “African American/Blacks” had the lowest (Figure 1) [2]. Moreover, Torre et a. discovered that according to the cumulative risk of incidence, men in developed countries are 4 times more likely to get testicular cancer than men from less developed areas [10].

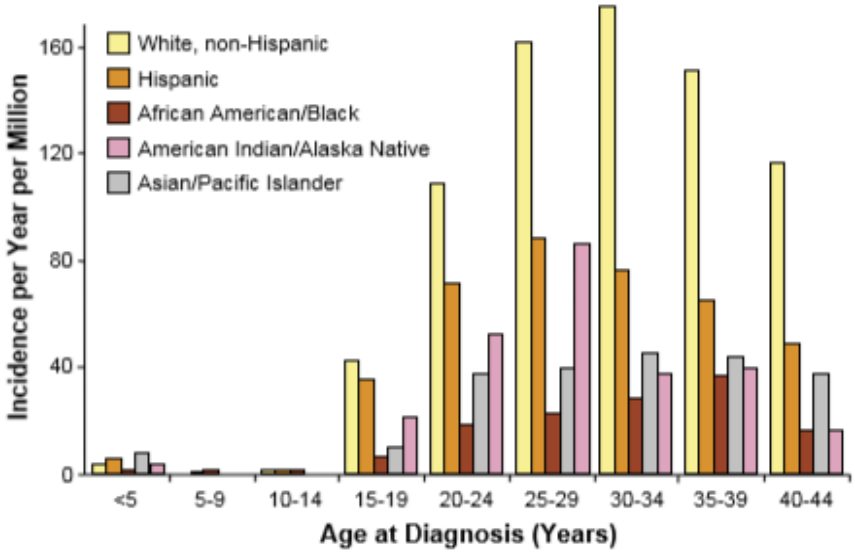



**Figure 1: "Incidence of Testicular Cancer in Males by Race/Ethnicity, SEER 1990-2000." [2]**

## 4. RISK FACTORS

According to Bob Djavan et al, known risk factors for testicular cancers are cryptorchidism and Klinefelter syndrome, as well as having a first or second grade relative with testicular cancer, testicular cancer in the contralateral testis or a testicular intraepithelial neoplasia (TIN) [3].

### 4.1. Cryptorchidism (also referred to as maldescended testis)

A maldescended testis is the most definite established risk factor for testicular cancer. The risk is 4-8 times higher if suffering from Cryptorchidism, even though the mechanism is unclear [5].

### 4.2. Testicular cancer in the contralateral testis

In a study from Osterlind et al., 2.6% of the 2850 men diagnosed with TC developed a contralateral testicular tumour. They estimated a cumulative risk of 5.2% to develop cancer in the contralateral testis within 25 years after the first diagnosis [11]. Colls et al. further published that the relative risk (RR) of developing a tumour in the contralateral testis is 27.5 times higher than in age-matched peers [12].

### 4.3. Testicular microlithiasis

Testicular microlithiasis (TM) are multiple 1-3mm microcalcifications composed of hydroxyapatite, spread within the parenchyma of the testis. Usually, they are just an incidental finding during a sonography examination of the scrotum and not a risk factor per se. According to Tan et al., TM was, in presence of risk factors, associated with a considerably higher risk of simultaneous TGCT and intratubular germ cell neoplasia (IGCN) [13]. However, studies also showed that microlithiasis is often associated with known and proven risk factors like cryptorchidism and infertility. The prevalence for microliths in patients having a germ cell tumour is 15-45%. Furthermore, in up to 20% of TGCT cases, microlithiasis is found in the contralateral testis [14].

### 4.4. Family history

Even though there is an increased risk for having testicular cancer if a family member already developed one, specific genetic factors have not been identified yet [5]. A men's risk of getting testicular cancer is 5 times higher if his brother was already diagnosed with the same [1]. Some studies suggest that the risk is even higher. Hemminki and Bowang published a 7,6 fold higher risk if the brother and 3,8 fold higher risk if the father had testicular cancer [15].

### 4.5. Other factors

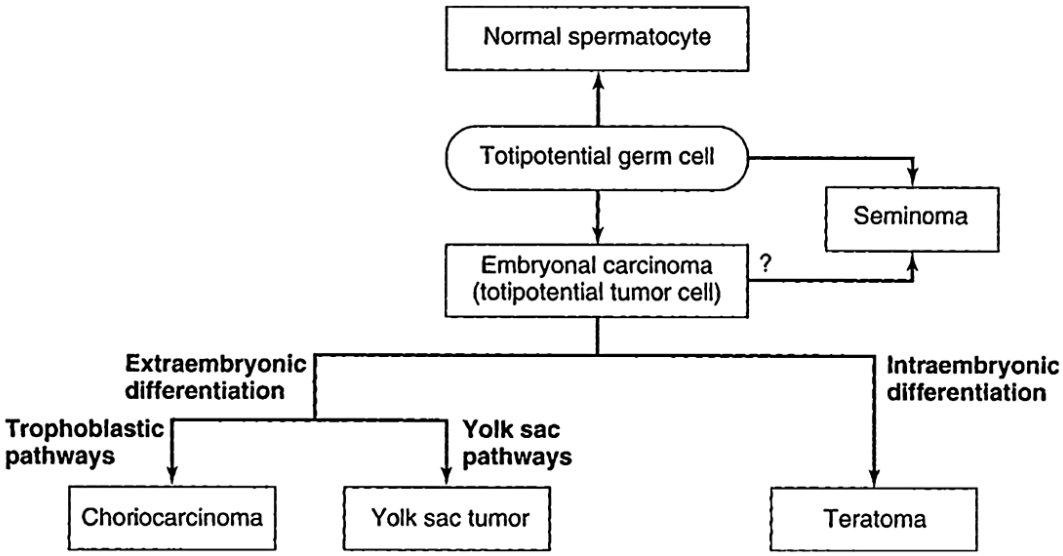
Heat is known to induce apoptosis in germ cells through p53. Low scrotal temperature leads to stabilization of p53 due to a heat-shock protein and prevents apoptosis. A dysregulation of this pathway could explain the connection between cryptorchidism or a sitting profession and the occurrence of testicular cancer [8].

## 5. HYPOTHESIS OF TGCT DEVELOPMENT

The development of TGCT starts within the male fetus before birth. Normally, male germ cells, which are totipotent during embryonal development, differentiate and become spermatocytes. Unfortunately, if there is a defect in that pathway, germ cells can evolve into totipotential tumour cells – seminoma or embryonal

carcinoma. If those tumour cells undergo further differentiation, other types of TGCT can occur. As you can see in Figure 2, the embryonal carcinoma can develop into a teratoma if choosing the intraembryonic pathway or into choriocarcinoma or yolk sac tumour if taking the extraembryonic differentiation. This display of pathways explains why specific histological types produce particular tumour markers [16].

**Figure 2: "Tumourigenic model for germ cell tumours of the testis" [16]**




## 6. CIS – Carcinoma in situ

The carcinoma in situ (CIS), also called testicular intraepithelial neoplasia (TIN), is a common precursor for TGCT [17]. Frequent observations of CIS surrounding invasive cancer within the adjacent parenchyma in 90% of cases and the findings of invasive testicular cancer in patients previously diagnosed with CIS underline that theory [18]. The CIS cells seem to be present at the time of birth, stay steady throughout infancy and then start to proliferate during puberty. This awakening of preexisting cells is probably caused by hormonal stimulation, which leads to successive progression into overt germ cell tumours. It is speculated that every man who harbors CIS will eventually develop an invasive tumour. The estimated risk for that transformation of untreated CIS within the next 5 years is 50%, the next 7 years 70% [17].

Moreover, CIS is found in 2-4% of men with cryptorchidism, in the contralateral

testis of 5% of men with TGCT but not even in 1% of the normal population. This prevalence seems to correspond pretty well with the lifetime risk of TGCTs [29].

## 7. WHO CLASSIFICATION OF TESTICULAR TUMOURS

The World Health Organization's (WHO) Classification is the currently used standard classification for testicular cancer. The classification of 2016 separates testicular tumours into two main groups, based on whether they develop out of a germ cell neoplasia in situ or not.

**"Germ cell tumours derived from germ cell neoplasia in situ:**

(1) Non-invasive germ cell neoplasia
   a. Germ cell neoplasia in situ
   b. Specific forms of intratubular germ cell neoplasia

(2) Tumours of one histological type (pure forms)
   a. Seminoma
   b. Seminoma with syncytiotrophoblastic cells
   c. Non-seminomatous germ cell tumours
   d. Embryonal carcinoma
   e. Yolk sac tumour, postpubertal-type
   f. Trophoblastic tumour
      i. Choriocarcinoma
      ii. Non-choriocarcinomatous
         - Trophoblastic tumours
      iii. Placental site trophoblastic tumour
      iv. Epithelioid trophoblastic tumour
      v. Cystic trophoblastic tumour
   g. Teratoma, postpubertal-type
   h. Teratoma with somatic-type malignancy

(3) Non-seminomatous germ cell tumour of more than one histological type
   a. Mixed germ cell tumours

(4) Germ cell tumours of unknown type

**Germ cell tumours unrelated to germ cell neoplasia in situ:**

(1) Spermatocytic tumour
(2) Teratoma, prepubertal-type
    a. Dermoid cyst
    b. Epidermoid cyst
    c. Well-differentiated neuroendocrine tumour (Monodermal teratoma)
(3) Mixed teratoma and yolk sac tumour, prepubertal-type
(4) Yolk sac tumour, prepubertal-type **”** [19]

The most commonly occurring testicular cancers are testicular germ cell tumours (TGCT). They account for 95% of all testicular cancers and we therefore focused our study on TGCT patients only. TGCT can be divided into seminoma and nonseminoma. The separation between those two main types is relevant because, depending on the histological components, there are different prognosis and therapy options. TGCT composed of more than one type of tissue count as nonseminoma and are treated with the same regimens [3]. The right testis has a slightly higher incidence than the left one (1.25:1), which is explained by its later descensus [8].

## 7.1. SEMINOMA

With approximately 50%, the pure seminoma is the most common type of germ cell tumour and occurs mainly in men between 30 and 50 years. Only 5% of the patients are over 60 and less than 0,5% haven’t hit puberty at the time of diagnosis [20][8].
Most of the time, a painless enlargement of the testis is the first symptom. Sonographic imaging usually shows a homogeneous hypoechoic and well-defined tumour, either multinodular or lobulated.
Initially, seminoma metastasize lymphatic into the para-aortic lymph nodes and later on, further invade the mediastinal and supraclavicular nodes. After that, haematogenous dissemination can take place, which may lead to metastasis in liver, lung, as well as bones and other organs [21].
Another manifestation is the “burned-out seminoma”. This form of appearance

occurs after an inflammatory tumour reaction which can possibly result in a complete destruction of a tumour with only a scar left thereafter [8].
About 80% of patients with seminomatous germ cell tumour (SGCT) are diagnosed with clinical stage (CS) I disease [20]. Warde et al have identified tumour size ≥4cm and invasion of rete testis as independent prognostic markers for an increased risk of relapse in a retrospective analysis [22]. However, there exist controversial data regarding validation of these risk factors in prospective studies. Since at least the negative predictive value of these two factors has been prospectively confirmed, rete testis infiltration and tumour size ≥4cm are proposed as risk factors for occult metastases by the European Germ-Cell Cancer Consensus Group (EGCCCG) [23]–[25]. Without any present risk factors, reported 5-year relapse rate is 12,2%, in patients with one or two risk factors the relapse rate ranges from approximately 16 to 32% [22]. For patients without any risk factors, active surveillance is the preferred treatment strategy because unnecessary treatment-related complications can be avoided. If risk factors are present, the patient should be educated about his risk of relapse and adjuvant treatment options.

## 7.2. NONSEMINOMA

The term nonseminoma (NS) includes every type of germ cell tumour that consists of something other or more than only seminoma tissue. This group represents 50% of all germ cell tumours with combined nonseminoma (mixed germ cell tumours) being as frequent as the pure components being presented below. Therefore, when histologically analyzed, this group shows a much more complex composition. The typical age for nonseminoma is 20-30 years, however, in contrast to seminoma, 4% already occur before puberty [20][8].

### 7.2.1. Embryonal carcinoma

This type of nonseminoma is the second most common germ cell tumour type (14-20%) [8]. The incidence of the embryonal carcinoma (EC) has its peak at the age of around 30, which is 10 years before the seminoma peak. It can occur in a pure form or as a component in more than 80% of germ cell tumours with a mixed

histological type. Some men seem to have a history of unresolved trauma in the affected testis.
Most of the time, the first symptoms are a painless swelling of the testis. Moreover, due to the tendency to grow faster, the embryonal carcinoma is more likely to present with pain than seminoma [21].
According to the theory mentioned above, it is built out of pluripotent stem cells and the origin of all other nonseminoma types. However, in contrast to other nonseminoma, the embryonal carcinoma is very malignant [8]. Its large, undifferentiated tumour cells have an epithelial appearance and are similar to cells forming the very early embryos inner cell mass. In the adjacent tissue of the testis, there is often more or less necrotic, sometimes calcified intratubular embryonal carcinoma present. Lymphatic and vascular invasion (LI, VI) are also common and need to be carefully differentiated from intratubular invasions [21].

### 7.2.2. Yolk sac tumour

The yolk sac tumour (YST) mimics the embryonal yolk sac, with cells having a variety of different appearances like papillary, glandular, solid or microcystic [26]. Pure yolk sac tumours make only 2% of all germ cell tumours but account for 75% of all tumours developing during infancy [8]. Normally, the tumour presents at the age of 16-17 months, however, rarely the development can delay up to eleven years [21]. In contrast, pure yolk sac tumours uncommonly occur later in life. In adults, YST only evolve in combination with other nonseminoma [8] as a part of about 40% of all mixed germ cell tumours.
In general, 90% of the patients present with an asymptomatic mass. At the time of diagnosis, approximately 10-20% of the children have already metastasis [21].

### 7.2.3. Choriocarcinoma

The choriocarcinoma (CC) belongs to the trophoblastic tumours and is, per definitionem, composed of both cytotrophoblasts and syncytiotrophoblasts [26]. Only less than 0,5% of all germ cell tumours are pure choriocarcinoma.
In contrast to other tumours, the choriocarcinoma does not have its own stroma and therefore starts to digest pre-existing vessels in order to get its supply. This

special mechanism accelerates the process of haematogenous dissemination and can lead to lethal bleedings due to lung metastases [8]. The average age of men with choriocarcinoma is 25-30 years and they present with symptoms like haemoptysis, dyspnea, anemia or melena, most likely caused by metastasis [21]. Occasionally, the development of hyperthyroidism is reported due to a cross-reactivity between human chorionic gonadotropin (hCG) and the thyroid stimulating hormone. The clinical examination does not have to show any mass in the testes. Either the primary tumour can be too small or the tumour has already totally regressed, leaving its metastases behind.
Since the CC has often already disseminated before diagnosis, most of the patients suffer from an advanced stage disease, causing the worse prognosis of this TGCT [21].

### 7.2.4. Teratoma

Teratoma rarely occur in their pure form and are descendants of all three germ layers - ectoderm, mesoderm and endoderm. They represent 3-7% of all germ cell tumours and are deduced from malignant, totipotent precursor cells [8][26].
They are differentiated into the mature type, organized out of well-differentiated tissue and the immature type, composed of fetal-like tissue [21].
Teratoma occur either during childhood, with 65% developing within the first two years of life or in young adults. The incidence in children is about 24-36%, while adults have a frequency of 2,7-7% for pure teratoma and 47-50% for occurrence in mixed germ cell tumours.
Patients mostly present with swelling or symptoms caused by metastases.
While teratoma occurring in the first, praepubertal age group are considered benign, postpubertal developing teratoma spread and have metastasis in 22-37% of cases [21]. Unfortunately, teratoma are insensitive to both, chemotherapy and radiotherapy [27]. Therefore, surgery is the treatment of choice.

## 8. TNM CLASSIFICATION

The Tumour-Nodes-Metastasis system (TNM) is very common and an internationally used system to classify solid tumours. The following structure is adopted from the 7th Edition of "TNM Staging System for Testis Cancer" [28], published by the American Joint Committee on Cancer (AJCC) in 2010. In this nomenclature, T is used to give information about the extent of the tumour. N provides knowledge about whether nearby lymph nodes are already inhibited and which diameter they have. M represents metastasis, giving an insight on tumour spread and localization [29][30].

**Table 1: "Primary Tumour" [28]**

| **Primary Tumour (T)** | |
|---|---|
| pTX | Primary tumour cannot be assessed |
| pT0 | No evidence of primary tumour (e.g. histologic scar in testis) |
| pTis | Intratubular germ cell neoplasia (carcinoma in situ) |
| pT1 | Tumour limited to the testis and epididymis without vascular/ lymphatic invasion; tumour may invade into the tunica albuginea but not the tunica vaginalis |
| pT2 | Tumour limited to the testis and epididymis with vascular/lymphatic invasion, or tumour extending through the tunica albuginea with involvement of the tunica vaginalis |
| pT3 | Tumour invades the spermatic cord with or without vascular/lymphatic invasion |
| pT4 | Tumour invades the scrotum with or without vascular/lymphatic invasion |

**Table 2: "Regional Lymph Nodes" [28]**

| **Regional Lymph Nodes (N)** | |
|---|---|
| **Clinical (N) or Pathologic (pN)** | |
| 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 5cm in greatest dimension; or multiple lymph nodes, any one mass greater than 2 cm but not more than 5 cm in greatest dimension |

| | |
|---|---|
| N3 | Metastasis with a lymph node mass more than 5 cm in greatest dimension |

**Table 3: "Distant Metastasis" [28]**

| **Distant Metastasis (M)** | |
|---|---|
| M0 | No distant metastasis |
| M1 | Distant metastasis |
| M1a | Nonregional nodal or pulmonary metastasis |
| M1b | Distant metastasis other than nonregional lymph nodes and lung |

## 9. STAGING

For prognosis and therapy decisions, the staging according to the International Germ Cell Cancer Collaborative Group (IGCCCG) classification (Table 4) is more relevant than the classic TNM classification as it also takes other factors like tumour markers into account.
However, it is important to add to this table that there is no poor prognostic group for seminoma, only for nonseminoma.

**Table 4: "Post-orchiectomy staging of metastatic seminoma and non-seminoma according to AJCC/Union for International Cancer Control (UICC) and IGCCCG classification" [20]**

| Clinical stage | TNM (AJCC/UICC) | | | Serum tumour markers (S) to be determined after orchiectomy | | | | IGCCCG prognostic group |
|---|---|---|---|---|---|---|---|---|
| | T[a] | N | M | S | LDH | HCG | AFP (ng/ml) | |
| IS | $T_{any}$ | N0 | M0 | S1 | <1.5xN and | <5000 and | <1000 | Good |
| | | | | S2 | 1.5–10xN or | 5000–50 000 or | 1000–10 000 | Intermediate |
| | | | | S3 | >10xN or | >50 000 or | >10 000 | Poor |
| IIA | $T_{any}$ | N1 | M0 | S0 | Normal | Normal | Normal | Good |
| | | (≤2 cm) | | S1 | <1.5xN and | <5000 and | <1000 | |
| IIB | $T_{any}$ | N2 | M0 | S0 | Normal | Normal | Normal | Good |
| | | (>2–5 cm) | | S1 | <1.5xN and | <5000 and | <1000 | |
| IIC | $T_{any}$ | N3 | M0 | S0 | Normal | Normal | Normal | Good |
| | | (>5 cm) | | S1 | <1.5xN and | <5000 and | <1000 | |
| IIIA | $T_{any}$ | $N_{any}$ | M1a | S0 | Normal | Normal | Normal | Good |
| | | | | S1 | <1.5xN and | <5000 and | <1000 | |
| IIIB | $T_{any}$ | N1-3 | M0 | S2 | 1.5–10xN or | 5000–50 000 or | 1000–10 000 | Intermediate |
| | | $N_{any}$ | M1a | | | | | |
| IIIC | $T_{any}$ | N1-3 | M0 | S3 | >10xN or | >50 000 or | >10 000 | Poor |
| | | $N_{any}$ | M1a | S3 | >10xN or | >50 000 or | >10 000 | Poor |
| | | | M1b | $S_{any}$ | Any level | Any level | Any level | Poor |
| | Primary mediast EGGCT | $N_{any}$ | $M_{any}$ | $S_{any}$ | Any level | Any level | Any level | Poor |

## 10. PRESENTATION

TGCT present mostly as a unilateral testicular swelling or nodule [29]. Typically, the mass is firm, non-tender and can easily be separated from the epididymis. However, it may be accompanied by a hydrocele, which can camouflage the tumour, making the diagnosis more difficult [16].

Only 10 to 20% of patients describe the malignant growth as painful. However, about 40% mention a dull ache and a feeling of heaviness and/or hardness of the testis [29]. Further 11% suffer from back and flank pain, while 7%, mainly patients with nonseminoma, present with gynecomastia [9]. Unfortunately, due to the lacking awareness of young men, the time between the patients first recognition of the tumour mass and the orchiectomy as first treatment extents between 3-6 months. This is even more unsettling knowing that the incidence of metastasis correlates with this delay [16].

Even though testicular cancer occurs in typical age groups and physicians should

be highly suspicious, it is sometimes still mistaken for other medical conditions like epididymitis. Furthermore, if the tumour is already in an advanced stage and spread, symptoms like back pain could be mistaken as vertebral disc problems.

Moreover, there is a minority of those tumours primary arising outside the scrotum [25]. If the tumour is grown extragonadal, the symptoms are harder to diagnose since they vary with the site. Some possible and common extragonadal sites are

- pulmonary metastasis, presenting with cough, dyspnea and hemoptysis;
- retroperitoneal adenopathy, causing nausea, weight loss and abdominal or back pain;
- mediastinal disease, leading to a superior vena cava syndrome.

Really rare symptoms are e.g. headache and seizure caused by brain metastasis, bone pain because of bone metastasis or gynecomastia, caused by elevated ß-human chorionic gonadotropin.[29].

## 11. DIAGNOSTIC

A suspicious testicular mass should initially be evaluated with inspection and palpation, ultrasound, chest x-ray and the measurement of tumour markers. Furthermore, a transillumination can be used to differentiate between a testicular mass and a hydrocele. Adjacent, radical inguinal orchiectomy is the next step, being both a diagnostic and therapeutic procedure. It is not only a local tumour control but also necessary for the histological analysis of the tumour type, which is mandatory for any further treatment. Subsequently, an abdominopelvic computed tomography (CT) should be prompted if the presumptive diagnosis “testicular cancer” is confirmed. A reevaluation of the tumour markers should also be made in order to get guidance on how successful the orchiectomy as a treatment worked and whether further therapy is needed [29]. Moreover, the tumour has to be staged and, in case the patients have high-risk features for contralateral TIN like a testicular volume <12ml, poor spermatogenesis, an age younger than 40 or history of cryptorchidism, a contralateral biopsy may be performed [9].

# 12. TUMOUR MARKERS

Tumour markers for testicular cancer are the oncofetal proteins alpha-fetoprotein (AFP) and human chorionic gonadotrophin **(**hCG), which are usually produced during the fetal period, and the cellular enzyme lactate dehydrogenase (LDH), which is not as specific as the other two markers but still important for follow up. The tumor markers are usually used in the framework of diagnosis, staging and prognosis, as well as to monitor treatment response [31].

## 12.1. AFP – Alpha-fetoprotein

The normal serum level of the alpha-fetoprotein is <15ng/ml with a half-life time of 3-5 days [31]. Normally, it is synthesized by either fetal yolk sac, intestine or liver [21]. Within the tumour, it is produced by trophoblastic elements and occurs in 50-70% of all immature teratoma and yolk sac tumours. That is the reason why an elevated AFP found in patients with diagnosed seminoma strongly suggest that this tumour cannot be a pure seminoma [31]. However, it is also elevated in hepatocellular cancer, benign liver diseases and neuronal dysraphy [32].

## 12.2. hCG – human chorionic gonadotrophin

The ß-subunit of hCG is the used laboratory value for testicular cancer, with normal serum levels <5mIU/ml and a half-life time of 24-36h.
In contrast to AFP, hCG is produced by syncytiotrophoblastic elements of the tumour and occurs in 100% of all choriocarcinoma, 40% of immature teratoma and 10% of seminoma [31].

## 12.3. LDH – Lactate dehydrogenase

LDH is elevated in about 10-20% of all seminoma cases [31]. It is very useful for treatment response monitoring and there further seems to be a direct relationship between the level of LDH and the tumour burden of the patient [21].
However, LDH is also elevated in leukemia, lymphoma, hemolysis as well as liver and lung diseases and therefore not too specific [32].

All the markers mentioned are used to access progress and development. They are often reevaluated throughout the treatment process – first in line with the diagnosis, then approximately 1-2 weeks after the orchiectomy and further during treatment [31]. Their monitoring should be carried on until either a normalization, a progression or a plateau development is found [20].
It is important not to mistake the normalization or absence of markers after orchiectomy with prove of nonexistent metastasis or cure. Furthermore, the elevation of markers does not automatically mean the patient has a metastatic disease since the markers can, in rare cases, also be elevated due to liver dysfunction or other diseases [31].

## 13. IMAGING

The scrotal ultrasound is the fastest and easiest way for accurate assessment of a testicular tumour. Not only is it possible to get information about location and size of the mass, ultrasound can be also used to differentiate between tumour and hydrocele or epididymal pathology. Therefore, ultrasound is the first imaging procedure performed and usually leads to an orchiectomy. Afterwards, further techniques are used for staging and prognosis [16].

- Chest X-ray
    - is used to evaluate pulmonary metastasis
- Computed tomography (CT)
    - is the most effective method for staging. In order to find extragonadal metastasis, chest, abdomen and pelvis are scanned.
- Magnetic resonance imaging (MRI)
    - can be used to provide information if the ultrasound should be indefinite. Furthermore, if already mentioned symptoms like headache, seizure and neurological deficits occur, MRI can be used to determine the existence of brain metastasis.
- Positron emission tomography (PET)
    - has no use for the primary tumour investigation or staging. However, may have limited efficiency to characterize residual mass.

[29]

## 14. PROGNOSIS

The IGCCCG classification is a prognostic classifying of testicular cancer, grading it into three prognostic groups – good, intermediate and poor (Table 5).

There are three groups of prognostic factors, the essential factors being the ones used for the IGCCCG separation:

– Essential prognostic factors: Essential factors are tumour-related factors and include the histological type, TNM-categories, tumour markers and the site of metastases

– Additional prognostic factors: Additional factors are rate of tumour marker decline and the host and environmental factors delay in prognosis and expertise of the physician.

– New and promising factors: Those factors are limited to the tumour, being the copy number of I(12p), the apoptotic index and both p53 and Ki67 [9]

**Table 5: "Prognostic classification of the IGCCCG - International Germ Cell Collaborative Group" [29]**

| PROGNOSIS | SEMINOMA | NONSEMINOMA |
|---|---|---|
| **Good** | - any primary site.<br>- no nonpulmonary visceral metastases.<br>- normal AFP;<br>- any concentration of HCG;<br>- any concentration of LDH<br>(90% of all seminoma) | - testis/retroperitoneal primary.<br>- no nonpulmonary visceral metastases.<br>- AFP <1,000 mg/mL;<br>- HCG <5,000 IU/L (1,000 mg/mL);<br>- LDH <1.5 × ULN<br>(56% of all nonseminoma) |
| **Intermediate** | - any primary site.<br>- no nonpulmonary visceral metastases.<br>- normal AFP;<br>- any concentration of HCG;<br>- any concentration of LDH<br>(10% of all seminoma) | - testis/retroperitoneal primary.<br>- no nonpulmonary visceral metastases.<br>- AFP≥1,000 and ≤10,000 ng/mL or<br>- HCG ≥5,000 mIU/mL and ≤50,000 IU/L<br>- LDH =1.5 × NL and ≥10 × NL<br>(28% of all nonseminoma) |

| | | |
|---|---|---|
| **Poor** | no patients classified as poor prognosis | - mediastinal primary or<br>- nonpulmonary visceral metastases or<br>- AFP >10,000 ng/mL or<br>- HCG >50,000 IU/L (10,000 ng/mL) or<br>- LDH >10 × ULN<br>(16% of all nonseminoma) |

LDH, lactate dehydrogenase; HCG, human chorionic gonadotropin; AFP, α-fetoprotein; ULN, upper limit of normal; NL, normal limit, IU, international unit

**Table 6: "Expected Survival for Disseminated Disease" [29]**

| | 5-year progression-free Survival (%) | | 5-year overall survival (%) | |
|---|---|---|---|---|
| PROGNOSIS | **SEMINOMA** | **NONSEMINOMA** | **SEMINOMA** | **NONSEMINOMA** |
| **GOOD** | 82 | 89 | 86 | 92 |
| **INTERMEDIATE** | 67 | 75 | 72 | 80 |
| **POOR** | -- | 41 | -- | 48 |

[29]

## 15. THERAPY

Therapy options depend on stage and prognosis of the cancer. In metastasized disease often a multidisciplinary team discusses the best therapy options and the order in which they will be administered [33]. It is important to inform the patients about all the possible treatment modalities available, their overall outcome and their acute and late toxicity [20]. Furthermore, they should be educated about infertility and sperm banking if they still wish to father children.

In stage I disease, prognostic factors can help counseling the patient so that he can decide whether he feels more comfortable with an adjuvant treatment or active surveillance. While therapy will lower the risk of recurrent diseases, it could cause acute and late toxicity or, even decades later, second malignancies. Active surveillance, on the other hand, results in a higher risk of relapse after surgery [20]

## 15.1. Surgical Therapy

There are two options for surgical therapy – either the radical inguinal orchiectomy or an organ-preserving operation.

### 15.1.1. Orchiectomy

Orchiectomy is the standard procedure for testicular cancer and as a rule performed before any other treatment [34]. It is indicated whenever there is a suspicious mass located within the testis. If there is doubt about the malignancy, the mass should be excavated and a histological instantaneous section should be performed [35]. Furthermore, there should always be a tumour marker screening before and after the surgery for reevaluation [34].
However, if the tumour already spread and there are major complications caused by metastasis, neoadjuvant chemotherapy should be performed immediately even before removing the testis. Depending on the remission under therapy, the orchiectomy can be done between the second and third cycle of chemotherapy [35]

### 15.1.2. Organ-preserving surgery

This approach is only an alternative for patients with small tumours and is highly experimental. It is therefore only recommended to use in clinical trials. However, if TIN is found in the remaining tissue of the testis, adjuvant radiotherapy is highly recommended [34].

## 15.2. Chemotherapy

There are several different chemotherapy regimens available, for testicular cancer, however, there are only a few currently used (Table 7).
The BEP schemata consist of bleomycin, etoposide and cisplatin and are the most widely used regimens for testicular cancer. Patients with a good IGCCCG prognosis receive three cycles, intermediate and poor prognosis are treated with four. Patients with contraindications to bleomycin and good prognosis can receive four cycles of only etoposide and cisplatin (EP). If men have contraindications and

an intermediate or poor prognosis, they are treated with four cycles of VIP/PEI – cisplatin, etoposide and ifosfamide. This regime is also used for salvage chemotherapy.

Further conventional salvage chemotherapy doses are four cycles of Paclitaxel/Ifosfamide/Cisplatin (TIP) or Vinblastine/Ifosfamide/Cisplatin (VeIP). The last two regimens Paclitaxel/Ifosfamide-Carboplatin/Etoposide (TI-CE) and Carboplatin/Etoposide (CE) are rarely used. Two cycles of TI are given before stem cell harvesting, followed by three cycles CE afterwards as a high dose treatment [20].

**Table 7: "Chemotherapy regimens in metastatic seminoma and non-seminoma"[20]**

| | | |
|---|---|---|
| BEP[a] | (Repeat cycles every 3 weeks) | |
| Cisplatin | 20 mg/m$^2$ | Day 1–5 |
| Etoposide | 100 mg/m$^2$ | Day 1–5 |
| Bleomycin | 30 mg | Day 1, 8, 15 |
| EP[b] | (Repeat cycles every 3 weeks) | |
| Cisplatin | 20 mg/m$^2$ | Day 1–5 |
| Etoposide | 100 mg/m$^2$ | Day 1–5 |
| VIP/PEI[c] | (Repeat cycles every 3 weeks) | |
| Cisplatin | 20 mg/m$^2$ | Day 1–5 |
| Etoposide | 75 mg/m$^2$ | Day 1–5 |
| Ifosfamide | 1.2 g | Day 1–5 |
| TIP[d] | (Repeat cycles every 3 weeks) | |
| Paclitaxel | 250 mg/m$^2$ | Day 1 |
| Cisplatin | 25 mg/m$^2$ | Day 2–5 |
| Ifosfamide | 1.5 g | Day 2–5 |
| VeIP[e] | (Repeat cycles every 3 weeks) | |
| Vinblastine | 0.11 mg/kg | Day 1 + 2 |
| Ifosfamide | 1.2 g/m$^2$ | Day 1–5 |
| Cisplatin | 20 mg/m$^2$ | Day 1–5 |
| TI-CE[f] | (TI cycles 1–2 every 2 weeks) | |
| Paclitaxel | 200 mg/m$^2$ | Day 1 |
| Ifosfamide | 2.0 g | Day 2–4 |
| | (CE cycles 3–5 every 3 weeks) | |
| Carboplatin | AUC = 7 | Day 1–3 |
| Etoposide | 400 mg/m$^2$ | Day 1–3 |
| CE[g] | (Two cycles, may be preceded by VeIP) | |
| Carboplatin | 700 mg/m$^2$ | Day 1 |
| Etoposide | 750 mg/m$^2$ | Day 1–3 |

### 15.3. Radiotherapy

Radiotherapy is, besides surgery and chemotherapy, a very effective treatment for cancer [9]. It is involved in both curative and palliative cancer treatment and can be applied either external or as an internal therapy. Commonly, it is administered in daily fractions with a predetermined total dose depending on the tissue tolerance and sensitivity of the tumour [36]. After having a prophylactic radiological therapy to the paraaortic lymph nodes, the recurrence rate for CS I seminoma declines to about 4%. Nowadays the administered adjuvant dose to the paraaortic lymph nodes is 20 Gray (Gy), since prospective studies have shown that 20 Gy are as effective as 30 Gy [37][38].

### 15.4. Active surveillance

Watchful waiting is a common regime for patients with testicular cancer stage I. It can spare them side effects from possibly unnecessary treatment since about 80% of men with CS I are cured after the initial surgery [37]. However, it is important to attend regular follow up examinations and evaluations during the active surveillance. There are precise guidelines for the follow-up of both, seminoma and nonseminoma.

A study form Warde et al. identified two independently statistically significant prognostic factors to predict relapse in patients with stage I seminoma – the size of the tumour and the invasion of the rete testis. If the tumour is bigger than 4cm, the patients are twice as likely to get a relapse as men are with smaller cancer. Furthermore, having an invasion of the rete testis increases the risk about 1.7 times. In their study population, only 12.2 % of men without any of those two factors relapsed within the following 5 years. However, in the groups having one or both factors, the relapse rate was approximately 16% and 31.5%. Their conclusion was that both factors are important risk factors for recurrence and that the risk of a relapse is 3.4 times higher if a patient has both risks [22].

However, given the good outcome of recurrent diseases, active surveillance is a reasonable option of treatment, even for patients with both risk factors [37].

For stage I nonseminoma, the most important factor for the prognosis of occult metastatic diseases is vascular invasion [39]. On that account, VI is used to

separate stage I nonseminoma into a low-risk and a high-risk group. Due to the relapse risk of 20% for stage I low-risk patients, active surveillance is the preferred treatment for this group. If vascular invasion is present, the relapse risk is 50% but can be reduced to 3-4% with administration of one or two adjuvant cycles of BEP chemotherapy [20].

# 16. TREATMENT GUIDELINES ACCORDING TO HISTOLOGICAL SUBTYPE

## 16.1. SEMINOMA

**Table 8: "Standard treatment strategies for seminoma" [20]**

| | **Stage I** | **Stage IIA** | **Stage IIB/IIC/III** |
|---|---|---|---|
| **First line** | Low risk*<br>Preferred :<br>• Surveillance<br><br>Alternatively :<br>▪ Carboplatin x 1 (AUC 7)<br>▪ Radiotherapy (20 Gy)<br><br>High risk#<br>Preferred:<br>• Surveillance<br>• Carboplatin x 1 (AUC 7)<br>Alternatively:<br>• Radiotherapy (20 Gy) | ▪ BEPx3 (or EPx4)<br><br>▪ Radiotherapy | ▪ BEPx3-4 (VIPx3-4) |
| **Residual disease** | n/a | Observation<br>Consider biopsy or resection of lesion > 3 cm, particularly if PET positive | |
| **Relapse** | Post-surveillance/carboplatin<br>▪ Localised: Radiotherapy<br>▪ Otherwise: BEPx3-4<br><br>Post-radiotherapy<br>▪ BEPx3 (EPx4) | Salvage chemotherapy<br><br>In localised lesions: consider radiotherapy<br><br>Surgery in case of a single resectable lesion | |

* low risk: absence of rete testis invasion and tumour <4cm
# high risk: rete testis invasion or tumour ≥4cm

### 16.1.1. Stage I Seminoma

This group represents approximately 80% of all patients presenting with seminoma. Unaffected by the chosen treatment strategy, the survival is almost 99%. This is why the priority for the treatment of patients with clinical stage I is to minimize acute toxicity and late treatment-related complications.
Tumour size ≥4cm and invasion of the rete testis have been identified as independent prognostic markers for an increased risk of relapse in a retrospective analysis by Warde et al. If risk factors are found in the orchiectomy specimen, patients should be counseled regarding adjuvant treatment options. Those options include adjuvant radiotherapy to para-aortic lymph nodes with a dose of 20 Gy or adjuvant chemotherapy with one single cycle of carboplatin at a dose of 7 x area under curve (AUC)[22][20].

### 16.1.2. Stage IIA Seminoma

The options for CS IIA are either a cisplatin-based chemotherapy with commonly 3 cycles BEP or radiotherapy with 30Gy [20]. The radiotherapy is homogeneously administrated with single doses of 2Gy. Targeted are the para-aortic and ipsilateral iliac nodal fields [34]. However, Tandstad et al. found that in the group of CS IIA seminoma, 10.9% of patients (3 of 29) treated with radiotherapy relapsed while none of the 73 patients receiving 3 cycles of BEP chemotherapy had a relapse [40].

### 16.1.3. Stage IIB/IIC Seminoma

Patients with stage IIB/IIC seminoma and good prognosis are typically treated with 3 cycles of BEP. Further treatment modalities are 4 cycles of EP, if patients have contraindications against bleomycin or radiation with 36 Gy, if the usage of chemotherapy in general is not reconcilable [20].

### 16.1.4. Stage III Seminoma

BEP chemotherapy is considered the preferable standard treatment. Depending on the IGCCCG prognosis, patients receive either three cycles if they have a good prognosis or four if their prognosis is intermediate. Alternatively, four cycles EP can be used for the good prognosis group and four cycles VIP for the intermediate patients if bleomycin can't be used due to contraindications [20].

### 16.1.5. Post-chemotherapy management

Patients who completely responded to the treatment do not need any further therapy. They will be followed-up according to guidelines [41]. If a patient has a residual tumour, a Fluorodeoxyglucose (FDG)-PET scan should be performed six or more weeks after the end of his chemotherapy. For a lesion bigger than 3cm, a PET scan is recommended, whereas, for a lesion smaller than 3cm, surveillance is preferred. If the PET scan is positive, a residual tumour is highly possible and a resection should be performed if possible [20].

## 16.2. NONSEMINOMA

**Table 9: "Standard treatment strategies for nonseminoma" [20]**

| | Stage I | Stage IIIII | | |
|---|---|---|---|---|
| | | Good | Intermediate | Poor |
| **First line** | Vascular invasion present<br>Preferred:<br>• Surveillance<br><br>Alternatively:<br>▪ 1-2xBEP<br>▪ RPLND (rarely)<br><br>Vascular invasion absent<br>Preferred:<br>▪ 1-2xBEP<br>▪ Surveillance<br>Alternatively:<br>▪ RPLND (rarely) | ▪ BEPx3 (EPx4)<br>▪ RPLND (if marker negative stage IIA) | ▪ BEPx4<br>▪ VIPx4 | ▪ BEPx4<br>▪ VIPx4 |
| **Residual disease** | n/a | Resection in case of lesion > 1 cm<br>Observation in case of lesion < 1 cm | | |
| **Relapse** | Post-surveillance or post-RPLND:<br>▪ BEPx3-4<br>Surgery in case of a single resectable lesion<br><br>Post-chemotherapy:<br>▪ Salvage chemotherapy<br>Surgery in case of a single resectable lesion | Salvage chemotherapy<br>Surgery in case of a single resectable lesion | | |

### 16.2.1. Stage I Nonseminoma

The survival rates of stage I nonseminoma are with 98-100% excellent. However, the group of CS I is separated into a low-risk group, defined by the absence of vascular invasion and a high-risk group with vascular invasion present [20]. According to the European Consensus Conference on germ cell tumours (GCT) in 2008, without receiving adjuvant treatment, patients with vascular invasion have a

48% risk of developing metastasis compared to a risk of only 14-22% in patients without VI [42].

### 16.2.2. Low-risk Stage I Nonseminoma

The standard treatment for the low-risk patients is surveillance. However, if due to any reasons surveillance is not feasible, one or two cycles of adjuvant chemotherapy with BEP can be given. Another option if both cannot be performed is the nerve-sparing RPLND, the retroperitoneal lymph node dissection [20].

### 16.2.3. High-risk Stage I Nonseminoma

The group of high-risk CS I has two standard treatment options, either surveillance with a relapse rate of 40-50%, or adjuvant chemotherapy. The survival is the same for both options, but still, patients treated with one or two cycles of BEP only have a relapse rate of only 3-4%. In case of contraindications to the standard therapy options, a nerve-sparing RPLND may be carried out in highly specified centers [20]. Tandstad et al. showed that one adjuvant BEP course reduces the relapse risk of both CS I nonseminoma with and without vascular invasion about 90%. Therefore, nowadays most centers only administer one adjuvant BEP cycle instead of two to reduce the risk of acute and long-term treatment-related complications [43].

### 16.2.4. Stage IIA (IIB) Nonseminoma, marker-negative

Metastatic nonseminoma should be treated in accordance with the recommendations of the IGCCG (Table 9).
Paraaortic lymph nodes with borderline normal size (close to 1cm) might not be metastasis, if marker negative, and therefore, two strategies exist to avoid over-treatment. A close follow-up until regression or progression can be performed with abdominal imaging every 6 weeks. In case of progressive disease, usually a curative chemotherapy with 3 cycles of BEP is the preferred treatment option. In

case of a single progressing lymph node with a negative tumour, nerve-sparing RPLND can be performed in highly specified centers.

Alternatively, a primary nerve-sparing RPLND can be performed. This option combines both, diagnostic and therapeutic approaches. Adjuvant chemotherapy with two cycles of BEP is given if vital tumour tissue is found in the specimen. In case the histology reveals a completely mature teratoma, only follow up is needed [20].

### **16.2.5.** Stage IS/II/III Nonseminoma

Patients with a good prognosis can be handled with either three cycles of BEP or, if there are any contraindications against bleomycin, with four cycles of EP. Intermediate and poor prognostic groups receive four cycles of BEP. If there are any bleomycin contraindications in these groups, four courses of VIP are the preferred alternative [20]. Furthermore, Fizazi et al. indicated that patients with a poor prognosis and an insufficient decline of tumour markers after the first course of BEP might benefit from an intensification of the dose [44].

### **16.2.6.** Post-chemotherapy management

Imaging and the determination of tumour markers should be carried out about four to eight weeks after patients received their last cycle of chemotherapy.
If there was a complete radiologic response and normalization of tumour markers to therapy, patients will be followed-up according to guidelines.

In case of residual lesions bigger than 1cm, a complete resection of all lesions is recommended. In case multiple visceral metastases are found, patients should be treated at specialized centers.
In case the resected specimens incorporate more than 10% of viable nonseminoma, two additional cycles of VIP chemotherapy should be considered [20].

# 17. TREATMENT-RELATED TOXICITY

The treatment-related complications depend on the treatment chosen and contain conditions form infertility to cardiovascular toxicity. Due to the growing knowledge, risk-adapted treatment strategies should be further explored and the toxicity of treatment should be incorporated into the choice of therapy modality.

## 17.1. FERTILITY

At diagnosis, numerous men with testicular cancer suffer from oligospermia. Performed orchiectomy further impairs spermatogenesis. Moreover, chemotherapy is known to have an impact on sperm production and men might experience fertility distress and thereby difficulties in reproduction. Almost all patients become oligospermic or azoospermic during the time of chemotherapeutic treatment. Fortunately, around 70-80% may recover full production within the following 5 years. Since surgery and chemotherapy influence sperm production, it is important to discuss sperm banking with all patients still wishing to father children especially if several cycles of chemotherapy are needed [29][45].

## 17.2. HYPOGONADISM

Male hypogonadism is, per definitionem, the decreasing of the serum testosterone levels under 8nmol/L. This condition is frequent in 11-35% of TGCT survivors. That is the reason why patients should be educated about signs and symptoms of low testosterone levels and, if diagnosed, offered a replacement to prevent sequelae [45]. There is not only evidence, that an androgen treatment for hypogonadism is beneficial for multiple target organs, Wang et al. and also de Haas et al. published, that survivors have an increased risk of metabolic syndrome (MS) if their testosterone level is <15nmol/L [46][47].

## 17.3. COMPLICATIONS OF THE RPLND

1-2% of the patients deciding on a retroperitoneal lymph node dissection will suffer from complications. Those can involve conditions like lymphocele, vascular

injuries, bowel perforation, pancreatitis, ejaculatory dysfunction or retrograde ejaculation [29].

### 17.4. SECONDARY MALIGNANCIES

Testicular cancer patients treated with cisplatin, etoposide or radiation have a 1.7 times higher risk for secondary malignancies [29]**.** A combination of chemo- and radiotherapy increases the risk threefold. It is especially high for gastrointestinal and urinary tract malignancies in the previous radiation fields.
While solid tumours occur more than a decade after the treatment, the chemotherapeutic induced leukemia usually emerges earlier [45]. Especially topoisomerase inhibitors like etoposide are associated with the risk of secondary leukemia. This elevated risk of developing a second malignancy may continue to exist until 35 years after finishing the chemotherapy or radiotherapy treatment. Travis et al. found that 35-year-old patients diagnosed with seminoma or nonseminoma have 40 years later a cumulative risk of 36% and 31% to develop a solid tumour. This means that 1 in 3 of these 75-year-old former patients got a solid cancer. In the general population, however, the cumulative risk was 23% with only 1 in 4 men getting a solid neoplasia [48].
Another cisplatin related disease pattern is the myelodysplastic syndrome, which can occur within 5-7 years after therapy with an alkylating agent. Eventually, this syndrome can progress to leukemia [29]**.**

### 17.5. PULMONARY TOXICITY

Fosså *et al.* reported, “the highest standardized mortality ratios for respiratory diseases were observed in men whose treatment included chemotherapy”. Moreover, they found statistically significant higher risks for death from not only respiratory diseases but also form all noncancerous causes, circulatory diseases and infections in men treated with chemotherapy [49].
Bleomycin, which is part of the most commonly used chemotherapy regime BEP, is known and feared for its pulmonary toxicity. The bleomycin-induced pneumonia (BIP) is caused by endothelial damage of the pulmonary lung vessels, determined by cytokines and free radicals induced by bleomycin. Eventually, it can even lead

to lung fibrosis. Most patients, however, recover after stopping the treatment or receiving corticosteroid treatment [50][51].
Sullivan et al discovered, that the demanding risk of lung toxicity was significantly associated with stage IV disease, age over 40 years, glomerular filtration rate (GFR) under 80ml/min before chemotherapy as well as cumulative bleomycin dose >300.000IU. All four proved to be statistically significant in multivariate analysis. The probability was between 5.3-11.4% for one risk factor, 11.5-32% for two and 32.5-50% for three. Within the two risk factor group, patients with GFR under 80ml/min and more than 300.000 IU bleomycin had the highest probability of suffering from bleomycin-induced pneumonia [52].

### 17.6. NEPHROTOXICITY

Cisplatin, the mainstay of systemic treatment in TGCT, can be associated with side effects on the kidneys. It can lead to a decreased glomerular filtration rate (GFR), in 20-30% of patients permanently [29]. Ramesh and Reeves found that cisplatin-induced nephrotoxicity is characterized by activation of proinflammatory cytokines and chemokines. Tumour necrosis factor (TNF)-α appears to be essentially involved in both the activation of the cytokine response as well as in the pathogenesis of cisplatin-induced renal injury. For their study, they injected mice with cisplatin, which led to profound renal failure. In addition, upregulation of TNF-α with increased levels in serum, kidney and urine were measured. They were able to show that TNF-α inhibitors reduced structural damage and renal dysfunction caused by cisplatin. Furthermore, mice with a TNF-α deficiency presented themselves resistant to cisplatin-induced nephrotoxicity [53].

Cornelison and Reed observed that intravenous hydration seems to have a lessening effect on the severity of the toxicity of cisplatin, but not on its incidence. Therefore patients receiving cisplatin-based chemotherapy should always be well hydrated before and after application of cisplatin [54].

## 17.7. NEUROTOXICITY

Additional to nephrotoxic effects, Cisplatin also attacks the neurologic system. In 20-30% of patients, it may cause persistent peripheral neuropathy. The most common manifestations are paresthesia and peripheral digital dysesthesia. Up to 20% further suffer from a form of ototoxicity, like high-frequency hearing loss or tinnitus [29]**.** Brydøy et al. published a 39% incidence of Raynaud like phenomena and a 29% incidence of paresthesia in their with cisplatin-based chemotherapy treated study population [55]. The findings of Glendenning et al. agree on the neurotoxic effects of cisplatin-based chemotherapy. They conducted a multivariate analysis, showing that the dose of cisplatin, carboplatin and age are significant predictors for peripheral neuropathy [56].

## 17.8. CARDIOVASCULAR TOXICITY

European studies show a significantly increased risk for cardiovascular diseases (CVD) ranging from 1.2 to 7 times higher among testicular cancer survivors treated with chemotherapy compared to patients managed with surveillance [57]–[61]. Either alone or in combination, Bleomycin, Cisplatin and Radiotherapy can enhance the risk of cardiovascular toxicity [29]**.** The risks of coronary heart diseases, congestive heart failure, myocardial infarction or stroke are about two- to threefold increased [45]. Further vascular complications with an increased risk are pulmonary emboli and venous thrombosis. They might all be caused by increased serum cholesterol or vascular injury due to chemo- or radiotherapy [62]. Bezan et al. found that the risk of thromboembolic events increased directly after the initiation of chemotherapy and seemed to be dose-dependent, supporting the theory of vascular toxicity induced by cisplatin [63]. In the comparison of cisplatin-based treatment regimens with the ones not including cisplatin for solid tumours, the risk of vascular thromboembolic events was significantly higher in patients treated with cisplatin [64].

Fung et al. showed that cisplatin-based chemotherapy led to a significantly increased cardiovascular mortality with a standardized mortality ratio (SMR) of 1.36 (95%CI, 1.03-1.78). The risk of CVD mortality was five-fold increased among patients with chemotherapy within the first year after diagnosis, however, no

longer after that time period. With 24.2%, cardiovascular diseases were the cause of almost one-quarter of all non-cancer-related deaths documented during observation. Cerebrovascular events were responsible for 16.3%, the risk also being significantly increased after chemotherapy. They suspected that the higher mortality within the first year could be caused by cisplatin-based chemotherapy, which is already reported to induce direct vascular damage [58][65]–[67] and to increase the risk of vascular thromboembolic events [64][68] by multiple studies [69].

An increase of microalbuminuria and circulating endothelial cells, which are indirect markers signaling diffuse endothelial damage has also been reported in long-term survivors [62].However, the reasons why it comes to a late cardiovascular toxicity are still not fully illuminated. It is suspected, that either direct endovascular damage with accelerated atherosclerosis or cisplatin-induced vascular aging might be the cause [45].Travis et al. suggest, that the vascular injury is induced by an inflammatory response leading to cytokine release and oxidative damage. Furthermore, changes in electrolytes and platelet aggregation have been observed [70]. Chemotherapy might also raise the risk of insulin resistance, hypercholesterolemia and hypertension [29]**.**

De Haas et al. evaluated men treated with chemotherapy retrospectively for cardiovascular risk factors and prevalence of metabolic syndrome. They found, that 24% of the patients became overweight, 24% developed hypercholesterolemia and 30% were diagnosed with hypertension. In those patients with metabolic syndrome, they further found inflammation and thrombophilia [47]. Results from a study from Togna et al. showed that cisplatin has the capability to trigger platelet aggregation and to enhance the formation of thromboxane in platelets. They concluded, that their findings demonstrated the skill of cisplatin to determine an arachidonic acid (AA) pathway activation in human platelets [71].

Nuver et al. support the theory of inflammation-induced atherosclerosis. They found that inflammation markers like high sensitive C-reactive protein (hsCRP) and fibrinogen were increased in patients treated with chemotherapy in comparison to control groups. Levels of von Willebrand factor (vWF) and plasminogen activator inhibitor-1 (PAI-1) were also higher than in control groups, proposing endothelial activation and/or endothelial injury. After seven years, 12%

of the patients and after 14 years, already 22% of patients had developed microalbuminuria as a sign of generalized endothelial dysfunction [72].
Not only chemotherapy but also radiotherapy seems to increase the risk for future cardiovascular events (CVE). Huddart et al compared patients treated with radiotherapy to patients managed with active surveillance. They reported an increased relative risk of 2.4 (95% CI 1.04 - 5.45) for cardiovascular events in the group treated with radiotherapy [59].
Moreover, Zagars et al. found a SMR of 1.61 and Hanks et al even a standard mortality rate of 2.3 for cardiac death after treatment with radiotherapy within their study populations [72,73]. A 20-year follow-up study performed with 990 patients showed that radiotherapy further leads to an elevation of hs-CRP levels and a higher diabetes prevalence probably due to partial irradiation to the pancreas. More precisely, RT showed the highest prevalence of newly developed diabetes within all the different treatment groups [58].
Wethal et al found endothelial dysfunction and elevated markers of chronic inflammation in men after receiving radiotherapy for testicular cancer. They associated this with premature atherosclerosis in the irradiated area [74].
In conclusion, the radiotherapy-induced vascular inflammation and the higher incidence of diabetes are possible explanations for the higher CVD-risk after treatment with radiotherapy.

# 18. OUR STUDY “LONG-TERM CARDIOVASCULAR COMPLICATIONS IN STAGE I SEMINOMA PATIENTS”

This chapter contains an excerpt of the study [75] this diploma thesis is based on.

## 18.1. INTRODUCTION

In our retrospective cohort study, we included only patients with histologically confirmed clinical stage I seminoma and investigated if there is any difference in long-term cardiovascular complications among the different adjuvant treatment modalities.

## 18.2. MATERIAL AND METHODS

### 18.2.1. Patient Population

All consecutive patients (n=950) with histologically confirmed TGCT, presenting to the Division of Oncology at the Medical University of Graz between January 1994 and December 2013, were retrospectively reviewed. Out of the 950 patients, 406 (44.9%) men had a tumour with seminomatous histology and CS I and were included in this retrospective cohort study. Patients were initially staged using computed tomographic (CT) scans of the abdomen, CT scan or X-ray of the chest and postoperative tumour markers α-fetoprotein (AFP), human chorionic gonadotropin (HCG) and lactate dehydrogenase (LDH). Tumour markers within normal limits after orchiectomy and the absence of metastases on imaging defined CS I. Postoperative management options were active surveillance, adjuvant radiotherapy and adjuvant single dose carboplatin. CT based adjuvant radiotherapy to the planning target volume, which includes the paraaortic lymph nodes, was delivered using photons through opposing static fields at daily single fraction doses of 2 Gy, five times a week, up to a total dose of 18 to 30 Gy. [38] Follow-up data were retrieved from the database of the Division of Clinical Oncology at the Medical University of Graz until January 2015. Follow-up investigations at our center were performed according to a local protocol and were adapted in 2007 and 2012 according to recent publications [41], [76]–[79] Electronic and paper medical records of all 406 consecutive SGCT patients were retrospectively reviewed and cardiovascular events (CVEs) were documented. Cardiovascular events were defined as myocardial infarction, cerebrovascular events (stroke, transient ischemic attack) or coronary heart disease and peripheral arterial disease which had to be objectively confirmed by percutaneous coronary intervention or magnetic resonance angiography. Hyperlipidemia, hypertension and diabetes mellitus were documented when patients received treatment or when diagnosis was listed in their medical records (joint public hospital trust with common IT system and electronic healthcare database). Patient records were anonymized and de-identified prior to analysis. The study was approved by the Institutional Review Board of the Medical University of Graz (No. 26-196 ex 13/1).

### 18.2.2. Statistical Analysis

All statistical analysis were performed using STATA (Windows version 13.0, Stat Corp.,Houston, TX, USA). Continuous variables, such as age, were summarized using medians (25th – 75th percentile), whereas count data such as the presence of infiltration of the rete testis, were reported as absolute frequencies (%). Means were compared between two or more groups using t-tests with or without correction for heteroscedasticity as appropriate, and Kruskal-Wallis tests. The median follow-up was estimated using the inverse Kaplan Meier method according to Schemper and Smith. The cumulative incidences of developing an arterial event was obtained with competing risk cumulative incidence estimators according to Maroubini and Valsecchi, treating death – from- any - cause as the competing event of interest. Uni- and multivariable modelling of CVE risk was performed with Fine and Gray proportional subdistribution hazards models. Due to the low event rate, we could not include a large number of predictor variables in the multivariable Fine and Gray models. Therefore, we prespecified a priori to adjust for age and smoking and thereby kept the number of events per predictor variable within an acceptable range. In comparing the CVE event rates between the three treatment cohorts, we could not model relative arterial event hazards because zero patients in the adjuvant carboplatin group developed an arterial event. Instead, we directly modelled the absolute risk difference between patients receiving adjuvant carboplatin, adjuvant radiotherapy and active surveillance. Uni- and multivariable modelling of the absolute risk difference was performed using an ordinary least squares linear probability model with robust standard errors. Missing data were present in some covariates, as reported in Table 10. However, data were not multiply imputed, and a complete case analysis was performed. Survivor functions were analysed with Kaplan Meier product limit estimators, log rank tests and uni- and multivariable Cox proportional hazards models. To study the impact of the occurrence of intermediate events, such as hypertension, on the risk of CVEs we fitted unidirectional illness-death multistate models [80] .

## Table 10: Baseline characteristics of the patient population – Distribution overall and by cardiovascular event

| Variable | Subjects with available data {%missing} | Overall (n=406) | CVE during follow up (n=23) | No CVE during follow-up (n=383) | P* |
|---|---|---|---|---|---|
| **Demographic characteristics** | | | | | |
| Age | 406 {0.0%} | 37.3 [32.4 - 44.1] | 46.7 [42.0 - 54.1] | 37.0 [32.0 - 43.5] | 0.0002 |
| BMI | 298 {26.6%} | 25.3 [23.1 – 27.5] | 25.3 [24.2 – 29.4] | 25.2 [23.0 – 27.5] | 0.353 |
| Family history of TGCT** | 282 {30.5%} | 28 (9.9%) | 28 (9.9%) | 28 (10.3%) | 0.999 |
| Smoker or Ex-Smoker | 329 {19.0%} | 147 (44.7%) | 13 (86.7%) | 134 (42.7%) | 0.001 |
| Karnofsky Index < 100% | 364 {10.3%} | 17 (4.7%) | 2 (12.5%) | 15 (4.3%) | 0.168 |
| Diabetes pretreatment | 369 {9.1%} | 9 (2.4%) | 5 (25.0%) | 4 (1.2%) | <0.0001 |
| Hypertension pretreatment | 368 {9.4%} | 20 (5.4%) | 3 (16.7%) | 17 (4.9%) | 0.066 |
| Hyperlipidemia pretreatment | 366 {9.9%} | 5 (1.4%) | 0 (0.0%) | 5 (1.4%) | 0.990 |
| Diabetes posttreatment | 367 {9.6%} | 6 (1.6%) | 1 (5.9%) | 5 (1.4%) | 0.249 |
| Hypertension posttreatment | 368 {9.4%} | 22 (6.0%) | 8 (44.4%) | 14 (4.0%) | <0.0001 |
| Hyperlipidemia posttreatment | 366 {9.9%} | 37 (10.11%) | 8 (47.1%) | 29 (8.3%) | <0.0001 |
| **Clinicopathological variables** | | | | | |
| TU size >4cm | 352 {13.3%} | 135 (38.4%) | 7 (43.8%) | 128 (38.1%) | 0.649 |
| Rete testis invasion | 232 {43.0%} | 101 (43.5%) | 1 (33.3%) | 100 (43.7%) | 0.597 |
| LVI | 352 {13.3%} | 651 (19.5%) | 3 (17.7%) | 62 (19.6%) | 0.568 |
| T Stage | 406 {0.0%} | / | / | / | 0.277 |
| ---pTis | / | 2 (0.5%) | 0 (00.0%) | 2 (0.5%) | / |
| ---pT1 | / | 299 (73.7%) | 14 (60.8%) | 285 (74.4%) | / |
| ---pT2 | / | 70 (17.2%) | 5 (21.7%) | 65 (17.0%) | / |
| ---pT3 | / | 34 (8.4%) | 4 (17.4%) | 30 (7.8%) | / |
| ---pT4 | | 1 (0.3%) | 0 (00.0%) | 1 (0.3%) | |
| **Laboratory parameters (preoperative)** | | | | | |
| ---Hemoglobin | 239 {41.1%} | 15.4 [14.8 - 16.3] | 14.6 [14.1 – 15.4] | 15.4 [14.9 – 16.4] | 0.047 |
| ---Leukocytes | 238 {41.4%} | 7.3 [5.7 – 8.8] | 10.2 [7.4 -12.0] | 7.2 [5.7 – 8.7] | 0.016 |
| ---Thrombocytes | 238 {41.4%} | 225.0 [198.0– 264.0] | 230.0 [196.0- 282.0] | 224.0 [198.0 – 264.0] | 0.75 |
| ---CRP | 209 {48.5%} | 1.4 [1.0 – 3.2] | 2.5 [1.4 – 8.2] | 1.3 [0.9 – 3.2] | 0.13 |
| ---Fibrinogen | 207{49.0%} | 293.0 [246.0 – 343.0] | 385.0 [346.0– 1000.0] | 293.0 [246.0 – 337.0] | 0.003 |
| ---LDH | 238 {41.4%} | 199.0 [167.0- 248.0] | 218.0 [140.0 – 225.0] | 198.0 [167.0 – 248.0] | 0.809 |
| **Laboratory parameters (postoperative)** | | | | | |
| ---CRP | 195 {52.0%} | 1.0 [1.0 – 2.3] | 3.8 [2.3 – 4.4] | 1.0 [0.9 – 2.1] | 0.008 |
| **Laboratory parameters (1 year post treatment)** | | | | | |
| ---CRP | 208 {48.8%} | 1.0 [0.8 – 2.3] | 2.8 [1.5 – 7.9] | 1.0[0.7 – 2.2] | 0.008 |

Continuous data are reported as medians with 25$^{th}$ percentile – 75$^{th}$ percentile in the squared brackets, categorical data are reported as absolute frequencies and percentages in parentheses. Percentages are calculated by referring only to the patients without missing values (i.e. not to the total number of patients if missing values are present).

*p represents test for difference between CVE and No CVE ($\chi^2$ tests for binary and categorical variables, ranksum-tests for continuous variables),

**Family history is defined as a history of testicular cancer in a first and/or second degree relative*

## 18.3. Results

### 18.3.1. Analysis at baseline

Overall, out of 950 testicular germ cell cancer patients from our in-house-research-data base, 406 patients with CS I seminoma were identified (Table 10).
Out of the 406 CS I seminoma patients, 57 (14.0%) received adjuvant radiotherapy (median dose 26 Gray), 37 (9.1%) patients received adjuvant carboplatin and 312 (76.9%) were managed with active surveillance (Table 11).
Out of 57 patients treated with adjuvant radiotherapy, 1 (1.8%) experienced a relapse. In the carboplatin group, 3 (8.1%) out of 37 experienced a relapse. In the 312 patients who had chosen active surveillance, 35 (11.2%) relapsed.
Age at diagnosis was comparable between patients managed with active surveillance (36.9 years) and patients receiving adjuvant carboplatin (37.2 years). However, patients treated with adjuvant radiotherapy (41.1 years) were significantly older than patients on active surveillance (p=0.02; Table 11).

## Table 11. Baseline characteristics – Distribution overall and by treatment modality

| Variable | Subjects with available data {%missing} | Overall (n=406) | Active surveillance (n=312) | Adjuvant carboplatin (n=37) | Adjuvant radiotherapy (n=57) | P* |
|---|---|---|---|---|---|---|
| **Demographic characteristics** | | | | | | |
| Age | 406 {00.0%} | 37.3 [32.4 - 44.1] | 36.9 [32.0 - 43.1] | 37.2 [31.3 - 46.1] | 41.1 [34.9-46.5] | 0.02 |
| BMI | 298 {26.6%} | 25.3 [23.1 – 27.5] | 25.3 [23.1 – 27.4] | 24.9 [23.0 – 27.5] | 25.5 [23.7-29.2] | 0.603 |
| Family history of TGCT** | 282 {30.5%} | 28 (9.9%) | 22 (10.2%) | 1 (3.3%) | 5 (13.5%) | 0.402 |
| Smoker or Ex-Smoker | 329 {19.0%} | 147 (44.7%) | 106 (42.1%) | 20 (58.8%) | 21 (48.8%) | 0.153 |
| Karnofsky Index < 100% | 364 {10.3%} | 17 (4.7%) | 9 (3.3%) | 1 (2.7%) | 7 (14.0%) | 0.01 |
| Diabetes pretreatment | 369 {9.1%} | 9 (2.4%) | 5 (1.8%) | 0 (0.0%) | 4 (7.4%) | 0.06 |
| Hyperlipidemia pretreatment | 366 {9.9%} | 5 (1.4%) | 4 (1.4%) | 0 (0.0%) | 1 (1.9%) | 0.745 |
| Hypertension pretreatment | 368 {9.4%} | 20 (5.4%) | 13 (4.6%) | 2 (5.6%) | 5 (9.6%) | 0.291 |
| Diabetes posttreatment | 367 {9.6%} | 6 (1.6%) | 6 (2.2%) | 0 (0.0%) | 0 (0.0%) | 0.783 |
| Hypertension posttreatment | 368 {9.4%} | 22 (6.0%) | 18 (6.4%) | 0 (0.0%) | 4 (7.7%) | 0.256 |
| Hyperlipidemia posttreatment | 366 {9.9%} | 37 (10.1%) | 26 (9.3%) | 1 (2.9%) | 10 (19.2%) | 0.04 |
| **Clinicopathological variables** | | | | | | |
| TU size >4cm | 352 {13.3%} | 135 (38.4%) | 77 (28.6%) | 26 (72.2%) | 32 (68.1%) | <0.0001 |
| Rete testis invasion | 232 {43.0%} | 101 (43.5%) | 59 (33.9%) | 19 (61.3%) | 23 (85.2%) | <0.0001 |
| Rete testis invasion and TU Size >4cm | 226 {44.3%} | 40 (17.7%) | 14 (8.3%) | 11 (36.7%) | 15 (55.6%) | <0.0001 |
| T Stage | 406 {00.0%} | / | / | / | / | <0.277 |
| ---pTis | / | 2 (0.5%) | 2 (0.6%) | 0 (0.0%) | 0 (0.0%) | / |
| ---pT1 | / | 299 (73.7%) | 266 (85.3%) | 6 (16.2%) | 27 (47.4%) | / |
| ---pT2 | / | 70 (17.2%) | 32 (10.3%) | 19 (51.4%) | 19 (33.3%) | / |
| ---pT3 | / | 34 (8.4%) | 12 (3.9%) | 12 (32.4%) | 10 (17.5%) | / |
| ---pT4 | | 1 (0.3%) | 0 (0.0%) | 0 (0.0%) | 1 (1.8%) | |
| **Laboratory parameters (preoperative)** | | | | | | |
| ---Hemoglobin | 239 {41.1%} | 15.4 [14.8 - 16.3] | 15.4 [14.9 – 16.4] | 15.9 [15.2 – 16.5] | 15.0 [13.9–15.6] | 0.002 |
| ---Leukocytes | 238 {41.4%} | 7.3 [5.7 – 8.8] | 7.4 [5.8 - 8.8] | 7.2 [6.1 – 8.0] | 6.9 [5.0–10.0] | 0.866 |
| ---Thrombocytes | 238 {41.4%} | 225.0 [198.0-264.0] | 227.0 [203.0-264.0] | 223.0 [199.0–271.0] | 211.0 [187.0–249.0] | 0.382 |
| ---CRP | 209 {48.5%} | 1.4 [1.0 – 3.2] | 1.3 [0.7 – 3.2] | 1.1 [1.0 – 2.2] | 2.4 [1.3 – 5.1] | 0.022 |
| ---Fibrinogen | 207 {49.0%} | 293.0 [246.0–343.0] | 291.0 [245.0–337.0] | 282.0 [248.0–336.0] | 325.0 [288.0–419.0] | 0.048 |
| ---LDH | 238 {41.4%} | 199 [167-248] | 195.0 [164.0–237.0] | 215.0 [187.0–288.0] | 246.0 [191.0–381.0] | 0.002 |
| **Laboratory parameters (postoperative)** | | | | | | |
| ---CRP | 195 {52.0%} | 1.0 [1.0 – 2.3] | 1.0 [0.9 – 2.3] | 1.0 [0.9 – 2.3] | 1.4 [1.0 – 2.1] | 0.195 |
| **Laboratory parameters (1 year post treatment)** | | | | | | |
| ---CRP | 208 {48.8%} | 1.0 [0.8 – 2.3] | 1.0 [0.7 – 2.2] | 1.0 [0.6 – 1.8] | 1.7 [1.0 – 2.9] | 0.001 |
| ---Change in CRP (mg/dl) (from postoperative to 1year post treatment) | 185 {54.4%} | 0.0 [-0.4 – 0.4] | 0.0 [-0.4 – 0.2] | 0.0 [-0.5 – 0.5] | 0.1 [-0.3 – 3.16] | 0.002 |

Continuous data are reported as medians with 25$^{th}$ percentile – 75$^{th}$ percentile in the squared brackets, categorical data are reported as absolute frequencies and percentages in parentheses. Percentages are calculated by referring only to the patients without missing values (i.e. not to the total number of patients if missing values are present).

*p represents test for difference between the treatment strategies,

**Family history is defined as a history of testicular cancer in a first and/or second degree relative;

### 18.3.2. Analysis of arterial cardiovascular complications at baseline

During a median follow-up of 8.6 years (21 days – 21.6 years), we observed 23 arterial events. 75% of patients were followed for more than 4.4 year and 25% of patients for more than 11.2 years, respectively. Only 11 patients had a follow up less than 1 year. The most frequent type of arterial event was myocardial infarction (Table 12). At the time of cardiovascular event 2 patients (8.7%) received low dose aspirin, one patient (4.3%) received oral anticoagulation with a vitamin K antagonist, 18 patients (78,3%) did not receive any type of antithrombotic therapy and in 2 patients (8.7%) antithrombotic treatment at the time of event could not be ascertained.

The cumulative 1, 5, 10, 15 and 20 year incidence of arterial cardiovascular events were 0.0% (95% CI: 0.0 – 0.0), 2.2% (95% CI: 1.0 – 4.2), 5.6% (95%CI: 3.2 -8.8), 13.1% (95% CI: 7.0 – 21.1) and 29.0% (95% CI: 12.2 – 48.2), respectively (Fig. 3). With 10 deaths occurring during follow-up mortality was present as a competing risk (10 year mortality rate: 3.1%, 95% CI: 1.6 – 6.0).

**Table 12: Overall Incidence of cardiovascular events**

| Cardiovascular Event (N=23) | No. of Patients (N=406) | Percentage (5.7%) |
|---|---|---|
| Subtype of Cardiovascular Event: | | |
| Myocardial Infarction | 10 | 43.5 |
| Coronary heart disease | 6 | 26.1 |
| Cerebrovascular event | 4 | 17.4 |
| Peripheral arterial disease | 3 | 13.0 |

### 18.3.3. Predictors of cardiovascular events

In univariable competing risk analysis, higher age, positive smoking status (current or ex-smoker), history of diabetes, history of hypertension, higher preoperative leukocyte count, C-reactive protein (CRP) and fibrinogen, higher postoperative CRP and higher CRP one year after treatment were significantly associated with an increased risk of CVE (Table 13).

In multi-state analysis, new onset of diabetes, hypertension and hyperlipidaemia

during follow-up predicted for an excessively increased CVE risk.
Due to the low event rate, we could not include a large number of predictor variables in the multivariable model. However, after adjusting for age and smoking, the development of hypertension and hyperlipidemia after tumour specific treatment prevailed as risk factors for CVE in multivariable analysis. Furthermore, inflammation markers like leukocytes and fibrinogen prevailed as risk factors. Post-treatment CRP failed to reach statistical significance (p 0.09) after adjustment for age and smoking, but was missing in 50% of patients (Table 10 and Table 13). Out of the 23 patients who developed a CVE during follow-up 4 patients died (median time between CVE and death=1.9 years), and one CVE (myocardial infarction) was fatal. In a multistate model, the onset of CVE was associated with a 49-fold increase of death (transition hazard ratio (THR)=49.0, 95CI: 10.3 – 233.0, p<0.0001). This strong association between CVE and mortality prevailed after adjusting for age (THR for CVE= 13.3, 95% CI: 2.6 – 68.1, p 0.002).

**Table 13: Predictors of cardiovascular event risk in TGCT patients - uni and multivariable competing risk regression**

| Variable | Univariable HR | 95%CI | p | Multivariable HR adjusted for age and smoking | 95% CI | p |
|---|---|---|---|---|---|---|
| **Demographic characteristics** | | | | | | |
| Age (per 5years increase above 35years) | 1.62 | 1.35 - 1.94 | <0.0001 | N/A | N/A | N/A |
| BMI (for 5kg/m² increase above 25kg/m²) | 1.61 | 0.82 – 3.16 | 0.171 | 1.29 | 0.61 – 2.73 | 0.501 |
| Smoker or Ex-Smoker | 8.43 | 1.88 – 37.84 | 0.005 | N/A | N/A | N/A |
| Karnofsky Index < 100% | 2.65 | 0.70 – 9.99 | 0.151 | 2.28 | 0.59 – 8.87 | 0.233 |
| Diabetes pretreatment | 6.16 | 2.67 – 14.22 | <0.0001 | 2.92 | 0.96 - 8.89 | 0.06 |
| Hypertension pretreatment | 4.84 | 1.37 – 17.16 | 0.015 | 1.35 | 0.15 – 11.86 | 0.79 |
| Hyperlipidemia pretreatment | N/E | N/E | N/E | N/E | N/E | N/E |
| Diabetes posttreatment | 16.1 | 1.50 -172.70 | 0.022 | 2.62 | 0.19 – 35.17 | 0.468 |
| Hypertension posttreatment | 37.0 | 2.78–107.17 | <0.0001 | 42.13 | 9.35 – 189.94 | <0.0001 |
| Hyperlipidemia posttreatment | 4.12 | 1.49 – 11.39 | 0.006 | 3.95 | 1.24 – 12.62 | 0.021 |
| **Clinicopathological variables** | | | | | | |
| TU size >4cm | 1.36 | 0.52 – 3.59 | 0.531 | 0.95 | 0.34 – 2.68 | 0.919 |
| Rete testis invasion | 0.53 | 0.06 – 4.87 | 0.575 | 1.01 | 0.08 – 11.96 | 0.995 |
| Rete testis invasion plus TU Size>4cm | 1.39 | 0.18 – 10.98 | 0.755 | 0.60 | 0.07 – 4.76 | 0.626 |
| **Laboratory parameters (preoperative)** | | | | | | |
| --Hemoglobin (per 1g/dl increase) | 0.77 | 0.62 – 0.96 | 0.020 | 0.88 | 0.62 – 1.24 | 0.461 |
| --Leukocytes | 1.37 | 1.13 – 1.66 | 0.001 | 1.51 | 1.15 – 1.98 | 0.003 |
| --Thrombocytes (per 100G/L increase) | 1.77 | 0.58 – 5.31 | 0.320 | 2.07 | 0.63 – 6.83 | 0.233 |
| --CRP (per 10mg/dl increase) | 1.19 | 1.12 – 1.26 | <0.0001 | 0.89 | 0.56 – 1.40 | 0.607 |
| --Fibrinogen (per 100 mg/dl) | 1.78 | 1.53 – 2.07 | <0.0001 | 1.54 | 1.23 – 1.94 | 0.0001 |
| --Preoperative LDH (per 100U/L increase) | 1.12 | 0.93 – 1.35 | 0.244 | 0.62 | 0.28 – 1.39 | 0.248 |
| **Laboratory parameters (postoperative)** | | | | | | |
| -- CRP (per 10mg/dl increase) | 2.18 | 1.12 – 4.24 | 0.022 | 2.31 | 0.85 – 6.27 | 0.099 |
| **Laboratory parameters (1 year post treatment)** | | | | | | |
| --CRP 1a (per 10mg/dl increase) | 23.8 | 4.08–139.21 | <0.0001 | 6.45 | 0.74 – 56.22 | 0.092 |

TGCT testicular germ cell tumor, CVE cardiovascular event, BMI body mass index, N/A not applicable, N/E not explored due to low positive findings, CRP C-reactive protein, LDH lactate dehydrogenase

### 18.3.4. Adjuvant therapy and CVE risk

During the follow-up period, we observed 9 CVEs in the 57 patients treated with adjuvant radiotherapy and 14 in the 312 patients managed with active surveillance, respectively. No CVE occurred in the 37 patients treated with single shot adjuvant carboplatin. Median follow-up was significantly longer in patients who had received adjuvant radiotherapy (9.7 years) and in patients on active surveillance (8.7 years) than in patients treated with adjuvant carboplatin (3.4 years, p< 0.0001). Follow-up time between patients on active surveillance and patients treated with adjuvant radiotherapy did not significantly differ (p 0.19). Overall, this corresponded to a 10-year-cumulative-cardiovascular-event-risk of 13.5%, 3.7% and 0.0% respectively in these patients groups (Fig. 4). In univariable linear probability modelling, patients receiving adjuvant carboplatin had a significantly lower probability of CVE than patients on active surveillance (risk difference (RD)=-4.5%, 95% CI: - 6.8% - (-2.2%), p<0.0001), which can be explained by the shorter follow-up time. However, patients receiving adjuvant radiotherapy had a significantly higher probability of CVE than patients on active surveillance (RD= 11.3%, 95% CI: 4.6 - 18.0%, p=0.001). This difference prevailed after adjusting for age and median follow-up time (RD= 9.0%, 95%CI: 2.3 – 15.8%, p=0.008). Further, we observed that patients receiving adjuvant radiotherapy had a significantly higher probability of CVE than patients receiving adjuvant carboplatin (16% vs. 0%; risk difference=16%, 95%CI: 6 – 25%, p=0.001). This difference also prevailed after adjusting for age, follow-up time, diabetes, hypertension and smoking (RD=11.0%, 95%CI: 1 - 20%, p=0.025). These findings prompted us to explore potential mechanisms by which adjuvant radiotherapy could increase thrombotic risk. As one mechanism could be vascular inflammation in the radiation involved field, we retrospectively ascertained CRP levels one year after treatment. Here, we found that pretreatment CRP was higher in the radio-therapy group than in the other two groups, whereas this difference disappeared after surgery (Table 11), suggesting an influence of tumour inflammation because patients in the radiotherapy group had significantly higher tumour size and higher pretreatment LDH levels (Table 11). Importantly, one year after treatment CRP levels were significantly higher in the radiotherapy group supporting the concept of vascular inflammation post adjuvant radiotherapy (Table 11).

**Figure 3: Cumulative-cardiovascular-event-risk during follow-up of testicular cancer patients**

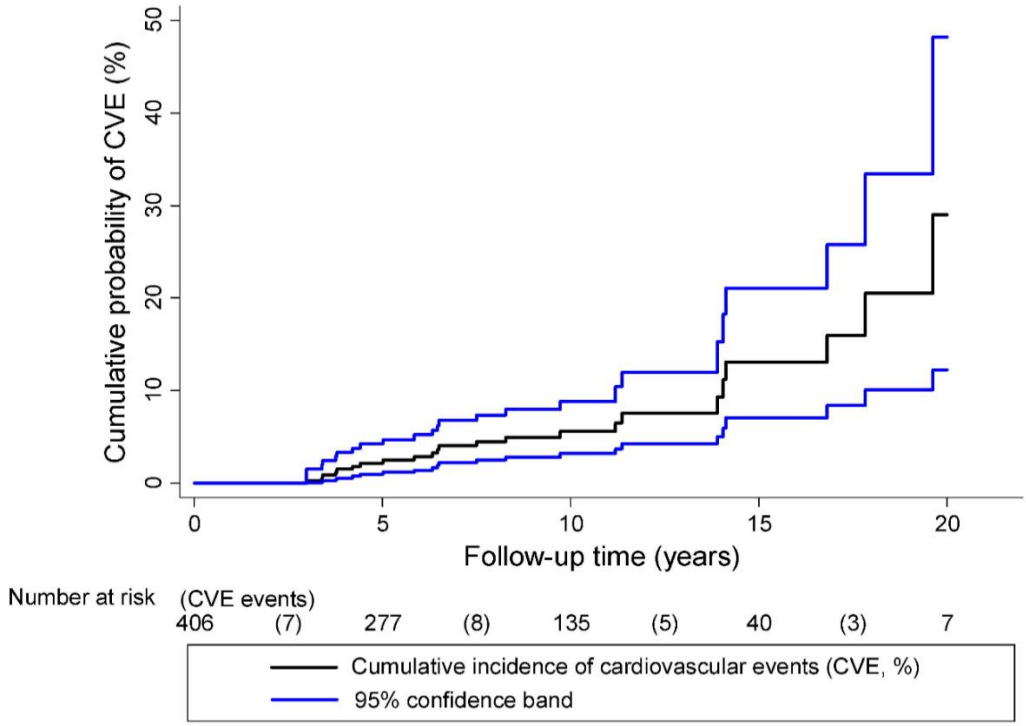
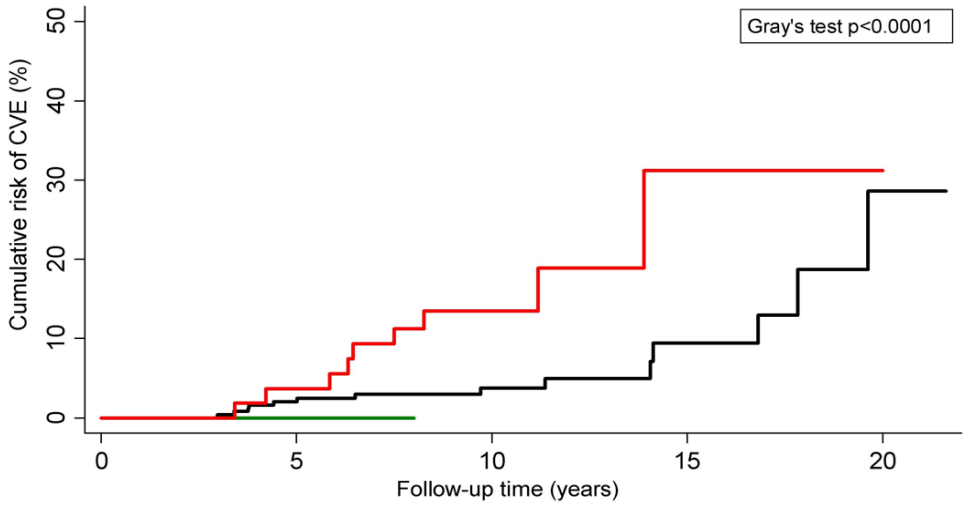



**Figure 4: Cumulative-cardiovascular-event-risk during follow-up of testicular cancer patients depending on adjuvant therapy**




| | Surgery or end of adjuvant treatment | After 5 years of follow-up | After 10 years of follow-up | After 15 years of follow-up | After 20 years of follow-up |
|---|---|---|---|---|---|
| Number at risk (*cardiovascular events*) | | | | | |
| Adjuvant Radiotherapy | 57 | 51 (*2*) | 20 (*5*) | 5 (*2*) | 1 (*0*) |
| Active Surveillance | 312 | 218 (*5*) | 115 (*3*) | 35 (*3*) | 6 (*3*) |
| Adjuvant Carboplatin | 37 | 8 (*0*) | 0 (*0*) | 0 (0) | 0 (*0*) |

## 18.4. DISCUSSION

In our retrospective cohort study, we concentrated on the occurrence of cardiovascular complications in patients with stage I seminoma and performed a comprehensive analysis focusing on the risk factors for their development. We found solid evidence, that there is a strong association between the onset of components of the metabolic syndrome and the occurrence of cardiovascular events. Moreover, ascertaining the predictors at baseline, we found that higher age, smoking status as well as a history of diabetes and hypertension were also highly associated with the development of cardiovascular events.

In a next step, we investigated if there is any difference among the adjuvant treatment modalities in regards of CVE.

Radiotherapy is known to significantly reduce the relapse rate of clinical stage I TGCT. However, as mentioned above, radiotherapy is linked with doubling the risk of second malignancies after five years with maxima between 10-20 years after treatment [81].

Regarding cardiovascular complications, Huddart et al. showed that 9.6% of patients who had received radiotherapy developed a cardiac event after a median follow-up of ten years. In contrast, in patients treated with orchiectomy alone, only 3.7% suffered from a cardiac complication. This resulted in a greater than two-fold, age-adjusted, relative risk for a cardiac event after treatment with radiotherapy (RR=2,4, 95% CI 1.04 - 5.45) [59].

After a follow-up longer than 15 years, Zagars et al. found a significantly elevated cardiac mortality rate with a standardized mortality ratio of 1.95 (95% CI: 1.24 – 2.94) [82]. However, it has to be taken into account that 8.3% of the patients from the study by Huddart et al. and 14.9% of the patients from the study by Zagars et al. received mediastinal radiotherapy which is nowadays no longer the standard of care for the adjuvant treatment of stage I seminoma. Including those patients could have led to higher incidental cardiovascular doses.

In our study, only patients who received radiotherapy limited to the paraaortic region were included and compared with other CS I seminoma patients who were managed with active surveillance or who received adjuvant single dose carboplatin. Despite the absence of mediastinal radiotherapy, the most frequent cardiovascular event among patients was myocardial infarction after a median

follow-up of 8.6 years. Travis et al. speculated, that an inflammatory response might mediate therapy-related vascular injuries [70]. In 2010, the analysis from Wethal et al. showed, that the risk for a cardiovascular disease was 2.79 (95% CI 1.22-6.34) times higher for patients who had a CRP ≥1.5mg/L compared to the group having a CRP <1.5mg/L [83].

We tried to investigate this hypothesis by looking into the CRP levels of our patients, especially the levels one year after they received their last adjuvant treatment or one year after surgery. We compared patients from all treatment modalities and found a significant difference between those groups. Patients treated with radiotherapy had a significantly higher CRP one year after treatment than patients from both, the carboplatin and the active surveillance group. This finding could support the theory of vascular inflammation after adjuvant radiotherapy.

To reduce long-term complications, alternative treatment strategies to radiotherapy in TGCT have been investigated. In 2005, Oliver et al. compared adjuvant radiotherapy with one injection carboplatin and showed the non-inferiority of latter [84]. Continuative, Timothy et al. performed a study with 1.447 patients and did not only agree on the non-inferiority of carboplatin but further found a statistically significant reduction in the risk of treatment induced second germ cell tumours compared to radiotherapy [85]. Due to those studies, a single dose of carboplatin has been considered an alternative to radiotherapy and therefore been used as such. Powles et al. were the first to investigate the long-term outcome after adjuvant carboplatin for stage I seminoma. They found, that there seems to be no association between the use of carboplatin and an excess in the risk of cardiovascular mortality when compared with age- and sex-matched general UK population, which is in line with our study results.

In conclusion, this study demonstrates a link between components of the metabolic syndrome at baseline and during follow-up with the occurrence of long-term cardiovascular complications. The observed association of adjuvant radiotherapy with higher CVE risk warrants further prospective investigations.

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