



# The prevalence and intensity of late effects in patients with testicular germ cell tumors: A first step of instrument development using a stepwise approach

Roos Enzlin<sup>a,c</sup>, Sigrid C.J.M. Vervoort<sup>b</sup>, Britt B.M. Suelmann<sup>c</sup>, Richard P. Meijer<sup>d</sup>, Saskia C.C.M. Teunissen<sup>e</sup>, Danielle Zweers<sup>c,\*</sup>

<sup>a</sup> Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066CX, Amsterdam, the Netherlands

<sup>b</sup> University Medical Center Utrecht, Department of Nursing Science, Julius Center for Health Sciences and Primary Care, Heidelberglaan 100 3584CX, Utrecht, the Netherlands

<sup>c</sup> University Medical Center Utrecht, Department Medical Oncology, Heidelberglaan 100, 3584CX, Utrecht, the Netherlands

<sup>d</sup> University Medical Center Utrecht, Department of Oncological Urology, Heidelberglaan 100, 3584CX, Utrecht, the Netherlands

<sup>e</sup> University Medical Center Utrecht, Department of Primary Care, Heidelberglaan 100, 3584CX, Utrecht, the Netherlands

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## ABSTRACT

**Purpose:** Patients with Testicular Germ Cell Tumors (TGCT) may suffer from several late effects due to their diagnosis or treatment. Follow-up care aims to identify the recurrence of cancer and support patients with TGCT in their experienced late effects. In the Netherlands, the validated Dutch version of the Edmonton Symptom Assessment System, Utrecht Symptom Diary (USD) is used to assess and monitor patient reported symptoms. As a first step to develop a specific USD module for TGCT-patients, it was necessary to identify the prevalence and intensity of late effects in patients with TGCT, covering the physical, social, psychical and existential domains of care.

**Methods:** A cross-sectional study was conducted. First, literature was systematically assessed to create a comprehensive list of symptoms. This generated list was reviewed by expert healthcare professionals and the research group. Lastly, a survey was distributed amongst patients with TGCT in follow-up care in the University Medical Center Utrecht (UMCU) outpatient clinic.

**Results:** In total, 65 TGCT-patients completed the survey. All described late effects were recognized by TGCT-patients, with 'fatigue', 'disturbed overall well-being', 'concentration problems' and 'neuropathy', indicated as most prevalent and scored with highest intensity. When prioritizing these late effects, patients assigned 'neuropathy' as most important.

**Conclusions:** This study provided insight into prevalence and intensity of late effects, as indicated by TGCT-patients. In clinical practice, follow-up care can improve by empowering patients to discuss important items in daily life with their health-care professionals.

## 1. Introduction

In Europe, testicular cancer is the most common cancer among young men (Znaor et al., 2020). Testicular cancer represents a wider range of malignant diagnoses, classified by histological characteristics based on the pathological classification of the World Health Organisation (WHO) (Moch et al., 2016; Williamson et al., 2017). The most common histology at diagnosis of testicular cancer consists of Testicular Germ Cell

Tumors (TGCT), representing 90–95% of cases (Laguna et al., 2020).

Treatment is offered according to the histology and staging at diagnosis and could consist of the following components; surgery, radiation, chemotherapy, and a combination of the previously mentioned options (Laguna et al., 2020). In Western Europe, the majority of patients will be cured of TGCT, with a ten-year survival rate of more than 95% (Laguna et al., 2020; Travis et al., 2010). Although the treatment schedules for TGCT may appear very promising in the field of survival, patients may

\* Corresponding author.

E-mail addresses: [r.enzlin@nki.nl](mailto:r.enzlin@nki.nl) (R. Enzlin), [svervoor@umcutrecht.nl](mailto:svervoor@umcutrecht.nl) (S.C.J.M. Vervoort), [B.B.M.Suelmann@umcutrecht.nl](mailto:B.B.M.Suelmann@umcutrecht.nl) (B.B.M. Suelmann), [rmeijer6@umcutrecht.nl](mailto:rmeijer6@umcutrecht.nl) (R.P. Meijer), [S.Teunissen@umcutrecht.nl](mailto:S.Teunissen@umcutrecht.nl) (S.C.C.M. Teunissen), [d.zweers@umcutrecht.nl](mailto:d.zweers@umcutrecht.nl) (D. Zweers).

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experience different serious side-effects, both in short- and long term (Honecker et al., 2018; Laguna et al., 2020; Travis et al., 2010). The most common long-term toxicities and late effects are second malignant neoplasms, leukaemia, infections, pulmonary complications, cardiovascular toxicity, Raynaud's phenomena, neurotoxicity, ototoxicity, nephrotoxicity, sexual difficulties, cognitive dysfunction, hypogonadism, fatigue, and reduced quality of life (Honecker et al., 2018; Laguna et al., 2020; Lauritsen et al., 2021; Travis et al., 2010). Late effects are defined as: 'Health problems that occur months or years after a disease is diagnosed or after treatment has ended. Late effects may be caused by cancer or cancer treatment. They may include physical, mental, and social problems' (National Cancer Institute, 2020). The onset of TGCT occurs often at a relatively young age, with a life expectancy of several decades after cure (Laguna et al., 2020; Travis et al., 2010). Therefore, these long-term problems may have serious impact on TGCT survivors' quality of life during the rest of their lives (Honecker et al., 2018; Laguna et al., 2020; Travis et al., 2010).

Follow-up care aims to identify the recurrence of cancer and support TGCT-patients in their experienced late effects. The clinical impression of healthcare professionals, such as nurses and oncologists, does not fully cover, or even underestimate (Oechsle et al., 2013), patients' symptom intensity and experienced distress (Rhondali et al., 2012; Söllner et al., 2001). Assessment of medical and psychosocial burden of late effects is recommended (Travis et al., 2010). Standardized application of an instrument to assess, monitor and understand late effects, measured using patients' symptoms, could decrease the burden for patients and their family (IKNL, 2018). Therefore, the use of an assessment tool or instrument to provide insight in patient reported outcome measures (PROMs) will improve follow-up care. Surprisingly, no comprehensive questionnaire currently exists to assess the late effects of cancer diagnosis and treatment during follow-up (Klonoff-Cohen and Polavarapu, 2020). There are several questionnaires aimed at cancer survivors in general, or aimed at adolescents and young adults (AYAs) but none were customized by type of cancer and its specific late effects (Klonoff-Cohen and Polavarapu, 2020).

In the Netherlands, the validated Dutch version of the Edmonton Symptom Assessment System (ESAS), Utrecht Symptom Diary (USD) is used to assess and monitor patient reported symptoms (van der Baan et al., 2020). The USD is an instrument that addresses several symptoms covering the physical and psychological domains of care (Bruera et al., 1991; Hui and Bruera, 2017; IKNL, 2018). For every symptom, patients are requested to assign a score using a Numeric Rating Scale (NRS) (van der Baan et al., 2020). By lacking an existing comprehensive instrument, the USD could be promising in follow-up care, to assess and monitor late effects in cancer patients and survivors. Various cancer- and treatment-specific complementary USD modules are developed (Ijzerman-Korevaar et al., 2018), however none is aimed at TGCT-patients. To develop such a specific USD module for TGCT-patients, it is necessary to first determine the existing late effects. Since experienced late effects could differ between different treatment-schedules and follow-up years (Chovanec et al., 2021), a distinction will be made between these groups, to assess whether one potential USD module is suitable for all treatment-schedules and follow-up years of TGCT-patients.

## 2. Aims

The primary aim of this study was to identify the prevalence and intensity of late effects in TGCT-patients currently in follow-up care, covering the physical, social, psychological and existential domains of care, as a first step of instrument development.

The secondary aims were:

- To identify the difference in prevalence and intensity of late effects between TGCT-patients who underwent different treatment-schedules (e.g. chemotherapy, radiotherapy, surgery or a combination).

- To identify the difference in prevalence and intensity of late effects between TGCT-patients during different years of follow-up care after treatment.

## 3. Method

### 3.1. Design

A cross-sectional study, using a stepwise approach, was conducted. Data concerning late effects of TGCT-patients were obtained between February 2021 and February 2022 in the University Medical Center Utrecht (UMCU). The study was reported according to The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (Von Elm et al., 2007). The first phase of the stepwise approach comprised of systematically assessing literature to determine all described late effects in TGCT-patients, where after a complete list of late effects was created. Secondly, to reach a certain level of completeness and content validity, this generated list was critically assessed by healthcare professionals and the research group. Lastly, the complete and revised generated list of late effects was converted into a survey. Afterwards, the survey was administered to TGCT-patients in follow-up care.

### 3.2. Population and domain

The population of this study consisted of both healthcare professionals and TGCT-patients.

In order to be eligible to participate in this study, a healthcare professional needed to meet the following criteria: providing follow-up care to TGCT-patients, and at least one-year experience in providing care to TGCT-patients, to ensure thorough insight in late effects.

In order to be eligible to participate in this study, a TGCT-patient needed to meet all of the following criteria: ≥18 years old, no cognitive impairment, able to fill in the online survey, and currently in follow-up care in the UMCU outpatient clinic.

### 3.3. Data collection and study procedures

#### 3.3.1. Literature review of late effects

For creating the list of late effects and the survey, as a first step, a literature review was undertaken to identify all described late effects in TGCT-patients. The literature review was conducted following the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019). The electronic databases PubMed, EMBASE, CINAHL and The Cochrane Library were searched for eligible articles up to December 20th 2020. The complete search strategy, inclusion- and exclusion criteria can be found in the appendix.

All identified late effects were listed, doubles were removed and different translations for the same late effect were merged, and translated into Dutch. Late effects were converted into understandable symptoms for TGCT-patients. This process was performed by two researchers (RE and DZ).

#### 3.3.2. Assessment of late effects by healthcare professionals

Thereafter, healthcare professionals, providing follow-up care to TGCT-patients, were asked to provide expert opinion and prioritization on the generated items through an online Castor EDC survey to reach completeness and content validity. Also, peer group discussion in the research group was held.

#### 3.3.3. Survey for TGCT-patients

In the next step, TGCT-patients were recruited by their nurse specialist (DZ) during consultation in the outpatient clinic of the UMCU. The complete and revised list of late effects was presented in an online Castor EDC survey for TGCT-patients. To measure the main study parameters, the prevalence and intensity of late effects in TGCT-patients,

every late effect was accompanied by an NRS score, as standard according to the USD (van der Baan et al., 2020). An NRS score of zero meant absence of the late effect, and numbers one to ten meant a prevalent effect, with higher scores representing higher intensity of the prevalent late effect. Patients were asked to score an NRS, based on experienced burden during the last three months. Besides, patients were invited to prioritize the late effects, according to their situation. Baseline data were assessed to measure the secondary study parameters; difference in prevalence and intensity of late effects in TGCT-patients who underwent different treatment schedules and during different years of follow-up after treatment. Baseline data such as age, comorbidity, treatment schedule, social status, employment status and WHO performance status were asked.

### 3.4. Data analysis

Both descriptive and inferential statistics were conducted using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp, Armonk, NY). The complete datasets of both healthcare-professionals and TGCT-patients were checked for missing values. Missing data occurred in <10% of data, therefore no imputation method was performed (Bennett, 2001; Field, 2013).

For data presentation of healthcare professionals, only descriptive statistics were used.

To meet the primary aim of this study, an estimated sample size of 45 patients was needed, based on a similar study (Ijzerman-Korevaar et al., 2018). For the primary aim, descriptive statistics were used to provide insight in overall prevalence and intensity of late effects.

To answer the secondary aims, a minimal sample size of 15 patients per category (e.g. treatment schedule or years in follow-up) was required (Johnson et al., 2011). To answer both secondary aims of this study, a total of 75 (5x15) patients was needed.

Due to an unequal distribution of patients in the different years of follow-up, and the different treatment schedules, analysis was performed using dichotomized categories (Field, 2013). For follow-up, 'early follow-up' was defined as the first two years of follow-up, including the category 'different' in which patients experienced recurrence of cancer and received additional treatments, therefore not progressing to the later follow-up years. 'Late follow-up' was defined as the last three years of follow-up. For treatment-schedules, analysis was performed using dichotomized categories. These categories included 'surgery, chemotherapy or radiation' and 'surgery combined with salvage chemotherapy'.

To test for differences in prevalent late effects between dichotomized categories of follow-up groups or treatment-schedules, a Chi-Square test was performed. Fisher's Exact test was performed instead when expected counts were not met (Field, 2013). To test for mean differences in intensity of late effects between dichotomized categories of follow-up groups or treatment-schedules, a Mann-Whitney *U* test was performed. Statistical significance was calculated two-sided and set at  $p < 0,05$ . In this new field of research, significance levels will provide insight and will be used to generate hypotheses for new research.

To gain insight in TGCT-patients' prioritization of late effects, patients were asked to prioritize three late effects which had most influence on their daily life or bothers them most.

### 3.5. Ethical considerations

This study was conducted according to the principles of the Declaration of Helsinki (64th version, October 2013) (World Medical Association, 2013), the Dutch code of conduct for research integrity (KNAW et al., 2018), the Medical Research Involving Human Subjects Act (WMO) (CCMO, 2020), and the General Data Protection Regulation (in Dutch: UAVG) (Overheid, 2018). The study was no subject to the WMO, according to the Medical Research Ethics Committee (MREC) of the UMCU, reference number 21–040/C.

Informed consent of all participants was obtained during the first questions of both online surveys. Surveys were only sent after healthcare professionals and patients provided permission to their colleague or nurse specialist (DZ) to be approached by e-mail by the executive researcher (RE).

## 4. Results

### 4.1. Literature review of late effects

Running the searches in the electronic databases resulted in 2029 articles. After the duplicates were removed, the search resulted in 1700 potentially relevant articles. Initial screening of titles and abstracts excluded a further 1441 articles. For the 259 remaining articles full-text was obtained. Of these remaining articles, 181 did not meet all eligibility criteria, resulting in the inclusion of 78 articles for the literature review (Fig. 1). Furthermore, screening reference lists did not result in more eligible articles.

### 4.2. Assessment of late effects

#### 4.2.1. Peer group discussion

After performing the review, merging and translating late effects to Dutch, and requesting expert-opinion, a peer group discussion in the research group was held to formulate assessable symptoms. This process resulted in the list of late effects or symptoms as presented in Fig. 2.

### 4.3. Healthcare professionals

#### 4.3.1. Demographic data

Ten out of thirteen approached healthcare professionals (nurse specialists (7), urologists (2) and an internist-oncologist (1)) responded to the survey-invitation. Their median age was 44 years (IQR 39,2–48,5). The median work experience in follow-up care for TGCT-patients was 7 years (IQR 3–13,5).

#### 4.3.2. Results

Four healthcare professionals recognized all described late effects from their daily clinical practice. Late effects 'sleep problem' and 'reduced appetite' were recognized by all health care professionals. The described late effects were prioritized, in which 'fatigue' was prioritized first most often (Table 1).

### 4.4. Survey for TGCT-patients

#### 4.4.1. Demographic data

In total, 108 participants were approached during follow-up consultation for participating in this study. The survey was completed by 65 participants (60,2%). The mean age of participants was 36.4 years ( $\pm 9,1$ ). Most participants are living together with their families. Of all participants, 90.8% indicated their performance status as WHO 0, meaning they are fully active and able to carry on all pre-disease performances. Sixteen TGCT-patients (24.6%) suffered from any comorbidity. The majority of the TGCT-patients (63.1%) received surgery, followed by multiple cycles of chemotherapy. Most of included TGCT-patients (29.2%) were currently in the second follow-up year (Table 2).

#### 4.4.2. Results

**4.4.2.1. Prevalence and intensity of late effects.** TGCT-patients indicated 'fatigue', 'disturbed overall well-being', 'concentration problems' and 'neuropathy' as most prevalent late effects. Intensity of late effects was scored highest for 'fatigue', 'disturbed overall well-being', 'concentration problems' and 'neuropathy' as well (Table 3).

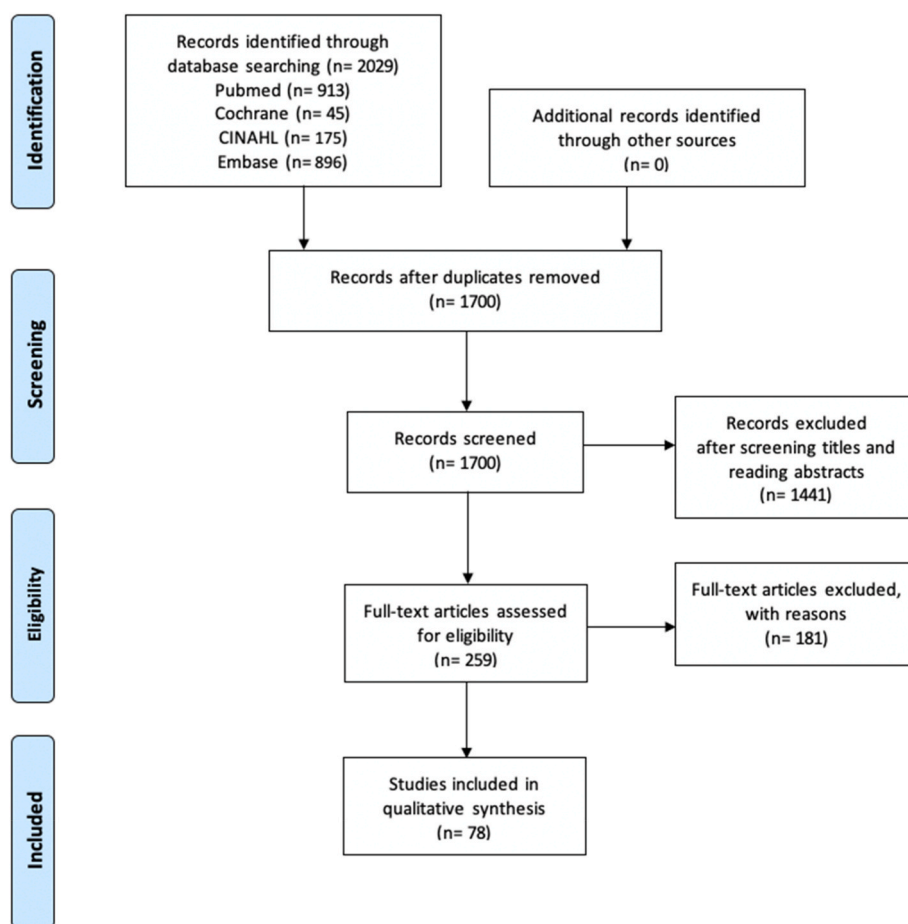


Fig. 1. Flowscheme of included studies (PRISMA) (Moher et al., 2009).

Pain	Tingling in hands and feet	Reduced appetite	Discoloration of fingers or toes
Changes in taste	Memory problems	Painful mouth	Sleep problem
Damaged oral mucosa	Concentration problems	Swallowing problems	Reduced self-confidence
Changes in weight	Concerns about fertility	Diarrhea	Changes in sexual life
Constipation	Reduced libido	Disturbed stool pattern	Erectile dysfunction
Feeling bloated	Nausea	Problems with urinating	Shortness of breath
Thirsty	Fatigue	Changes in hair	Anxiety
Hearing impairment	Depressed mood	Tinnitus	Listless
Skin problems	Dizzy	Palpitations	Drowsy
Sweating	Quickly irritated	Overall well-being	

Fig. 2. Complete list of late effects.

Table 1

Priority of late effects by health-care professionals.

Late effect	Priority 1, n	Priority 2, n	Priority 3, n	Total, n
Fatigue	5	–	2	7
Overall well-being	2	1	1	4
Concentration problems	1	1	–	2
Neuropathy	1	2	1	4
Depressed mood	1	–	–	1
Anxiety	–	1	2	3
Discoloration of fingers or toes	–	1	–	1
Tinnitus	–	1	–	1
Changes in weight	–	1	–	1
Reduced self-confidence	–	1	1	2
Concerns about fertility	–	1	1	2
Erectile dysfunction	–	–	1	1
Changes in sexual life	–	–	1	1

#### 4.4.2.2. Prevalence and intensity of late effects by years of follow-up.

Patients indicated ‘palpitations’ ( $p = 0.020$ ) as significantly more prevalent during ‘late follow-up’ (Table 4). A trend was seen for more prevalent changes in sexual life for patients during early follow-up ( $p = 0.053$ ).

#### 4.4.2.3. Prevalence and intensity of late effects by treatment-schedule.

Patients indicated ‘neuropathy’ ( $p = 0.005$ ), ‘memory problems’ ( $p = 0.009$ ), ‘changes in hair’ ( $p = 0.016$ ), and ‘hearing impairment’ ( $p = 0.006$ ) as significantly more prevalent in the group ‘surgery combined with salvage chemotherapy’.

‘Changes in hair’ ( $p = 0.014$ ), ‘neuropathy’ ( $p = 0.009$ ), ‘memory problems’ ( $p = 0.008$ ), ‘hearing impairment’ ( $p = 0.004$ ), ‘tinnitus’ ( $p = 0.000$ ) and ‘concentration problems’ ( $p = 0.050$ ) showed differences between groups, with higher intensity in the group ‘surgery combined with salvage chemotherapy’ (Table 5).

#### 4.4.2.4. Prioritizing late effects.

Most patients (67.7%) indicated ‘not



**Table 2**  
Characteristics of TGCT-patients.

Characteristics	Included patients (n = 65)
Age, median (IQR)	35.0 (29.5-43.5)
Social status, n (%)	
- Single	11 (16.9)
- Living together with partner	20 (30.8)
- Married	27 (41.5)
- Different	7 (10.8)
Social status children, n (%)	
- Yes, living at home	29 (44.6)
- Yes, living elsewhere	2 (3.1)
- No	34 (52.3)
Employment status, n (%)	
- Not employed	2 (3.1)
- Sickness benefits	1 (1.5)
- On payroll	43 (66.2)
- Self-employed without employees	7 (10.8)
- Social assistance benefit	0 (0)
- Different	12 (18.5)
WHO performance status, n (%)	
- 0) Fully active, able to carry on all pre-disease performance without restriction	59 (90.8)
- 1) Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	4 (6.2)
- 2) Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	2 (3.1)
- 3) Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	0 (0)
- 4) Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	0 (0)
Treatment, n (%)	
<i>Surgery, adjuvant chemotherapy or radiation</i>	<i>24 (36.9)</i>
- Surgery (orchiectomy)	13 (20.0)
- Surgery, followed by one cycle of chemotherapy	6 (9.2)
- Surgery, followed by radiation	5 (7.7)
<i>Surgery combined with salvage chemotherapy</i>	<i>41 (63.1)</i>
- Surgery, followed by multiple cycles of chemotherapy	31 (47.7)
- Different (i.e. multiple lines of chemotherapy or surgery, chemotherapy and radiation)	10 (15.4)
Year of follow-up care, n (%)	
<i>Early follow-up</i>	<i>31 (47.6)</i>
- 1 year	6 (9.2)
- 2 years	19 (29.2)
- Different (i.e. recurrences)	6 (9.2)
<i>Late follow-up</i>	<i>34 (52.3)</i>
- 3 years	14 (21.5)
- 4 years	8 (12.3)
- 5 years	12 (18.5)

-applicable' in all three prioritization categories. In the first place 'neuropathy', 'fatigue' and 'concerns about fertility' scored 17%, 9.2% and 9.2% respectively. Secondly, 'fatigue' and 'memory problems' were scored by 7.7% of patients. In third place, 'changes in sexual life' scored 7.7%, 'fatigue' and 'tinnitus' were scored by 4.6% of patients (Table 6).

## 5. Discussion

This study aimed to provide unique insights in the prevalence and intensity of late effects in TGCT-patients, as a first step of instrument development. More than half of included TGCT-patients indicated 'fatigue', 'disturbed overall well-being', 'concentration problems' and 'neuropathy', as most prevalent late effects. For intensity, the same late effects showed the highest median score on the NRS as well, although the highest median was 'only' two on the NRS.

When late effects were distinguished by years of follow-up, only 'palpitations' and 'changes in sexual life' showed a tendency for more prevalence during early follow-up. For intensity of late effects, a trend was seen for 'palpitations', which was scored significantly higher in the group 'late follow-up'.

**Table 3**  
Prevalence and intensity of late effects according to TGCT-patients.

Late effect	Prevalence, n (%)	Intensity of late effects, NRS, median (range)
Fatigue	39 (60.0)	2 (0-9)
Overall well-being (disturbed)	37 (56.9)	1 (0-9)
Concentration problems	36 (55.4)	1 (0-9)
Neuropathy	34 (52.3)	1 (0-10)
Quickly irritated	27 (41.5)	0 (0-10)
Concerns about fertility	27 (41.5)	0 (0-10)
Changes in sexual life	27 (41.5)	0 (0-8)
Depressed mood	26 (40.0)	0 (0-8)
Reduced self-confidence	25 (38.5)	0 (0-7)
Memory problems	25 (38.5)	0 (0-8)
Tinnitus	24 (36.9)	0 (0-8)
Skin problems	24 (36.9)	0 (0-8)
Thirsty	24 (21.5)	0 (0-8)
Reduced libido	24 (36.9)	0 (0-8)
Listless	23 (35.4)	0 (0-9)
Sleep problems	22 (33.8)	0 (0-8)
Pain	21 (32.3)	0 (0-5)
Anxiety	20 (30.8)	0 (0-10)
Hearing impairment	20 (30.8)	0 (0-7)
Sweating	20 (30.8)	0 (0-8)
Changes in weight	18 (27.7)	0 (0-10)
Diarrhea	16 (24.6)	0 (0-7)
Erectile dysfunction	15 (23.1)	0 (0-5)
Feeling bloated	15 (23.1)	0 (0-7)
Problems with urinating	14 (21.5)	0 (0-5)
Disturbed stool pattern	14 (21.5)	0 (0-6)
Raynaud's phenomena	14 (21.5)	0 (0-8)
Drowsy	13 (20.0)	0 (0-7)
Shortness of breath	11 (16.9)	0 (0-6)
Constipation	11 (16.9)	0 (0-4)
Palpitations	11 (16.9)	0 (0-5)
Dizzy	9 (13.8)	0 (0-7)
Changes in taste	8 (12.3)	0 (0-8)
Damaged oral mucosa	7 (10.8)	0 (0-8)
Nausea	7 (23.1)	0 (0-5)
Reduced appetite	5 (7.7)	0 (0-5)
Painful mouth	4 (10.8)	0 (0-10)
Swallowing problems	4 (6.2)	0 (0-5)

When late effects were distinguished by treatment-schedules, 'neuropathy', 'memory problems', 'changes in hair', and 'hearing impairment' showed differences in prevalence and intensity as well.

Correspondingly, late effects 'neuropathy', 'memory problems', 'changes in hair', 'hearing impairment' and 'concentration problems' are widely known both in clinical practice and in literature for their impact in TGCT-survivors (Chovanec et al., 2021; Fung et al., 2018, 2019), as well as other cancer survivors (Buccafusca et al., 2019; Joly et al., 2019). Similarly as in this study, a recent systematic review showed TGCT-patients experienced a relatively low burden of disease and treatment compared to other types of cancer, although patients receiving chemotherapy and/or radiotherapy experienced more impact on their mental health status (Alexis et al., 2020).

The tendency of differences between treatment groups as found in this study could be explained by clinical experience and the widely known toxicities of bleomycin and platinum-based chemotherapies (Farmacotherapeutisch Kompas, 2021a, 2021b).

For differences between follow-up years, in this study, a trend was seen for palpitations and changes in sexual life.

Palpitations are defined as a rapid pulsation or irregular beating of the heart and is one of the common presenting problems in the emergency room (Essa and Lip, 2021). Based on our findings and literature no satisfactory explanation can be identified why palpitations are more frequently experienced during late follow-up, in this study (Essa and Lip, 2021).

Patients indicated a trend of a higher prevalence of 'changes in sexual life' in the group 'early follow-up'. TGCT-patients may experience lower overall satisfaction in sexual life shortly after treatment, due to

**Table 4**

Prevalence of late effects by years of follow-up and by treatment schedule.

Late effect	Prevalence in 'early follow-up' n (%) (n = 31)	Prevalence in 'late follow-up' n (%) (n = 34)	P-value	Prevalence in 'surgery adjuvant chemo or radiation' n (%) (n = 26)	Prevalence in 'surgery combined with salvage chemo' n (%) (n = 39)	P-value
Fatigue	58,1 (18)	61,8 (21)	0.355 <sup>A</sup>	13 (50)	26 (67)	0.179 <sup>A</sup>
Overall well-being (disturbed)	54,8 (17)	64,5 (20)	0.407 <sup>A</sup>	15 (58)	22 (56)	0.919 <sup>A</sup>
Neuropathy	51,6 (16)	52,9 (18)	0.344 <sup>A</sup>	8 (31)	26 (67)	<b>0.005<sup>A</sup></b>
Concentration problems	48,4 (15)	61,8 (21)	0.981 <sup>A</sup>	11 (42)	25 (64)	0.083 <sup>A</sup>
Quickly irritated	45,2 (14)	38,2 (13)	0.155 <sup>A</sup>	11 (42)	16 (41)	0.918 <sup>A</sup>
Changes in sexual life	48,4 (15)	35,3 (12)	0.053 <sup>A</sup>	13 (50)	14 (36)	0.258 <sup>A</sup>
Reduced libido	41,9 (13)	32,4 (11)	0.114 <sup>A</sup>	12 (46)	12 (31)	0.208 <sup>A</sup>
Memory problems	35,5 (11)	41,2 (14)	0.750 <sup>A</sup>	5 (19)	20 (51)	<b>0.009<sup>A</sup></b>
Changes in hair	35,5 (11)	38,2 (13)	0.591 <sup>A</sup>	5 (19)	19 (49)	<b>0.016<sup>A</sup></b>
Changes in weight	32,3 (10)	23,5 (8)	0.156 <sup>A</sup>	6 (23)	12 (31)	0.497 <sup>A</sup>
Tinnitus	32,3 (10)	41,2 (14)	0.987 <sup>A</sup>	3 (12)	21 (54)	<b>0.001<sup>A</sup></b>
Concerns about fertility	29,0 (9)	52,9 (18)	0.258 <sup>A</sup>	11 (42)	16 (41)	0.918 <sup>A</sup>
Depressed mood	29,0 (9)	50,0 (17)	0.355 <sup>A</sup>	9 (35)	17 (44)	0.469 <sup>A</sup>
Reduced self-confidence	29,0 (9)	51,6 (16)	0.474 <sup>A</sup>	8 (31)	17 (44)	0.298 <sup>A</sup>
Hearing impairment	29,0 (9)	32,4 (11)	0.706 <sup>A</sup>	3 (12)	17 (44)	<b>0.006<sup>A</sup></b>
Skin problems	25,8 (8)	51,6 (16)	0.304 <sup>A</sup>	7 (27)	17 (44)	0.173 <sup>A</sup>
Sleep problems	25,8 (8)	41,2 (14)	0.545 <sup>A</sup>	9 (35)	13 (33)	0.915 <sup>A</sup>
Pain	25,8 (8)	38,2 (13)	0.697 <sup>A</sup>	10 (39)	11 (28)	0.386 <sup>A</sup>
Sweating	25,8 (8)	35,3 (12)	0.867 <sup>A</sup>	5 (19)	15 (39)	0.100 <sup>A</sup>
Listless	22,6 (7)	51,6 (16)	0.179 <sup>A</sup>	9 (35)	14 (36)	0.916 <sup>A</sup>
Disturbed stool pattern	22,6 (7)	20,5 (7)	0.468 <sup>A</sup>	7 (27)	7 (18)	0.389 <sup>A</sup>
Problems with urinating	22,6 (7)	20,5 (7)	0.468 <sup>A</sup>	5 (19)	9 (23)	0.712 <sup>A</sup>
Erectile dysfunction	22,6 (7)	23,5 (8)	0.646 <sup>A</sup>	4 (15)	11 (28)	0.229 <sup>A</sup>
Diarrhea	22,6 (7)	26,5 (9)	0.836 <sup>A</sup>	6 (23)	10 (26)	0.814 <sup>A</sup>
Anxiety	19,4 (6)	41,2 (14)	0.208 <sup>A</sup>	6 (23)	14 (36)	0.273 <sup>A</sup>
Feeling bloated	16,1 (5)	29,4 (10)	0.462 <sup>A</sup>	5 (19)	10 (26)	0.548 <sup>A</sup>
Raynaud's phenomena	16,1 (5)	26,5 (9)	0.618 <sup>A</sup>	3 (12)	11 (28)	0.109 <sup>A</sup>
Constipation	16,1 (5)	20,5 (7)	1.000 <sup>B</sup>	5 (19)	7 (18)	1.000 <sup>B</sup>
Thirsty	12,9 (4)	29,4 (10)	0.266 <sup>A</sup>	4 (15)	10 (26)	0.324 <sup>A</sup>
Drowsy	12,9 (4)	26,5 (9)	0.378 <sup>A</sup>	4 (15)	9 (23)	0.448 <sup>A</sup>
Shortness of breath	12,9 (4)	20,5 (7)	0.751 <sup>B</sup>	3 (12)	8 (21)	0.344 <sup>B</sup>
Changes in taste	12,9 (4)	11,8 (4)	0.709 <sup>B</sup>	2 (8)	6 (15)	0.460 <sup>B</sup>
Damaged oral mucosa	12,9 (4)	8,8 (3)	0.437 <sup>B</sup>	2 (8)	5 (13)	0.693 <sup>B</sup>
Dizzy	9,7 (3)	17,6 (6)	0.590 <sup>B</sup>	2 (8)	7 (18)	0.241 <sup>B</sup>
Swallowing problems	9,7 (3)	2,9 (1)	0.299 <sup>B</sup>	1 (4)	3 (8)	0.644 <sup>B</sup>
Nausea	6,5 (2)	14,7 (5)	0.461 <sup>B</sup>	2 (8)	5 (13)	0.513 <sup>B</sup>
Palpitations	3,2 (1)	29,4 (10)	<b>0.020<sup>B</sup></b>	4 (15)	7 (18)	1.000 <sup>B</sup>
Reduced appetite	3,2 (1)	11,8 (4)	0.393 <sup>B</sup>	2 (8)	3 (8)	1.000 <sup>B</sup>
Painful mouth	3,2 (1)	8,8 (3)	0.636 <sup>B</sup>	3 (12)	1 (3)	0.293 <sup>B</sup>

<sup>A</sup> Chi-square test used.<sup>B</sup> Fisher's exact test due to expected counts less than 5 in one of the cells.

psychological and physical complaints as erectile dysfunction, lower levels of testosterone and negative changed body image (Chovanec et al., 2020; Rossen et al., 2012), with satisfaction increasing during follow-up years. A recent systematic review substantiates this finding as well, describing overall satisfaction with sexual life was even higher in TGCT-survivors (11–14 years after treatment) than in healthy controls (Bogefors et al., 2017; Chovanec et al., 2021). Hypothetically, after experiencing difficulties in sexual life, TGCT-survivors may appreciate their overall sexual life more.

The stepwise approach toward a first draft of instrument development can be considered a strength of this study, as well as the thorough and systematic literature review. Another strength is the gap this study is aiming to resolve, since no instrument currently exists to assess the late effects of TGCT-patients during follow-up (Klonoff-Cohen and Polavarapu, 2020).

Another strength of this study is the fact that prior to distributing the survey to TGCT-patients, healthcare professionals provided their opinion and prioritization on the complete list of late effects. Healthcare

professionals recognized all described late effects and prioritized 'fatigue', 'disturbed overall well-being', 'neuropathy' and 'concentration problems' based on their clinical practice in follow-up care for TGCT-patients. This is in complete accordance with the late effects indicated as most prevalent and scored with highest intensity by TGCT-patients.

Nevertheless, this study contains several limitations. Since testicular cancer represents one percent of neoplasms in male worldwide (Laguna et al., 2020), this domain is quite small. In the Netherlands, about 832 men are diagnosed with testicular cancer yearly (Integraal Kankercentrum Nederland, 2021). Although the sample size of this study contained only 65 patients from the outpatient clinic of the UMCU, this sample still represents a substantial part of Dutch TGCT-patients in follow-up care. Besides, this sample group of 65 patients is also considered representative of the TGCT population since all treatment-groups and follow-up years are present.

The start of follow-up care was marked as complete remission on CT-scan, 6 months after completion of treatment. In the Netherlands, TGCT-patients are in follow-up care for a minimum of five years (Algaba et al.,

**Table 5**  
Intensity of late effects by treatment-schedule.

Late effect	Group	Mean sum of ranks	p-value <sup>a</sup>
Changes in hair	Surgery, adjuvant chemotherapy or radiation	26.90	p = 0.014
Neuropathy	Surgery, salvage chemotherapy	37.06	
	Surgery, adjuvant chemotherapy or radiation	25.88	p = 0.009
Memory problems	Surgery, salvage chemotherapy	37.74	
	Surgery, adjuvant chemotherapy or radiation	26.35	p = 0.008
Hearing impairment	Surgery, salvage chemotherapy	37.44	
	Surgery, adjuvant chemotherapy or radiation	26.90	p = 0.004
Tinnitus	Surgery, salvage chemotherapy	37.53	
	Surgery, adjuvant chemotherapy or radiation	24.15	p = 0.000
Concentration problems	Surgery, salvage chemotherapy	38.90	
	Surgery, adjuvant chemotherapy or radiation	27.65	p = 0.050
	Surgery, salvage chemotherapy	36.56	

<sup>a</sup> Asymp. Sig. (2-tailed).

**Table 6**  
Priority of late effects according to TGCT-patients.

Late effect	Priority 1, n (%)	Priority 2, n (%)	Priority 3, n (%)	Total, n (%)
Neuropathy	11 (17)	3 (4.6)	2 (3.1)	16 (24.6)
Fatigue	6 (9.2)	5 (7.7)	3 (4.6)	14 (21.5)
Concerns about fertility	6 (9.2)	3 (4.6)	1 (1.5)	9 (13.8)
Reynaud	5 (7.7)	3 (4.6)	–	8 (12.3)
Tinnitus	5 (7.7)	4 (6.2)	3 (4.6)	12 (18.5)
Pain	4 (6.2)	2 (3.1)	2 (3.1)	8 (12.3)
Changes in sexual life	3 (4.6)	4 (8.9)	5 (7.7)	12 (18.5)
Memory problems	2 (3.1)	5 (7.7)	2 (3.1)	9 (13.8)
Not applicable	9 (13.8)	16 (24.6)	19 (29.2)	44 (67.7)

2021), as followed in this study. However, some may consider another marking point of follow-up care, which may influence results in follow-up groups.

For answering the secondary aims, a minimum of 75 patients was needed, this sample size was not met due to data collection during the Covid-19 pandemic, which probably led to decreased response.

Besides, a non-equal distribution of participants amongst treatment-schedules and follow-up years was found. However, an appropriate solution was found by dichotomizing both the treatment- and follow-up groups for statistical analysis. These results however, should be interpreted with caution. In our study, results will be used to explore a trend toward differences between groups and formulate hypotheses for further research developing the new USD-module for TGCT-patients.

For further research validation of the new USD item list should be performed to provide an appropriate USD-module for TGCT-patients in follow-up care. With standardized application of the validated USD-module, follow-up care can improve by empowering patients to discuss important items in daily life with their health-care professional.

## 6. Conclusion

This study provides unique insights into the prevalence and intensity of late effects in TGCT-patients. All described late effects were recognized by TGCT-patients, with ‘fatigue’, ‘disturbed overall well-being’, ‘concentration problems’ and ‘neuropathy’, indicated as most prevalent and scored with highest intensity. This broad exploration is of great value to get insight into the burden of late effects for TGCT patients during follow-up care and develop a specific TGCT USD-module for

standardized monitoring of individually experienced symptom burden.

## Declaration of interests

None declared.

## CRediT authorship contribution statement

**Roos Enzlin:** Conceptualization, Methodology, Software, Investigation, Formal analysis, Writing – original draft. **Sigrid C.J.M. Vervoort:** Conceptualization, Methodology, Validation, Writing – review & editing, Supervision. **Britt B.M. Suelmann:** Writing – review & editing. **Richard P. Meijer:** Writing – review & editing. **Saskia C.C.M. Teunissen:** Writing – review & editing. **Danielle Zweers:** Conceptualization, Methodology, Validation, Writing – review & editing, Supervision.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejon.2023.102303>.

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