As a consequence of the successful use of chemotherapy in the treatment of curable neoplasms such as testicular cancer, and the increasing application of (neo)adjuvant chemotherapy for various tumor types, including breast cancer, the number of patients with a presumed normal life expectancy after treatment is rising. Attention for long-term side effects is therefore of growing importance. Evaluation of chronic cardiovascular toxicity is of particular relevance since it may negatively influence the life expectancy after chemotherapy. A number of cytostatic agents is well-known for their toxic effects to the myocardium. Among these the most important are the anthracycline antibiotics, such as doxorubicin and its analogue epirubicin, and related compounds such as mitoxantrone. By far the most important aspect of cardiotoxicity induced by these agents is congestive heart failure, resulting from a cumulative dose-related myocardial damage. This damage occurs during chemotherapy, but it may take a long time before congestive heart failure develops. By means of non-invasive detection techniques myocardial damage can be determined in an early stage before congestive heart failure develops which may allow early medical intervention with the goal to prevent further progression. Until recently, other cytostatic agents such as used in the treatment of patients with disseminated testicular cancer, were not known to cause severe chronic cardiovascular toxicity. However, several reports have indicated that a part of the patients who survives disseminated testicular cancer develops an unfavorable cardiovascular risk-profile and therefore may be prone to develop cardiovascular disease.

The aim of this thesis as formulated in the introduction in chapter 1 was to investigate the long-term effects of chemotherapy on the cardiovascular system, which was mainly studied in testicular cancer and breast cancer patients, treated at the University Hospital Groningen, the Netherlands.

Chapter 2 is a review of the literature on cardiovascular toxicity related to the use of cytostatic agents. Four patient groups with a good life expectancy after successful chemotherapy were selected to review this issue: survivors of metastatic testicular cancer and of malignant lymphomas treated with curative chemotherapy, and breast- and colon cancer patients treated with adjuvant chemotherapy. Besides direct toxic effects of chemotherapy on the cardiovascular system also the indirect toxic effects such as chemotherapy related metabolic and hormonal imbalances that may aggravate cardiovascular damage, are discussed. In survivors of testicular cancer the most evident type of long-term vascular toxicity is Raynaud's phenomenon. Furthermore, a part of this patient group develops an unfavorable cardiovascular risk-profile consisting of hypercholesterolemia and hypertension, which to our experience results in an increased risk of coronary artery disease. In survivors of malignant lymphomas and in patients treated with adjuvant chemotherapy for breast cancer the main type of cardiotoxicity is related to the use of anthracyclines, which can result in congestive heart failure. This risk of cardiotoxicity may be aggravated by the use of thoracic irradiation. In patients treated with adjuvant chemotherapy for colorectal cancer, only acute cardiotoxicity (mainly angina pectoris) is reported related to the use of 5-fluorouracil but this does not appear to be detrimental in the long-term.

In Chapter 3 a review of the literature is presented on the detection of anthracycline-induced cardiotoxicity. Although endomyocardial biopsy is considered to be
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the most sensitive and specific test for this purpose, its use is limited by its invasive-ness. In daily practice oncologists usually make use of the non-invasive determination of the left ventricular ejection fraction to detect early cardiotoxicity, but this method is not suitable to identify cardiotoxicity in an early stage. Based on increasing knowledge into the pathophysiology of anthracycline-induced cardiotoxicity and heart failure in general, new methods including the determination of diastolic function parameters, heart rate variability, and natriuretic peptides have been proposed to identify patients at risk for the development of congestive heart failure in an early stage. However, most of these newer methods have not yet been adequately evaluated to allow them to be recommended for use in routine clinical practice.

In Chapter 4 the results are presented of a follow-up study in testicular cancer survivors who had been treated 10 to 20 years previously with cisplatin based chemotherapy. Since in previous studies it was shown that a number of testicular cancer patients develops an unfavorable cardiovascular risk-profile after chemotherapy, consisting of hypercholesterolemia, overweight and hypertension, we investigated whether these cured patients in the long-term, are at an increased risk of developing cardiovascular morbidity and mortality. Therefore 87 patients treated with cisplatin containing chemotherapy who were still in remission for at least 10 years and whose age was 50 years or less at the time of the analysis, were evaluated for the occurrence of cardiovascular events. Major cardiac events were found in 5 of the 87 patients (age at time of event 30-42 years; 9-16 years after chemotherapy): 2 patients had a myocardial infarction and 3 patients angina pectoris with proven myocardial ischemia. An increased risk for coronary artery disease, as compared to the general male Dutch population was found. Of these 87 patients, 62 were additionally evaluated for cardiac damage and cardiovascular risk factors. Their cardiovascular risk profile was compared to that of 40 patients with comparable age and follow-up duration treated with orchidectomy only for stage I testicular cancer. Echocardiography in the patients treated with chemotherapy showed a normal systolic left ventricular function in most patients, but the diastolic left ventricular function was disturbed in 33%. Moreover, 79% had hypercholesterolemia, 39% hypertension, 25% still experienced Raynaud’s phenomenon, and 22% had microalbuminuria probably reflecting endothelial dysfunction. Compared with stage I patients, the chemotherapy treated patients had higher blood pressures, higher total serum cholesterol- and triglyceride levels and were more insulin resistant. The pathogenesis of the observed increased risk of coronary artery disease is unclear, but this may be linked with several factors, including metabolic and hormonal changes related to gonadal toxicity, possibly resulting in the development of a syndrome X-like state. The latter is suggested by the combination of overweight, microalbuminuria, hypertension, insulin resistance and dyslipidemia found in some of these patients. Furthermore, the induction of chronic endothelial dysfunction may play a role. Accurate follow-up, focused on cardiovascular complications and aiming at intervention in these young cancer-survivors, appears to be of great importance in the near future.

Exposure to cisplatin combination chemotherapy seems with the current data an important contributing factor in the occurrence of cardiovascular disease in long-term survivors of metastatic testicular cancer. The interval between chemotherapy treatment in these patients and the development of cardiovascular disease may take
more than 10 years.

For this reason we hypothesized in chapter 5 whether the observed increased risk of cardiovascular disease might be related to prolonged retention of cisplatin in the body. Therefore we measured plasma platinum concentrations using a very sensitive assay. In this assay high-pressure decomposition of samples was performed, followed by an adsorptive voltammetric measurement. Plasma platinum concentrations in the patients studied were compared with those of 20 control patients who were cured from stage I testicular cancer by orchidectomy without chemotherapy. In all 61 tested patients who were 10-20 years after cisplatin administration, platinum was detectable with a mean concentration of 64.9 pg/g plasma, whereas in the control group platinum concentrations were not detectable. The height of the platinum concentration was related to the cumulative dose administered and inversely related to the renal function. These results suggest that platinum is recirculating in the plasma between potential body stores such as the liver, bone, and muscle. These chronic low plasma concentrations of platinum may play a role in the development of cardiovascular morbidity after chemotherapy.

In chapter 6 we describe the results of the investigations regarding the magnesium status in long-term survivors of testicular cancer. Hypomagnesemia in general has been associated with hypertension, abnormal lipid metabolism, and accelerated atherosclerosis, and the occurrence of vascular ischemic events. Cisplatin can cause proximal-tubule damage that results in renal magnesium wasting. The time during which this magnesium depletion persists after treatment is not known. Since about 99% of the total body magnesium is located intracellularly, determination of the red-blood cell magnesium concentration might be a better indicator of the magnesium status than the serum magnesium concentration. In addition, a low intracellular magnesium content is associated with hypertension and insulin-resistance. Both red-blood cell magnesium concentration (assessed by an indirect method) and the serum magnesium concentration were measured in 50 survivors of testicular cancer who were 10 to 20 years after treatment. These data were compared with the magnesium status of a control group of 17 patients with testicular cancer not treated with chemotherapy. We found that although the mean serum concentration of magnesium in both groups did not differ, the red-blood cell magnesium content in the group of patients treated with chemotherapy was significantly lower than in the control group. These data suggest that up to 20 years after cisplatin-containing chemotherapy survivors of testicular cancer are still magnesium deficient, although the serum magnesium concentration is normal. This disturbed magnesium equilibrium might play a role in the development of unfavorable cardiovascular risk profile observed in these patients.

In chapter 7 we describe a (pilot) study performed in breast cancer patients, who had been treated with anthracyclines and irradiation, in order to investigate early signs of cardiotoxicity in these patients. These patients had all participated in high-dose chemotherapy schedules including autologous bone- or stem cell transplantation. We tested whether analysis of the heart rate variability calculated from a 24-hr Holter registration, as measure for the autonomic tone, and assessment of the diastolic function by echocardiography could help to identify early signs of cardiotoxicity. Therefore twenty females treated for breast cancer with high-dose anthracycline-
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based chemotherapy were evaluated. None of these patients had signs or symptoms of heart disease and all had a normal systolic left ventricular function. One or more echocardiographic diastolic parameters were abnormal in 50% of the patients. HRV frequency parameters were even abnormal in 85% of the patients. Mean values of both time domain and frequency domain parameters were decreased, in particular the parasympathetic indexes compared to a control group consisting of healthy age-matched females. It was concluded that autonomic impairment occurs in a large proportion of asymptomatic patients with normal systolic LV function after high-dose anthracycline-based chemotherapy and seems to be an early sign of cardiotoxicity after treatment.

To explore these findings further in a more homogenous population we evaluated in chapter 8 in a cross-sectional design the cardiac function by means of various detection techniques in 56 breast cancer patients two or more years after epirubicin-containing chemotherapy combined with locoregional irradiation. Patients had been treated within a randomized phase III study comparing 5 cycles of 5-fluorouracil, epirubicin (90 mg/m²), and cyclophosphamide (FEC) (n=30) with 4 cycles of FEC followed by high-dose chemotherapy consisting of cyclophosphamide (6g/m²), thiotepa and carboplatin (n=26). The main findings of this study showed that 11% of all patients had a decreased systolic function and 38% an impaired diastolic function. HRV parameters reflecting vagal activity in the whole patient group were significantly impaired compared to healthy age-matched controls. In 30% of the patients exertional dyspnea was present. These patients were characterized by an impaired diastolic function and a reduced HRV compared to patients without these symptoms. No difference in cardiotoxicity was found between the treatment regimens. This study showed that in a substantial number of breast cancer patients treated with a relatively low cumulative dose of epirubicin signs of mild chronic cardiotoxicity are present two or more (maximum 6.5) years after treatment.

Following this cross-sectional study, we describe in chapter 9 the results of a prospective evaluation of the cardiac function of 40 breast cancer patients who were treated in the same phase III trial as described in chapter 8. Of them 21 patients were treated with 5 cycles of FEC and 19 with 4 cycles of FEC followed by high-dose chemotherapy consisting of cyclophosphamide, thiotepa and carboplatin. The cardiac function of these patients was evaluated before chemotherapy, after completion of chemotherapy but before radiotherapy, after radiotherapy and one year after chemotherapy. During the studied period, none of the patients in this study developed congestive heart failure. However, various indications of an impairment of the cardiac function were observed including a decline in the mean left ventricular ejection fraction (LVEF), resulting in an abnormal LVEF in 17% of the patients. Plasma levels of natriuretic peptides increased gradually in the course of time and an increase in the QTc time was observed. No persistent alterations were found in the diastolic function and the HRV, although the HRV was temporarily reduced shortly after chemotherapy in patients treated with the high-dose regimen. The observed changes in cardiac function indicate mild cardiotoxicity one year after start of treatment which in some of these patients may result in an increased risk for development of late-onset congestive heart failure.
In chapter 10 suggestions with respect to further research are described. It is important to outline the prevalence of cardiovascular toxicity due to cytostatic agents and to investigate the pathogenesis. Thereafter attempts should be made to ameliorate or even prevent the cardiovascular side effects of cytostatic agents. The ultimate goal will be adding to a successful treatment of patients with cancer, a maximization of their chances of a long and healthy life by designing strategies for primary and secondary prevention of long-term toxic effects of chemotherapy.