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General introduction

Chapter 1
Introduction and aim

Background

Testicular cancer is a disease that primarily affects young men between the age of 15 and 35 years. In this age group, it is the most common type of cancer in men. The incidence of testicular cancer is steadily increasing (Figure 1). The incidence rates in the northern and western part of Europe are the highest worldwide. Since the introduction of platinum-based chemotherapy in the late seventies, metastatic testicular cancer has become a curable disease with survival rates around 80%. Approximately 95% of testicular cancers are germ cell tumors. Germ cell tumors are subdivided based on histology in two categories: seminoma (55%) and non-seminoma (45%). Treatment strategy for metastatic disease depends on histology, location of disease and classification in prognosis groups based on the International Germ Cell Cancer Collaboration Group criteria. In general, in case of metastatic disease, the treatment consists of surgery with subsequent platinum-based combination chemotherapy. In case of limited disseminated seminoma, radiotherapy is a treatment option. In stage I disease, watchful-waiting or active surveillance has become the main strategy instead of adjuvant chemotherapy or radiotherapy.

![Figure 1](image1.png)

As a result of both the increasing incidence and high cure rates, the number of survivors of testicular cancer is increasing. In the Netherlands, in 2017 the estimated number of testicular cancer patients diagnosed with testicular cancer in the prior 20 years was approximately 11,300 (Figure 2). In 2015, there were an estimated 257,800 men living with a history of testicular cancer in the United States (data from Surveillance, Epidemiology, and End Results (SEER)). Due to the successful treatment, testicular cancer could serve as a model for the care for long-term cancer survivors: survivorship care. It has become increasingly clear that potential harmful long-term and late side effects of the treatment can have a major impact on the health-related quality of life after treatment. Long-term effects are side effects that appear during treatment and persist when the treatment is finished. In contrast, late effects are side effects that develop gradually and become

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1. Reference 1
2. Reference 2
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manifest months to years after treatment. The health status of survivors should be monitored for long-term and late effects and, if indicated, preventive strategies and/or therapeutic options should be explored.

Figure 2. 20-years prevalence of testicular cancer in The Netherlands (data Figure 1 and 2 from The Netherlands Comprehensive Cancer Organization).

Long-term and late toxicity in testicular cancer survivors
In general, testicular cancer survivors have a very good prognosis as demonstrated by SEER data; the life-expectancy of a testicular cancer patients diagnosed at age 30 years was estimated as 45 years; two years less than a man of the same age without cancer. However, after the treatment a significant proportion of testicular cancer survivors is affected by long-term and late toxicity of the treatment. The most threatening late effects are second cancers and cardiovascular disease. Other long-term and late effects of treatment that are frequently observed after platinum-based chemotherapy are neurotoxicity, renal toxicity and hypogonadism.

Early observations of acute cardiovascular toxicity during platinum-based chemotherapy were reported in the eighties. In the nineties, an increased prevalence of several cardiovascular risk factors was noticed. In 2006, the 20-year risk for cardiovascular disease was estimated to be 18.1% in a large Dutch cohort of 2500 testicular cancer survivors. Cardiovascular risk factors, sometimes clustered in the metabolic syndrome, were more frequently observed in comparison with age-matched controls. Patients treated with the standard chemotherapy regime consisting of bleomycin, etoposide, and cisplatin have a hazard ratio for coronary artery disease of 5.7 (95% confidence interval [CI], 1.9–17.1) compared to age-matched controls. Early onset cardiovascular disease was also found in a population-based study with more than 15,000 patients with a standardized mortality ratio of 1.36 (95% CI, 1.03–1.78). Another distinct example of vascular toxicity that is frequently observed shortly after the treatment in testicular cancer...
patients is Raynaud’s phenomenon, a typical discoloration of the fingers after exposure to cold temperatures or emotion.\textsuperscript{17} The etiology of late cardiovascular side-effects of chemotherapy is not yet fully elucidated. Firstly, it may be that chemotherapeutic agents directly induce vascular damage or toxic changes. There are signs of vascular damage observed, such as microalbuminuria.\textsuperscript{18} It is known that residuals of the platinum component of the treatment is circulating for many years after the treatment.\textsuperscript{19} It is unknown whether this circulating platinum is causally related to late cardiovascular toxicity.

Secondly, risk factors may play a role in the development of cardiovascular disease. Hypogonadism is often observed in testicular cancer survivors and is considered to be a contributing factor to the risk at cardiovascular disease. Low testosterone is in part the result of the treatment, but it could also be influenced by obesity and altered androgen metabolism. Because it is observed that not all survivors are susceptible for developing both short-term and long-term effects, identifying genetic susceptibility could help in indicating specific subgroups that are particularly at risk for late effects. Specific variations in genes (single nucleotide polymorphisms (SNPs)) may identify patients who are especially vulnerable for developing long-term toxicity. Such a group of selected patients are candidates to develop and test interventional therapies to manage and prevent long-term and late toxicity. This method was for example used to evaluate the influence of a SNP in the gene encoding bleomycin hydrolase, $BLMH$, on outcome of testicular patients treated with bleomycin-cisplatin combination chemotherapy. Survival of patients was associated with the SNP in this bleomycin hydrolase gene, whereas bleomycin lung toxicity itself was not.\textsuperscript{20}

**Implications for the organization of survivorship care**

The growing population of cancer survivors demands new ways to organize the care after cancer. Collaboration between medical oncologists and primary care physicians may improve early detection and management of cardiovascular risk factors and lead to complementary psychosocial support close to where patients live. The high prevalence of cardiovascular disease risk factors and the metabolic syndrome in testicular cancer survivors makes collaboration between primary care and oncology especially important.\textsuperscript{14} If the primary care physician is involved in early follow-up after completion of treatment, the long-term care after completion of the follow-up is better secured. Because most of the patients treated for testicular cancer will not develop a relapse, they will be discarded from oncologic follow-up after ten years. However, especially this patient group stays at an increased risk for cardiovascular events for several decades after the treatment.

Since patients are often more familiar with their own primary care physician, the primary care physician is well-equipped to manage psychosocial issues of the patients, as well as their family members, both early and late after the cancer diagnosis. Also, after follow-up, the primary care physician is the most approachable and primarily the coordinating care provider. In an observational study by Dahl, testicular cancer survivors had a higher chance to seek help from the primary care physician.\textsuperscript{21} A study by De Padova et al. described the opinion of patients and care
providers. It was observed in this study that among patients and care providers uncertainties exist about the roles and responsibilities of the different physicians, supporting the need for adequate survivorship care planning.\textsuperscript{22}

Primary care-led follow-up was successfully implemented for different types of cancer, e.g. breast cancer, colon cancer and melanoma.\textsuperscript{23-25} Shared-care follow-up for childhood cancer survivors was studied in our center by Blauuwbroek \textit{et al}.\textsuperscript{26,27} They concluded that both cancer survivors and primary care physicians are willing to participate in shared-care follow-up. However, currently, in the case of testicular cancer, the collaboration between oncologists and primary care physicians is poorly coordinated and organized. As an example of shared-care follow-up, the study by Blauuwbroek was organized with a web-based survivorship care plan, accessible for patients and health care providers. Participation and satisfaction levels for both patients and primary care physicians were high. The development of a web-based communication system made it feasible to organize follow-up appointments in primary care and secondary care units.

Currently, standard follow-up care after testicular cancer takes place exclusively in secondary and tertiary care such as a comprehensive cancer center. Therefore, the safety of shared-care follow-up, with narrow collaboration between primary and secondary health care providers, has to be evaluated before other aspects and potential benefits can be explored. A new model of shared survivorship care will demand a more active role of the patients. Also, clear communication between the different care providers and the patient will be important. Exploratory studies are needed to advance the methods of follow-up and further optimize the quality of survivorship care.

\textbf{Aim of the thesis}

The studies described in this thesis, aim to improve our understanding of the mechanisms of treatment-related morbidity in testicular cancer patients and to develop and evaluate a new model of shared-care survivorship care after testicular cancer.

\textbf{Outline of the thesis}

The focus of the first part of this dissertation lies on cardiovascular late toxicity of testicular cancer survivors. The presented studies evaluate short- and long-term markers for and development of late toxicity.

In \textit{chapter 2}, a review is presented of late toxicity of platinum-based treatment after testicular cancer. Among the most frequently occurring adverse conditions are cardiovascular disease and secondary neoplasms. Recommendations are given for survivorship care.

In \textit{chapter 3}, serum platinum (Pt) decay after chemotherapy was assessed and modelled and the relationship between long-term circulating Pt levels and known late effects was determined. In 99 testicular cancer survivors, treated with platinum-based chemotherapy, serum and 24-hour urine samples were collected during follow-up (1–13 years after treatment). To build
a population pharmacokinetic model, measured Pt data were simultaneously analysed, together with cisplatin dose, age, weight and height using NONMEM software. Based on this model, area under the curve 1–3 years after treatment was calculated for each patient. Predicted long-term Pt exposure was related to renal function and to late effects of treatment assessed median 9 (3–15) years after treatment.

The indirect effects of chemotherapy regarding cardiovascular disease risk factors, such as changes in metabolic processes, have to be taken into account too and are perhaps more important that direct toxic effects of the cancer treatment on vascular structures. Genetic variations resulting in changes in susceptibility for late toxicity can provide insight in which patients are particularly at risk for late effects and can also provide insight in the pathways along which late effects tend to develop. Genetic variation in androgen metabolism could in turn be associated with variation in adverse cardiometabolic changes after treatment. In chapter 4, a functional SNP in the gene SRD5A2 is described. The gene SRD5A2 encodes 5-alpha-reductase, the enzyme that converts testosterone into the more potent metabolite dihydrotestosterone.

Vascular events during treatment occur in a subgroup of patients. An intervention to prevent these events is not yet available. Acute changes during the period of active chemotherapy may predict how and in what subpopulation of patients late effects will develop. In chapter 5, acute changes during the chemotherapy are described. Changes in vascular markers could be used as biomarkers for early damage as a result of the treatment. The aim of this study is to identify risk factors for early cardiovascular damage.

In the second part of this dissertation, research on the organization of survivorship care is presented. A clear follow-up plan is an essential part in the organization of shared-care follow-up after treatment, during which visits alternate between oncologist and primary care physician. In the seminal report “Lost in transition”, it was argued that each patient should receive a survivorship care plan in order to receive the appropriate after care.

Although this report was published more than a decade ago, the implementation of this recommendation is limited. Since then, research has lost focus of the central idea, namely the plan itself. In chapter 6, a letter to the editor is presented that was written as part of a discussion on survivorship care planning. The use and development of a mobile application for generating survivorship care plans is explained in details in chapter 7. The purpose of this mobile application is to provide patients with a concise and simple care plan during survivorship care. The aim is to develop a tool that is available for other hospitals, both in the Netherlands and in other countries, treating patients with disseminated testicular cancer. With this care plan containing tool, patients can become more in control and navigation of his own care.

In chapter 8 a shared-care survivorship care study is described. The study is designed as an observational cohort study with a stopping rule to check for the safety of follow-up. Safety boundaries are defined for the occurrence of failed responses to signals indicating cancer recurrence. Secondary outcomes are feasibility, cardiovascular risk management, psychosocial status and experiences of patients and primary care physicians, as measured with an evaluation questionnaire.

Finally, data from this thesis are summarized in chapter 9. Findings from the current studies are placed into perspective and recommendations are given for future research.
References

7. IKNL: http://www.cijfersoverkanker.nl, 2018
General introduction
