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Blood Pressure and Body Mass Index in Long-Term Survivors of Testicular Cancer

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ABSTRACT

Purpose
To evaluate blood pressure and body mass index (BMI) in long-term survivors of testicular cancer (TC) treated with different modalities.

Patients and Methods
One thousand eight hundred fourteen patients treated for unilateral TC in Norway (1980 to 1994) were invited to participate in a follow-up study (1998 to 2002), including measurements of systolic blood pressure (SBP), diastolic blood pressure (DBP), and BMI. Of these patients, 1,289 patients (71%) participated in the study. The patients were categorized into four treatment groups: surgery (n = 242), radiotherapy (n = 547), and two chemotherapy groups, cumulative cisplatin dose ≤ 850 mg (n = 402) and cumulative cisplatin dose more than 850 mg (n = 98). A control group consisted of healthy males from the Tromsø Population Study (n = 2,847).

Results
At diagnosis, age-adjusted regression analyses showed no differences between the treatment groups for any variables. After a median follow-up time of 11.2 years, age-adjusted SBP and DBP were significantly higher for both chemotherapy groups compared with the surgery group. Chemotherapy-treated patients had increased odds for hypertension at follow-up compared with the surgery group, and the odds were highest for the cisplatin more than 850 mg group (odds ratio = 2.4; 95% CI, 1.4 to 4.0). The cisplatin more than 850 mg group had a significantly higher 10-year BMI increase and a higher prevalence of obesity at follow-up than the surgery group. Compared with healthy controls, chemotherapy-treated patients had, at follow-up, increased SBP, increased DBP, excessive BMI increase, and a higher prevalence of hypertension.

Conclusion
Five to 20 years after therapy, cured TC patients treated with cisplatin-based chemotherapy had significantly higher levels of blood pressure, a higher prevalence of hypertension, and an excessive weight gain compared with patients treated with other modalities and compared with healthy controls.

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INTRODUCTION

Testicular cancer (TC) is the most common malignancy among young men, and the incidence rate has now exceeded 10 per 100,000 men in Norway.[1] The prognosis for metastatic disease has improved considerably after the introduction of cisplatin-based combination chemotherapy,[2,3] and today, more than 95% of all patients are cured.[1] The combination of increased incidence and improved prognosis has led to an increasing number of TC survivors (TCS). Although there are indications for higher mortality rates among long-term TCS,[4] these young men are presumed to have a lifetime almost comparable to age-matched healthy males once they have achieved a

durable remission. Thus, the impact of long-term morbidity after treatment becomes increasingly important.

The major acquired risk factors for cardiovascular disease in the general population are smoking, hypertension, obesity, and an unfavorable lipid profile.[5,6] During the last decade, several studies have reported an increased risk of cardiovascular events (angina pectoris and myocardial infarction) in TCS years after treatment with cisplatin-based chemotherapy.[7-9] A recent publication by Huddart et al[7] reported a higher prevalence of cardiovascular events in TC patients treated with radiotherapy (RT) alone or in combination with chemotherapy compared with patients who were observed with a surveillance program. However, the authors did not identify any corresponding risk factors. Other investigators have suggested that TCS may have an unfavorable lipid profile, hypertension risk, or excessive weight gain as late side effects after cisplatin-based chemotherapy.[8-16] However, the majority of these studies have limited power as a result of small series and generally lack control groups.

Because an increased cardiovascular risk may be life threatening for cured TC patients, it is imperative to further estimate the risk potential and clarify possible mechanisms for the development of cardiovascular morbidity in these individuals. The aim of our study was to evaluate the cardiovascular risk factors of blood pressure, hypertension, body mass index (BMI), and obesity in long-term TCS treated with different modalities (surveillance/surgery, RT, and chemotherapy) through the following research questions: do any of these cardiovascular risk factors differ according to administered treatment, and do TCS differ from healthy controls with respect to any of these cardiovascular risk factors?

PATIENTS AND METHODS

Patients

All Norwegian long-term survivors ($\geq$ 5 years) of unilateral TC who were between 18 and 75 years of age and treated between 1980 and 1994 were invited to participate in a national multicenter follow-up survey. The follow-up was carried out during 1998 to 2002. Patients with extragonadal germ cell tumor, bilateral orchiectomy for any reason, secondary malignancy, or mental retardation were excluded, leaving 1,814 patients who were eligible and, thus, invited to participate in the study. One thousand four hundred thirty-eight patients (79%) accepted the invitation, signed the informed consent form, and completed a 219-item questionnaire including data on medical history, family status, educational level, and smoking habits. Of these patients, 1,289 patients who underwent a follow-up examination, including a clinical examination and blood tests, at one of five university hospitals form the study population. This group constituted 71% of all eligible patients. The study was recommended by the Ethical Review Board of Region South.

All patients were orchiectomized at diagnosis. Staging was performed according to the Royal Marsden Staging System.[17] For this study, the patients were categorized into the following four groups related to initial treatment after orchiectomy and eventual relapse treatment: surgery only; RT only; chemotherapy with a cumulative dose of cisplatin $\leq$ 850 mg (Cis $\leq$ 850); and chemotherapy with a cumulative dose of cisplatin more than 850 mg (Cis $>$ 850).

The surgery group comprised patients who did not receive treatment with RT or chemotherapy. This group consisted of 242 patients, of whom 131 (54%) had undergone retroperitoneal surgery only. The remaining patients (n = 111) did not receive any other treatment than orchiectomy and were on a surveillance program without developing chemotherapy-requiring relapses. The RT group comprised 547 patients, of whom the majority received a modified dog-leg (n = 488) or para-aortic (n = 34) RT field for seminoma stage I or IIA. From the early 1980s to mid-1990s, the applied RT dose was gradually reduced from 40 to 27 Gy. Among the remaining 25 patients, two patients had received additional mediastinal irradiation.

The chemotherapy groups consisted of 500 patients, of whom 98 were in the Cis $>$ 850 group and 402 were in the Cis $\leq$ group. Most patients (n = 477; 95%) received cisplatin-based chemotherapy, which involved primarily the combinations of cisplatin, etoposide, and bleomycin (n = 263) or cisplatin, vinblastine, and bleomycin (n = 152). Sixty-two patients received other cisplatin-based regimens. The remaining 23 patients who received carboplatin-based chemotherapy were included in the Cis $\leq$ 850 group. The median cisplatin doses in the Cis $\leq$ 850 and Cis $>$ 850 group were 723 mg (range, 185 to 850 mg) and 1,143 mg (range, 855 to 2,455 mg), respectively. Of the chemotherapy-treated patients, 321 (64%) underwent retroperitoneal surgery, and 53 (11%) received additional RT (mostly abdominal).

Measurements

Resting blood pressure was measured manually or with an automatic device. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Data for blood pressure, weight, and height at the time of diagnosis (pretreatment data) were obtained from medical records. At follow-up, blood samples were drawn by venipuncture between 8 AM and 12 PM. Levels of total serum testosterone assessments were based on commercial immunoassay technology at each hospital laboratory and were assessed as nanomolar per liter (nmol/L), with similar reference ranges at each hospital. Data on antihypertensive treatment, family status, educational level, and smoking habits were obtained from the questionnaire and were dichotomized for the present analyses.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and BMI at time of diagnosis were identified as pre SBP, pre DBP, and pre BMI, respectively, whereas these variables at follow-up were identified as post SBP, post DBP, and post BMI, respectively. Hypertension was defined as SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg, according to the WHO guidelines.[18] Individuals treated for hypertension were also included in the hypertension group, irrespective of measured blood pressure values. The applied 10-year BMI change was calculated as the difference between post and pre BMI, divided by the observation time in years, multiplied by 10 [(post BMI $-$ pre BMI) $\times$ 10/observation time]. In agreement with the WHO guidelines,[19] obesity at follow-up was defined as BMI $\geq$ 30 kg/m^2.

Control Group

The control group was recruited from the Tromsø Study, which was a longitudinal population-based epidemiologic study conducted in Tromsø, Northern Norway. Tromsø covers a relatively large geographical area with both urban and rural population, and the Tromsø Study is representative of the Norwegian population with regard to cardiovascular risk factors such as blood pressure and BMI.[20-23] This study was initiated in 1974 primarily to identify possible risk factors for cardiovascular disease, and large parts of the population have gone through repeated health examinations. The following five surveys have been performed: Tromsø 1 (1974), Tromsø 2 (1979/1980), Tromsø 3 (1986/1987), Tromsø 4 (1994/1995), and Tromsø 5 (2001). Methods and attendance rates have been previously published.[20] The Tromsø 5 Study was carried out during approximately the same time period as our follow-up survey.

The control group consisted of 2,847 males (born after 1925) who attended the Tromsø 5 survey and had participated in at least one earlier survey. Men treated with testosterone substitution were excluded. The median age was 63 years (range, 30 to 76 years). SBP, DBP, and BMI values from Tromsø 5 were compared with the patients' values at follow-up. SBP, DBP, and BMI values from Tromsø 2, 3, or 4 were compared with the patients' values at diagnosis. We selected one of the surveys before Tromsø 5 as reference for pretreatment data. Patients diagnosed during 1980 to 1983 were matched to controls from Tromsø 2, patients diagnosed during 1984 to 1989 were matched to Tromsø 3, and patients diagnosed during 1990 to 1994 were matched to Tromsø 4.

Statistical Analyses

Categorical data were analyzed using the χ^2 test, and continuous data were analyzed using the Student's t test. Multiple linear regression with BMI or blood pressure as the dependent variable was performed to evaluate possible differences between treatment groups and between patients and controls. Dichotomous variables, such as familial status, educational level, smoking, hypertension, and obesity were analyzed using multiple logistic regression. The surgery group was used as reference group when comparing the impact of different treatment modalities. All analyses were adjusted for age. All P values are two tailed, with statistical significance set at $P < .05$. The regression coefficient β is used to indicate change in the dependent variable when comparing different treatment groups. The data were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows version 11.0 (SPSS Inc, Chicago, IL).

RESULTS

Patient Characteristics

Of 1,814 patients eligible for the study, 1,438 accepted the invitation, and 1,289 underwent the follow-up examination (responders; Table 1). The responders were older than nonresponders at time of diagnosis (median age, 32 *v* 31 years, respectively; $P = .02$), but age at follow-up was not significantly different between responders and nonresponders (median age, 44 *v* 43 years, respectively; $P = .87$). Stage, histology, and treatment were not significantly different between the two groups (Table 1).

Patient characteristics are listed in Table 2. For the total study population, the median age was 32 years (range, 15 to 64 years) at diagnosis and 44 years (range, 23 to 75 years) at follow-up. The median observation time was 11.2 years

Table 1. Characteristics of Responders Versus Nonresponders

Characteristic	Responders (n = 1,289)		Nonresponders (n = 525)		*P*
	No.	%	No.	%	
Age at diagnosis, years					
Median	32		31		.02
Range	15-64		15-65		
Age at follow-up, years					
Median	44		43		.87
Range	23-75		23-75		
Stage*					
I	902	70	358	68	.71
IM/II	254	20	116	22	
III	29	2	11	2	
IV	104	8	40	8	
Histology					
Nonseminoma	640	50	268	51	.59
Seminoma	649	50	257	49	
Treatment group					
Surgery	242	19	110	21	.29
Radiotherapy	547	42	219	42	
Chemotherapy, Cis ≤ 850†	402	31	168	32	
Chemotherapy, Cis > 850‡	98	8	28	5	

*The Royal Marsden Staging System.
†Cumulative dose of cisplatin ≤ 850 mg.
‡Cumulative dose of cisplatin > 850 mg.

Table 2. Patient Characteristics According to Treatment Type

Characteristic	Surgery (n = 242)		Radiotherapy (n = 547)		Chemotherapy: Cisplatin ≤ 850 mg (n = 402)		Chemotherapy: Cisplatin > 850 mg (n = 98)		Total (N = 1,289)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age at diagnosis, years										
Median	29		36		30		27		32	
Range	16-64		18-64*		15-64		15-62		15-64	
Age at follow-up, years										
Median	41		48		42		37		44	
Range	24-73		28-75*		23-74		25-73†		23-75	
Years since diagnosis										
Median	11.8		11.1		11.9		9.5		11.2	
Range	5-21		5-21		5-22‡		5-20†		5-22‡	
Family status§										
Married/cohabitant	193	81	415	78	301	77	66	70	975	78
Living alone	46	19	117	22	90	23	28	30	281	22
Missing data	3	—	12	—	11	—	4	—	33	—
Educational level§‖										
Low/middle	148	62	315	59	244	62	66	71	773	62
High	90	38	216	41	147	38	27	29	480	38
Missing data	4	—	16	—	11	—	5	—	36	—
Smoking habits§										
Daily smoker	67	29	183	35	153	39	29	31	432	35
Nonsmoker	167	71	344	65	236	61	63	69	810	65
Missing data	8	—	20	—	13	—	6	—	47	—
Histology										
Seminoma	9	4	545	99.5	82	20	13	13	649	50
Nonseminoma	233	96	2	0.5	320	80	85	87	640	50
Stage¶										
I	236	98	518	95	136	34	12	12	902	70
IM/II	6	2	29	5	191	47	28	29	254	20
III	—	—	—	—	19	5	10	10	29	2
IV	—	—	—	—	56	14	48	49	104	8

*Difference *v* surgery is statistically significant at $P < .001$.
†Difference *v* surgery is statistically significant at $P < .01$.
‡Exception: only 4.3 years of follow-up for one patient.
§At follow-up, information obtained from the questionnaire.
‖Low/middle: primary/middle/high school; high: college/university.
¶The Royal Marsden Staging System.

(range, 4 to 22 years). The RT group was significantly older than the surgery group at diagnosis (36 *v* 29 years, respectively; $P < .001$) and at follow-up (48 *v* 41 years, respectively; $P < .001$), whereas the Cis > 850 group was significantly younger than the surgery group at follow-up (37 *v* 41 years, respectively; $P = .005$) and had a shorter observation time (9.5 *v* 11.8 years, respectively; $P = .007$). The Cis ≤ 850 group consisted of more smokers than the surgery group ($P = .007$). There were no significant differences between the treatment groups with regard to family status or educational level.

Blood Pressure

Data on blood pressure, BMI, and total testosterone levels for patients are listed in Table 3, whereas data for control individuals are listed in Table 4. Mean pre SBP and pre DBP were 135 mmHg (standard deviation [SD], 18 mmHg) and 83 mmHg (SD, 11 mmHg), respectively, for all patients, and there were no significant differences between the treatment groups. Overall, the mean post SBP and post DBP were 134 mmHg (SD, 19 mmHg) and 83 mmHg (SD, 12 mmHg), respectively. Univariate analyses revealed age and total testosterone as important predictors for blood pressure ($P < .001$), hypertension ($P < .001$), and BMI ($P < .001$) in both patients and healthy controls. Therefore, further statistical analyses were adjusted for age and total testosterone. Blood pressure analyses were additionally adjusted for BMI.

Data for age-adjusted SBP, DBP, and BMI at follow-up are listed in Table 5. Compared with the surgery group, the chemotherapy-treated patients had significantly higher blood pressure at follow-up. Age-adjusted post SBP was 4.1 mmHg ($P = .005$) and 5.0 mmHg ($P = .02$) higher for the

Table 3. Blood Pressure, Hypertension, BMI, and Serum Testosterone According to Treatment Group

Measure	Surgery (n = 242)	Radiotherapy (n = 547)	Chemotherapy: Cisplatin ≤ 850 mg (n = 402)	Chemotherapy: Cisplatin > 850 mg (n = 98)	Total (N = 1,289)
Blood pressure at diagnosis					
Systolic pressure, mmHg					
Mean	134.3	137.0	134.2	133.6	135.3
SD	16.4	18.6	16.5	18.0	17.5
Diastolic pressure, mmHg					
Mean	82.1	84.3	83.4	81.8	83.4
SD	9.8	11.7	10.4	12.5	11.1
Missing data, No.	8	9	1	0	18
Blood pressure at follow-up					
Systolic pressure, mmHg					
Mean	130.1	135.5	133.7	132.4	133.7
SD	17.6	18.9	20.6	17.4	19.2
Diastolic pressure, mmHg					
Mean	81.7	84.0	83.5	84.2	83.4
SD	11.5	10.7	12.4	12.2	11.5
Missing data, No.	1	4	8	1	14
Antihypertensive treatment at follow-up					
No.	15	67	29	10	121
%	7.0	13.8	8.1	11.8	10.6
Missing data, No.	27	63	45	13	148
Hypertension at follow-up*					
No.	87	276	184	48	595
%	39	54	50	53	50
Missing data, No.	20	38	31	8	97
BMI at diagnosis, kg/m^2					
Mean	24.0	24.5	23.7	24.0	24.1
SD	3.1	3.1	3.5	4.0	3.4
Missing data, No.	56	142	22	3	223
BMI at follow-up, kg/m^2					
Mean	26.5	26.4	26.5	27.1	26.5
SD	3.5	3.5	4.4	4.6	3.9
Missing data, No.	3	3	4	1	11
Obesity at follow-up†					
No.	30	69	65	24	188
%	13	13	16	25	15
Missing data, No.	3	3	4	1	11
10-year BMI change, kg/m^2‡					
Mean	2.25	1.64	2.44	3.22	2.18
SD	2.24	2.16	2.51	3.03	2.44
Missing data, No.	59	143	21	3	226
Serum total testosterone at follow-up, nmol/L					
Mean	16.2	15.1	15.4	14.5	15.4
SD	5.1	5.8	5.8	5.7	5.7
Missing data, No.	0	5	3	0	8

Abbreviations: BMI, body mass index; SD, standard deviation.
*Hypertension is defined as systolic blood pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg. Individuals on antihypertensive medication are included.
†Obesity is defined as BMI ≥ 30 mg/m^2.
‡The 10-year BMI change is the difference between BMI at follow-up and BMI at diagnosis, divided by observation time in years, and multiplied by 10.

Cis ≤ 850 and the Cis > 850 groups, respectively; and post DBP was 1.9 mmHg ($P = .04$) and 3.4 mmHg ($P = .01$) higher, respectively. Table 5 further lists age-adjusted post SBP and post DBP according to treatment group after adjusting for serum testosterone and for serum testosterone and BMI. After adjusting for total testosterone, post SBP remained significantly higher in both the Cis ≤ 850 and the Cis > 850 groups ($P = .008$ and $P = .04$, respectively), and post DBP was higher in the Cis > 850 group ($P = .03$) compared with the surgery group. When BMI was added to the model, post DBP was significantly higher in both chemotherapy groups

Table 4. Blood Pressure, BMI, and Serum Testosterone Among Controls (N = 2,847)

Measure	Mean	SD
Blood pressure at baseline, mmHg		
Systolic pressure	137.0	18.0
Diastolic pressure	83.1	12.1
Blood pressure at follow-up, mmHg		
Systolic pressure	143.3	18.8
Diastolic pressure	85.8	12.8
Hypertension at follow-up, %	64.9	
BMI at baseline, kg/m^2	25.1	3.2
BMI at follow-up, kg/m^2	26.9	3.6
Obesity at follow-up, %	17.8	
10-year BMI change, kg/m^2	1.3	2.1
Serum total testosterone at follow-up, nmol/L	14.1	5.4

Abbreviations: BMI, body mass index; SD, standard deviation.

($P = .03$ for both groups), and post SBP was higher in the Cis ≤ 850 group ($P = .005$).

When comparing all patients to the healthy controls, SBP and DBP at time of diagnosis were significantly higher among the patients (SBP: $\beta = 5.0$, $P < .001$; DBP: $\beta = 4.8$, $P < .001$), whereas there were no differences between all patients and controls at follow-up. Table 6 lists age-adjusted comparisons of post SBP and DBP between controls and patients divided into two treatment groups (surgery/RT or chemotherapy). Chemotherapy-treated patients tended to have a higher post SBP ($\beta = 1.7$, $P = .08$) and post DBP ($\beta = 1.3$, $P = .06$) compared with controls. These differences became significant after adjusting for total testosterone ($P = .03$ for both SBP and DBP). Adding BMI to the model further increased the average difference in post SBP to 2.3 ($P = .02$) and in post DBP to 1.8 ($P = .007$) between chemotherapy-treated patients and controls. Neither post SBP nor post DBP for patients in the surgery/RT group differed from that of the healthy controls.

Prevalence of Hypertension at Follow-Up

According to our definition of hypertension at follow-up, the percentage of individuals with hypertension was 39% in the surgery group, 54% in the RT group, 50% in the Cis ≤ 850 group, and 53% in the Cis > 850 group (Table 3). The overall age-adjusted association between treatment groups and hypertension was highly significant ($P < .001$). Table 7 lists the treatment group–specific age-adjusted odds ratios (OR) and 95% CIs of having hypertension. Both chemotherapy groups had significantly higher prevalence

Table 5. Multiple Linear Regression: Age-Adjusted SBP, DBP, and BMI at Follow-Up As Dependent Variables

	Model 1*		Model 2†		Model 3‡	
Variable	β	P	β	P	β	P
SBP						
Surgery	Reference	—	Reference	—	Reference	—
Radiotherapy	1.00	.47	0.70	.61	0.99	.47
Cis ≤ 850 mg	4.10	.005	3.80	.008	3.97	.005
Cis > 850 mg	5.01	.019	4.26	.044	4.03	.052
Age	0.77	< .001	0.74	< .001	0.74	< .001
Total testosterone	—	—	−0.39	< .001	−0.17	.062
BMI	—	—	—	—	1.10	< .001
DBP						
Surgery	Reference	—	Reference	—	Reference	—
Radiotherapy	0.79	.38	0.62	.49	0.80	.36
Cis ≤ 850 mg	1.92	.037	1.74	.058	1.90	.034
Cis > 850 mg	3.40	.012	2.93	.031	2.93	.027
Age	0.26	< .001	0.24	< .001	0.24	< .001
Total testosterone	—	—	−0.24	< .001	−0.09	.12
BMI	—	—	—	—	0.73	< .001
BMI						
Surgery	Reference	—	Reference	—	—	—
Radiotherapy	−0.17	.57	−0.29	.32	—	—
Cis ≤ 850 mg	−0.08	.80	−0.25	.42	—	—
Cis > 850 mg	0.59	.21	0.18	.68	—	—
Age	0.01	.30	−0.002	.82	—	—
Total testosterone	—	—	−0.19	< .001	—	—

NOTE. Comparisons were made between treatment groups using the surgery group as reference.
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; Cis ≤ 850 mg, cumulative cisplatin dose of ≤ 850 mg; Cis > 850 mg, cumulative cisplatin dose of > 850 mg.
*Adjusted for age.
†Adjusted for age and serum testosterone.
‡Adjusted for age, serum testosterone, and BMI.

Table 6. Multiple Linear Regression: Age-Adjusted SBP and DBP at Follow-Up As Dependent Variables

Variable	Model 1*		Model 2†		Model 3‡	
	β	P	β	P	β	P
SBP						
Control group	Reference	—	Reference	—	Reference	—
Surgery/RT	−1.15	.15	−0.73	.35	−0.47	.54
Chemotherapy	1.72	.08	2.01	.033	2.32	.017
Age	0.63	< .001	0.62	< .001	0.63	< .001
Total testosterone	—	—	−0.32	< .001	−0.17	.001
BMI	—	—	—	—	0.79	< .001
DBP						
Control group	Reference	—	Reference	—	Reference	—
Surgery/RT	−0.02	.97	0.21	.70	0.47	.37
Chemotherapy	1.27	.062	1.48	.030	1.81	.007
Age	0.19	< .001	0.19	< .001	0.20	< .001
Total testosterone	—	—	−0.18	< .001	−0.002	.401
BMI	—	—	—	—	0.77	< .001

NOTE. Comparisons were made between healthy controls and two treatment groups (surgery/RT or chemotherapy).
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; RT, radiotherapy; BMI, body mass index.
*Adjusted for age.
†Adjusted for age and serum testosterone.
‡Adjusted for age, serum testosterone, and BMI.

of hypertension compared with the surgery group, which was highest in the Cis > 850 group, with an OR of 2.4 (95% CI, 1.4 to 4.0). The significantly elevated ORs were maintained after adjustments for total testosterone and BMI.

Compared with the healthy controls, the total patient group had increased odds of having hypertension (OR = 1.4; 95% CI, 1.2 to 1.7). Subgroup analysis showed that all treatment groups, except the surgery group, had a significantly higher prevalence of hypertension. The prevalence was highest in the Cis > 850 group (OR = 2.3; 95% CI, 1.5 to 3.7; Fig 1).

BMI

Mean BMI for all patients at diagnosis was 24.1 kg/m^2 (SD, 3.4 kg/m^2; Table 3), and analyses showed no differences between the treatment groups. At follow-up, mean BMI was 26.5 kg/m^2 (SD, 3.9 kg/m^2). The Cis > 850 group had a slightly, although not significantly, higher post BMI compared with the surgery group ($\beta = 0.6$, $P = .21$; Table 5). Analyses of 10-year BMI change in patients and controls were adjusted for age and observation time in years. Mean 10-year BMI change was 2.2 kg/m^2 (SD, 2.4 kg/m^2) for all patients. The Cis > 850 group had a higher 10-year BMI increase compared with the surgery group ($\beta = 0.7$, $P = .02$), whereas the other treatment groups did not differ significantly.

Pre BMI in the patient group was slightly lower but not significantly different from the pre BMI of the healthy controls ($\beta = -0.17$, $P = .2$). However, post BMI was

Table 7. Multiple Logistic Regression: Age-Adjusted OR of Having Hypertension* in Different Treatment Groups

Treatment Group	Model 1†		Model 2‡		Model 3§	
	OR	95% CI	OR	95% CI	OR	95% CI
Surgery	1.00	Reference	1.00	Reference	1.00	Reference
Radiotherapy	1.24	0.88 to 1.75	1.21	0.86 to 1.71	1.23	0.86 to 1.75
Cis ≤ 850 mg	1.62	1.14 to 2.32	1.58	1.10 to 2.25	1.61	1.12 to 2.34
Cis > 850 mg	2.37	1.40 to 4.01	2.23	1.31 to 3.78	2.12	1.22 to 3.67
Age	1.07	1.06 to 1.09	1.07	1.06 to 1.09	1.08	1.06 to 1.09
Total testosterone	—	—	0.97	0.95 to 0.99	0.99	0.97 to 1.01
BMI	—	—	—	—	1.14	1.10 to 1.19

Abbreviations: OR, odds ratio; Cis ≤ 850 mg, cumulative dose of cisplatin of ≤ 850 mg; Cis > 850 mg, cumulative dose of cisplatin of > 850 mg; BMI, body mass index.
*Hypertension is defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg. Individuals treated for hypertension are included in the hypertension group.
†Adjusted for age.
‡Adjusted for age and total testosterone.
§Adjusted for age, total testosterone, and BMI.

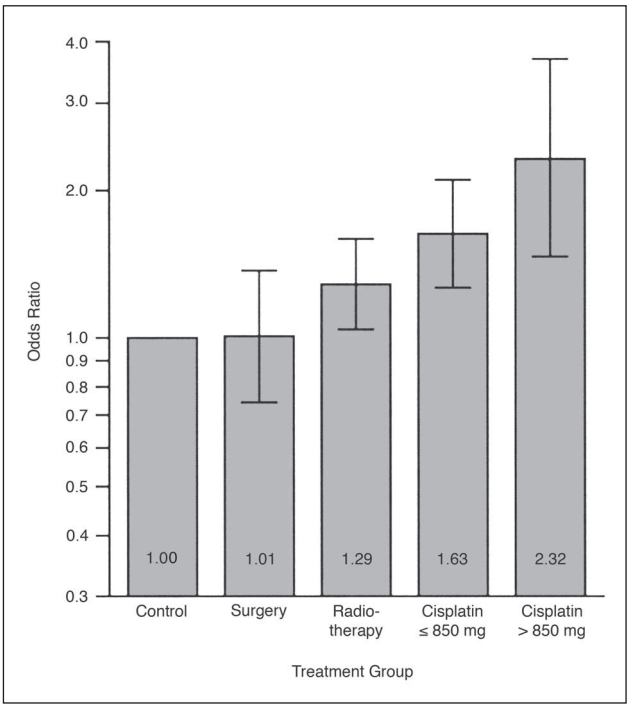

Fig 1. Age-adjusted odds ratios (OR) of having hypertension in different treatment groups compared with healthy controls. Bars indicate 95% CIs for OR.

significantly lower for patients than controls ($\beta = -0.5$, $P < .001$). Subgroup analyses showed that the Cis > 850 group did not differ from controls ($P = .95$), whereas the other patient groups had lower post BMI, with significantly lower values for the RT group ($\beta = -0.6$, $P = .002$) and the Cis ≤ 850 group ($\beta = -0.6$, $P = .007$). Adjustments for testosterone did not alter these results significantly. In subgroup analyses, the Cis ≤ 850 and Cis > 850 groups had a higher 10-year BMI increase than controls ($\beta = 0.3$, $P = .009$ and $\beta = 1.0$, $P < .001$, respectively).

Prevalence of Obesity at Follow-Up

The percentage of individuals who were obese (BMI ≥ 30 kg/m^2) at follow-up was 16% and 25% in the Cis ≤ 850 and Cis > 850 groups, respectively, and 13% in the surgery and RT groups (Table 3). The overall age-adjusted association between treatment groups and obesity was significant ($P = .003$). When compared with the surgery group, the chemotherapy groups had increased age-adjusted odds of being obese, with an OR of 1.4 (95% CI, 0.9 to 2.2) for the Cis ≤ 850 group and a significantly increased OR of 2.4 (95% CI, 1.3 to 4.4) for the Cis > 850 group. The RT group did not differ significantly from the surgery group, with an OR of 0.9 (95% CI, 0.6 to 1.5). The observed difference between treatment groups was weakened when we adjusted for total testosterone. The OR for the Cis > 850 group was reduced to 1.8 (95% CI, 1.0 to 3.4).

Compared with healthy controls, the total patient group had a significantly lower prevalence of obesity (OR = 0.8; 95% CI, 0.6 to 1.0). The lower prevalence of obesity was statistically significant for the surgery group and the RT group (Fig 2). The Cis > 850 group had an increased, although not significant, prevalence of obesity (OR = 1.4; 95% CI, 0.9 to 2.3).

DISCUSSION

In the present series, TCS treated with cisplatin-based chemotherapy had increased age-adjusted SBP and DBP and a higher prevalence of hypertension at follow-up compared with TCS who underwent surgery or RT only and also compared with healthy controls. These associations remained significant after adjusting for serum testosterone and BMI, and were more pronounced for those patients treated with cumulative cisplatin doses greater than 850 mg. Cisplatin-based treatment was also associated with an excessive weight gain and an increased prevalence of obesity.

The major strength of this study is the case-control study design, which allows comparisons between the TCS and healthy controls. In addition, blood pressure and BMI assessments in the healthy controls coincided in time with assessments in our patients at diagnosis and follow-up. Another essential strength is the large unselected patient population, allowing comparisons between different treatment groups. However, a limitation is the age difference between the TCS and controls. Although the difference in median age at follow-up between the patient population

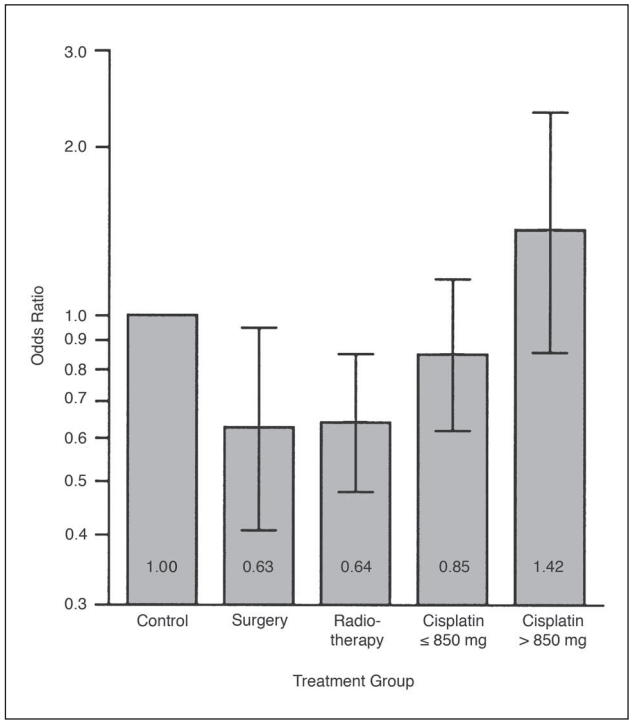

Fig 2. Age-adjusted odds ratios (OR) of being obese in different treatment groups compared with healthy controls. Bars indicate 95% CIs for OR.

and the healthy controls (44 *v* 63 years, respectively) was compensated for by age adjusting all statistical analyses, it may not have completely equalized the impact of age on blood pressure, hypertension, and BMI. If so, a significant age bias would underestimate the observed associations between treatment with cisplatin-based chemotherapy and blood pressure, hypertension, and BMI. Another limitation that may represent a source of bias is the 525 TCS who did not participate in the follow-up examination. However, a systematic bias is unlikely because the nonresponders and responders are equally distributed according to initial stage, histology, treatment group, and age at follow-up.

In accordance with our results, Meinardi et al[8] reported significantly higher SBP and DBP in cisplatin-treated patients compared with patients who were observed with a surveillance program. Several investigators have also suggested that hypertension is a possible complication in TCS after treatment with cisplatin-based chemotherapy.[8-15] The reported hypertension rates were between 13% and 39%, whereas we observed even higher rates for the chemotherapy-treated patients. Possible explanations for the higher prevalence of hypertension in our study are the inclusion of patients receiving antihypertensive medication and the applied definition of hypertension, which is according to the latest, more liberal WHO guidelines from 1999.[18] Our findings also support the data presented by Bokemeyer et al,[9] demonstrating that a cumulative cisplatin dose of more than 400 mg/m^2 was associated with a higher hypertension rate than a cumulative cisplatin dose of less than 400 mg/m^2 (24% *v* 10%, respectively).

In a study of 739 TCS, Huddart et al[7] observed a twofold higher prevalence of antihypertensive treatment among patients treated with both RT and chemotherapy when compared with surveillance (21% *v* 9%, respectively), whereas the prevalence in patients treated with RT or chemotherapy alone did not differ significantly. They did not detect any differences in blood pressure between the treatment groups. In our study, the patients receiving both chemotherapy and RT (n = 53) did not, when analyzed separately, differ with regard to hypertension risk from TCS treated with chemotherapy alone. Thus, our results do not support the findings in the British study. One possible explanation for the discrepancy between our results and those presented by Huddart et al[7] is that the hypertension and blood pressure data in the British study were not age adjusted.

To our knowledge, this is the first study to compare blood pressure in TCS with blood pressure of healthy controls. Our patients' blood pressure measurements at time of diagnosis were probably biased and temporarily increased because of stress and anxiety related to the initial hospitalization. This may explain the higher pre BP in patients than controls. Chemotherapy-treated patients had higher post SBP, higher post DBP, and increased prevalence of hypertension compared with healthy controls. We did not identify increased blood pressure levels as a late side effect after irradiation, and our RT patients had only a slightly increased OR of having hypertension compared with healthy controls. Theoretically, partial irradiation of the kidneys could lead to RT-induced nephropathy,[24] which might cause hypertension by activating the renin-angiotensin system.[25] Thus, our data indicate that elevated blood pressure and hypertension are long-term complications after treatment with cisplatin-based chemotherapy, rather than related to the TC itself or late sequelae after orchiectomy or RT.

Several studies have suggested an inverse relationship between blood pressure and serum testosterone.[26,27] The inverse association between hypertension and total testosterone has been reported to be stronger than between hypertension and free testosterone.[26] Leydig-cell dysfunction has been proposed as a possible complication after cisplatin treatment,[28,29] and subnormal levels of total testosterone may cause increased blood pressure in chemotherapy-treated patients. Obesity may also contribute to elevated blood pressure.[21,30] In this study, however, the higher blood pressure and hypertension rate in the chemotherapy-treated patients were maintained after adjusting for testosterone and BMI, indicating that other mechanisms are involved as well. Nephrotoxicity is a well-known side effect of cisplatin-based chemotherapy, particularly after high cumulative doses or in combination with RT.[9,31,32] Cisplatin-treated TCS have a high prevalence of microalbuminuria,[33] and there are indications that cisplatin-treated patients with microalbuminuria have higher SBP and DBP than patients with a normal albumin excretion,[8] suggesting that endothelial damage may contribute to the increased BP. In a study by Hansen et al,[11] there was no correlation between increased blood pressure and renal dysfunction after cisplatin-based chemotherapy in TCS. However, the number of patients was limited. Thus, any possible relationship between hypertension and cisplatin-induced renal damage needs to be further investigated.

Our findings, which indicate no differences in BMI between the different treatment groups at follow-up, are consistent with previous studies.[7,8,34] However, several studies have demonstrated that being overweight (BMI $\geq$ 25 kg/m^2) may be a chemotherapy-related side effect in TCS, with reported rates at 32%[9] and 48%.[15] Our results are in line with these findings, with 25% of heavily cisplatin-treated patients ($>$ 850 mg) being obese (BMI $\geq$ 30 kg/m^2). The present study demonstrates that heavily cisplatin-treated TCS, compared with the surgery group and healthy controls, have an excessive BMI increase. Thus, our results confirm the findings by Nord et al,[16] who examined BMI change in a subset of our patient population. Because our analyses were age adjusted, factors other than age may explain this excessive weight gain. Furthermore, because the

total patient population at follow-up had a lower BMI and lower odds of being obese than the healthy controls, we suggest that the unfavorable weight gain in heavily chemotherapy-treated patients is a result of the cisplatin-based therapy, rather than a consequence of the malignant disease or sequelae after orchiectomy.

It has been demonstrated that moderately obese men have a reduced sex hormone–binding globulin–binding capacity, leading to lower levels of total testosterone, whereas free testosterone levels are unchanged.[35] Several reports have shown an inverse association between BMI and total testosterone,[36,37] and the results by Giagulli et al[35] suggest that low levels of total testosterone may be the consequence and not the cause of obesity. In our study, the Cis > 850 group remained more obese compared with the surgery group, even after adjusting for total testosterone. Because obesity is an important predictor of hypertension[21,30] and an independent risk factor for cardiovascular disease,[6] one should be aware of the possible clinical implications of the excessive weight gain observed in cisplatin-treated TCS.

In conclusion, we have identified hypertension and augmented weight gain as potential long-term cardiovascular risk factors in TCS treated with cisplatin-based chemotherapy and particularly in patients treated with cumulative doses of more than 850 mg. Our results demonstrate the importance of establishing good follow-up routines to identify high-risk patients before they develop cardiovascular events. Because cisplatin-treated TCS seem to constitute a risk group for cardiovascular disease, they should have their blood pressure measured regularly. They should also receive general primary prevention information about diet, exercise, obesity, and smoking. Furthermore, these data support the efforts to minimize cumulative chemotherapy doses in good prognosis TC patient groups.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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