Journal of Cancer Research and Clinical Oncology (2019) 145:2335–2342
https://doi.org/10.1007/s00432-019-02965-5

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Adjuvant carboplatin therapy in patients with clinical stage 1 testicular seminoma: is long-term morbidity increased?

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Received: 27 October 2018 / Accepted: 1 July 2019 / Published online: 8 July 2019

Abstract

Purpose Clinical stage (CS) 1 testicular seminoma is cured in almost 100% of cases following either retroperitoneal radiotherapy, carboplatin monotherapy, or surveillance strategies. Little is known about potential long-term effects of carboplatin. We, therefore, examined late sequelae of this drug in seminoma patients.

Patients and methods We retrospectively identified 451 patients with CS1 testicular seminoma treated between 1994 and 2014, of whom 243 underwent carboplatin therapy [median follow-up (F/U) 96 months], 81 received radiotherapy (median F/U 142 months), and 127 underwent surveillance (median F/U 40 months). Satisfaction regarding management, as well as the following events during F/U, were analysed by questionnaire: subsequent malignant neoplasms (SMNs), cardiovascular events, arterial hypertension, peptic ulcer, tinnitus, peripheral neuropathy, hypogonadism, and infertility. The relative frequencies of the events were analysed using descriptive statistics. The frequency of observed SMNs was compared with the expected number.

Results Patients receiving carboplatin tolerated the treatment less well (71.2%) than those under surveillance (81.9%). After carboplatin, 12 SMNs (5.0%) were noted vis-a-vis 5.0 expected. There were three cases of prostatic cancer and 3 melanomas among the SMNs. Half of these SMNs occurred early after treatment. Among the other health events, only reported hypogonadism (13.2%) appeared to be marginally increased in frequency.

Conclusions This study found a 2.4-fold higher than expected rate of SMN—and a slightly increased rate of hypogonadism—in the long-term period following carboplatin treatment. Although further studies are needed to confirm these preliminary findings, these results are probably informative for clinicians caring for seminoma patients.

Keywords Seminoma · Carboplatin · Radiotherapy · Surveillance · Late toxicity · Second cancer

Abbreviations

CI	Confidence interval
CS	Clinical stage
GCT	Germ-cell tumour
F/U	Follow-up
RKI	Robert Koch Institut (Berlin)
SMN	Subsequent malignant neoplasm

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00432-019-02965-5) contains supplementary material, which is available to authorized users.

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Introduction

Nearly 80% of all testicular seminoma patients present with clinical stage (CS) 1, which is defined by the absence of metastases following both radiological and biochemical assessment (Rajpert-De Meyts et al. 2016; Ruf et al. 2014; Dieckmann et al. 2018). The cancer-specific survival of patients with CS1 testicular seminoma is almost 100%, which can be achieved with various management modalities following orchiectomy. Adjuvant chemotherapy with one or two courses of carboplatin evolved as an equally effective alternative to traditional retroperitoneal radiotherapy in the 1990s (Dieckmann et al. 2000; Oliver et al. 2005). Surveillance strategies with curative treatments applied only at the time of progression have also been shown to offer the same cure rates (Horwich et al. 1992; Mortensen et al. 2014). The central argument for the development of alternative strategies has been a concern regarding the unfavourable late effects of radiotherapy. Accordingly, based on accumulating evidence of an increased risk of second cancers and cardiovascular morbidity following treatment with radiotherapy (Lewinshtein et al. 2012; Horwich et al. 2014; Patel et al. 2017), this management modality is widely abandoned by current guidelines (Albers et al. 2015). Cisplatin-based chemotherapy protocols employed in testicular germ-cell tumours (GCTs) also involve late carcinogenic effects, albeit to a lesser extent than traditional radiotherapy (Fung et al. 2013; Kier et al. 2016; Travis et al. 2005; Groot et al. 2018). Therefore, concerns have arisen that the cisplatin analogue carboplatin, used for the treatment of CS1 seminoma patients, might likewise trigger subsequent malignant neoplasms (SMNs). So far, however, no increased mortality related to cardiovascular disease, nor excess incidences of SMNs, has been observed (Powles et al. 2008; Terbuch et al. 2017). However, there is still a paucity of data regarding the long-term toxicity of carboplatin. We, therefore, conducted a retrospective study on patients with CS1 seminoma, and examined the health-related events that occurred during follow-up, with a particular focus on patients who had undergone adjuvant carboplatin treatment.

Patients and methods

All patients with pure CS1 seminoma presenting in two urologic departments (Bundeswehrkrankenhaus Hamburg and Albertinen-Krankenhaus Hamburg) between 1994 and 2014 were retrospectively identified from hospital archives. To obtain information regarding health-related events during follow-up (F/U), we contacted the patients directly and requested that they respond to a questionnaire. Cases that could not be traced were excluded from the study. In eight of the non-responders, some core case information was able to be obtained from enquiries made to the patients' family physicians, office urologists, or relatives. These cases were included into the analysis for the available items. Finally, we excluded patients with relapsing disease or with second testicular cancers from our analysis, as the treatment delivered for these events would have influenced the development of late toxicities.

Treatment decisions for surveillance, radiotherapy, or carboplatin monotherapy were taken at the discretion of local physicians after informed consent of patients. Preferences surrounding the treatment modalities have changed over time (Dieckmann et al. 2016; Zengerling et al. 2013). Therefore, the three subgroups consisted of different patient numbers with different median F/U intervals. Follow-up examinations were usually performed by office urologists according to contemporary guidelines (Hartmann et al. 2011).

The 14-item questionnaire (see Supplementary Information; translated version) aimed to gather information pertaining to the following health-related events during F/U: SMNs, hypertension or other cardiovascular diseases, infertility, hypogonadism, tinnitus, and peripheral neuropathic symptoms. Hypertension and hypogonadism were only accepted in cases that received corresponding medication. Infertility was defined as childlessness despite serious attempts to induce conception. Finally, overall satisfaction with treatment was explored with cross-comparisons between the three treatments.

The data set used for subsequent analysis was exclusively generated from the responses of patients to the questionnaire and from the third-party enquiries in eight non-responders. None of the patients were subject to any clinical examinations for the purposes of this study. The data retrieved from these sources were initially tabulated using the commercially available database software (MS Excel 2015). The final analysis was performed using the SPSS software (version 20). Relative proportions regarding the frequency of events during F/U were calculated. A Chi-squared test was used for comparisons of proportions. A p value < 0.05 was considered statistically significant.

To determine the frequency of non-testicular SMN following primary treatment, we compared the observed numbers of SMN with the expected numbers in the three treatment subgroups using the cancer incidence database from the Robert Koch Institut (RKI), Berlin. This institute publishes the annual estimated incidence rates of all neoplastic diseases occurring in Germany, and provides estimations of the expected 10-year cancer incidence rates of German individuals in relation to gender and age, using 10 year age cohorts (i.e., < 35 years, 35–44 years, 45–54 years, etc.). To

calculate the expected number of second malignancies, we defined the age-specific risk for each patient by extrapolation from the cancer risk of the 10 year age categories given in the 2015 issue of the RKI cancer incidence tables (Robert Koch Institut 2015). The total number of expected SMNs of each treatment group was then calculated by imputing the person-years of risk according to the individual F/U intervals and subsequent summarizing of all individually calculated risks. The study received approval from the ethical committee of Ärztekammer Hamburg (PV5025/2015). All of the study activities conformed to the Helsinki Declaration of the World Medical Association (as amended by the 64th General Assembly, 2013).

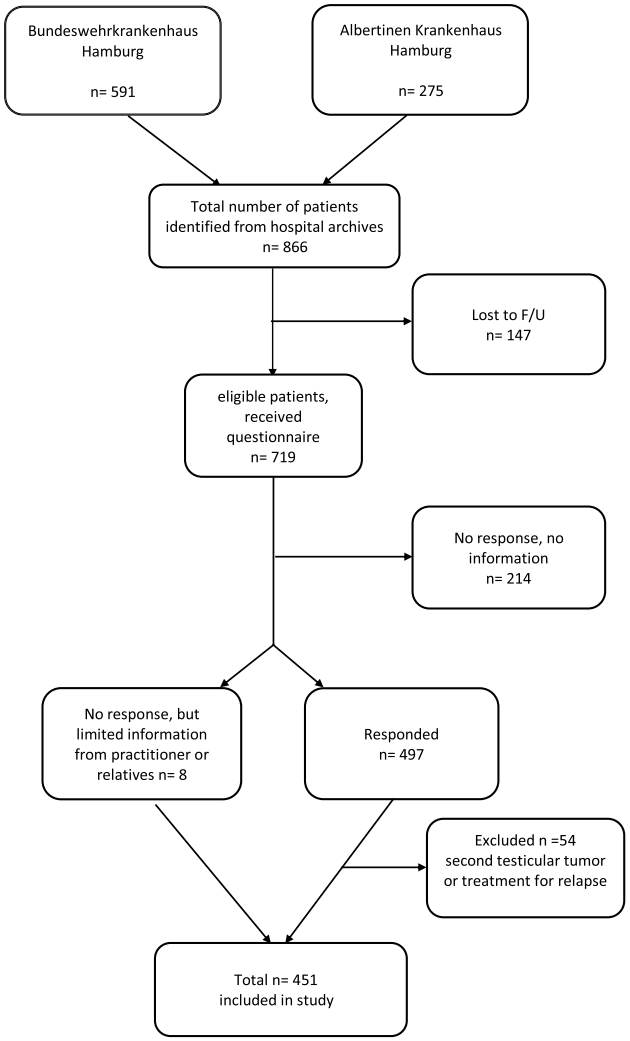

Fig. 1 Study profile: mode of patient enrolment

Results

A total of 451 patients were identified for further evaluation (Fig. 1). Management after orchiectomy consisted of adjuvant carboplatin therapy at a dosage of AUC7 in 243 patients, amongst whom 161 received one course, and 82 received two courses. Surveillance was applied in 127 patients, and abdominal radiotherapy of 20–26 Gy in 81 patients. Further clinical details are given in Table 1. Median F/U of the entire cohort was 90 months (range 14–324 months). The F/U was shorter than 2 years in 10.3% of patients, and more than 10 years in 32.9% of patients. Median F/U was 96 months, 142 months, and 40 months, in the carboplatin group, the radiotherapy group, and the surveillance group, respectively (Table 1). Overall survival was 98.2%. None of the patients in this cohort died of the disease; however, eight succumbed to seminoma-unrelated reasons, three to second cancers, two to cardiovascular events, two to other diseases, and one to suicide.

A total of 20 out of 447 eligible patients (4.5%) developed SMNs (excluding contralateral testis cancer and two cases of basal skin carcinoma; Table 2), with one patient developing a third malignancy. SMNs occurred in 5.0%, 0.8%, and 8.6% of carboplatin, surveillance, and radiotherapy patients, respectively.

A total of 9.3 second malignancies would have been expected in the entire cohort, which is only half the number actually observed ($n = 20$). Table 2 shows the expected versus observed numbers of SMN in the three treatment subgroups. It appears that patients undergoing any form of adjuvant treatment face a roughly twofold relative risk

Table 1 Clinical features of patients included in the study

	Patients (*n*)	Age (years)		Follow-up (months)
		Median (range)	IQR	Median (range)
All patients	451	39 (18–75)	32–45	90 (14–324)
Carboplatin all	243 (53.9%)	39 (22–72)	33–45	96 (14–246)
Carboplatin 1 course	161 (35.7%)	40 (22–72)	34–46	77 (14–246)
Carboplatin 2 courses	82 (18.2%)	37 (23–58)	32–43	134 (15–214)
Active Surveillance	127 (28.2%)	39 (18–75)	18–75	40 (14–221)
Radiotherapy	81 (18.0%)	37 (19–67)	30–44	142 (28–324)

IQR Interquartile range

Table 2 Frequencies of subsequent malignant neoplasms (SMN)

	Eligible (*n*)	SMN observed (*n*)	% of treatment group	SMN expected (*n*)	O/E ratio
All patients	447	20	4.5	9.3	2.2
Carboplatin (all)	242	12	5.0	5.0	2.4
Carboplatin 1 course	160	8	5.0	3.1	2.6
Carboplatin 2 courses	82	4	4.9	1.8	2.2
Surveillance	124	1	0.8	1.8	0.6
Radiotherapy	81	7	8.6	2.6	2.7

O/E observed versus expected

Table 3 Subsequent malignant neoplasms arising after treatment of seminoma clinical stage 1—synopsis of histologic types

Surveillance		Radiotherapy		Carboplatin	
Type of malignancy	Interval (months)	Type of malignancy	Interval (months)	Type of malignancy	Interval (months)
Hodgkin's lymphoma	32	Colonic Cancer	43	Acute lymphatic leukemia	2
		Prostate Cancer	50	Prostate cancer	10
		Colonic Cancer[a]	75	CUP syndrome	16
		Bladder Cancer	80	Melanoma	19
		Thyroid Cancer	91	Neuroendocrine Malignancy	34
		Melanoma	126	Prostate Cancer	57
		Ureteric Cancer	321	MGUS	74
				Melanoma	97
				Renal Cell Cancer	111
				Pancreatic Cancer	164
				Prostate Cancer	210
				Melanoma	n.a.

CUP cancer of unknown primary, *MGUS* monoclonal gammopathy of undetermined significance, *n.a.* not available

[a]This patient developed laryngeal carcinoma 175 months after seminoma as third malignancy

of developing a second malignancy, in comparison with those under surveillance.

A list of the individual SMN types and intervals after seminoma treatment is given in Table 3. It is noteworthy that among the 20 SMNs, there were four cases of melanoma and prostatic cancer. Only 0.6 cases of melanoma would have been expected in the entire cohort (Robert Koch Institut, 2015). Thus, the number of melanomas observed is more than sixfold the expected number.

With respect to major cardiovascular events, seven patients (1.6%; $n = 442$ eligible) developed myocardial infarction, two with fatal outcomes. Three (3/238; 1.3%) occurred in carboplatin patients, two in surveillance patients (2/123; 1.6%), and two in the radiotherapy group (2/81; 2.5%). The median interval between treatment and the major cardiovascular event was 81 months (range 24–192 months).

Hypertension with a need for medication developed in 32 patients (13.4%; eligible $n = 239$) after carboplatin treatment. The frequencies of hypertension in the three treatment groups and the frequencies of other health-related conditions occurring during F/U are listed in supplementary Table 1.

Hypogonadism with testosterone supplementation was reported by 31 patients (13.2%) receiving carboplatin. Table 4 shows the hypogonadism rates in the entire cohort and the other treatment groups. Age was associated with the development of hypogonadism: of the patients younger than 40 years, 9.5% (23 out of 241) developed hypogonadism, as opposed to 14.7% (29 out of 197) of those older than 40 years ($p = 0.04$).

Paternity was achieved by 17.6% of carboplatin patients, and the same frequency was found in the entire cohort of seminoma patients (supplementary Table 2), with a median time to conception of 30 months (range 1–179 months). Documented infertility was encountered in 5.9% of carboplatin patients and in 7.2% of all patients. Paternity/infertility was associated with age at diagnosis: none of the 50 patients aged > 50 years achieved paternity, while 19.7% (76 out of 385) of those < 50 years achieved paternity ($p = 0.001$). However, noteworthy, 31 (8.1%) of the patients < 50 years

Table 4 Frequency of hypogonadism treated with testosterone supplementation therapy

	Eligible (*n*)	Frequency of hypogonadism (*n*) (%)	Median age of treatment group (years)	Median age at diagnosis of patients developing hypogonadism (years)
All patients[a]	440	52 (11.8%)	39	41
Carboplatin (all)	234	31 (13.2%)	39	42
Carboplatin 1 course	156	24 (15.4%)	40	44
Carboplatin 2 courses	78	7 (9%)	37	34
Surveillance	125	12 (9.6%)	39	41
Radiotherapy	81	9 (11.1%)	37	39

[a]Patients with hypogonadism antecedent to orchiectomy were excluded from this analysis

reported undesired childlessness, as opposed to only 1.8% ($n=1$) of the patients > 50 years ($p=0.10$, not significant).

Regarding satisfaction with postoperative management, 95% of all patients would recommend the treatment they received to others. There was only a slight difference between the management modalities with regard to overall satisfaction rate (Table 5). The surveillance regimen was ranked as well-tolerated by 81.9% of patients, as opposed to significantly lower rates of reported tolerance in the carboplatin and radiotherapy groups (71.2% and 77.8%, respectively; $p=0.02$ for comparison of surveillance versus carboplatin; $p=0.5$ for surveillance versus radiotherapy).

Discussion

The greatest concern with respect to the treatment of young seminoma patients is the risk of developing SMNs. The initiation of cancers as a result of ionizing radiation has for decades been accepted knowledge (Brown and Doll 1965; Hay et al. 1984; Horwich et al. 2014). However, there is also evidence that SMNs can be triggered by cisplatin-based chemotherapy (Kier et al. 2016), with most SMNs developing more than 10 years following treatment (Travis et al. 2005; van den Belt-Dusebout et al. 2007). Among our patients receiving carboplatin, the number of SMNs observed (5.0%) was double the expected number.

Five previous studies (Powles et al. 2008; Steiner et al. 2011; Oliver et al. 2011; Aparicio et al. 2014; Chau et al. 2015) reported SMN rates of 0.9–2.0% after adjuvant carboplatin treatment (Table 6). The majority of these patients received only one cycle of carboplatin therapy, and the F/U time varied from 3.9 to 9 years. SMN histologies have been detailed in only some of the studies, and skin melanoma and prostatic cancer represented the most frequently encountered entities. The SMN rate observed in our study was higher than expected (observed versus expected ratio: 2.4), and it also exceeds the rates reported previously (Table 6). There is no simple explanation for this unexpected finding. Chance findings due to small sample size could be hypothesized; however, only three studies involved larger patient populations. One other hypothesis to explain the high number of SMNs found in our study might be that cancers with high incidence in the general male population like prostatic cancer and a malignancy frequently associated with GCTs such as melanoma might have influenced this study´s results by chance. Also of note is the finding that half of our SMN cases occurred early during the first 5 years post-treatment. In line with this observation, a UK-based study reported the occurrence of three SMNs within the first year after treatment (Chau

Table 5 Satisfaction with clinical management

	Eligible (*n*)	Well tolerated (*n*) (%)	Overall well tolerated but some problems (*n*) (%)	Overall not well tolerated (*n*) (%)	Poorly tolerated (*n*) (%)	No opinion (*n*) (%)	Recommendation to others (%)
All patients	451	340 (75.4%)	84 (18.6%)	4 (0.9%)	5 (1.1%)	18 (4.0%)	95
Carboplatin (all)	243	173 (71.2%)	57 (23.5%)	2 (0.8%)	5 (2.1%)	6 (2.5%)	96
Carboplatin 1 course	161	113 (70.2%)	38 (23.6%)	–	5 (3.1%)	5 (3.1%)	94
Carboplatin 2 courses	82	60 (73.2%)	19 (23.2%)	2 (2.4%)	–	1 (1.2%)	99
Surveillance	127	104 (81.9%)	10 (7.9%)	1 (0.8%)	–	12 (9.4%)	91
Radiotherapy	81	63 (77.8%)	17 (21%)	1 (1.2%)	–	–	95

Table 6 Synopsis of studies reporting subsequent malignant neoplasms (SMN) after carboplatin treatment

First author	Year	Country	Sample size (*n*)	Cycles	SMN (*n*)	SMN (%)	Median F/U (years)	Remarks
Powles	2008	UK	199	1 cycle (85%)	4	2	9	
Steiner	2011	Austria	258	2 cycles (all)	5	1.9	6.25	2 MM, 2 prostatic cancer
Oliver	2011	UK	554	1 cycle (all)	5	0.9	6.5	
Aparicio	2014	Spain	348	2 cycles (all)	6	1.7	6.7	2 lung cancer, 2 pancreatic cancer
Chau	2015	UK	517	1 cycle (all)	6	1.2	3.9	
Present study	2019	Germany	242	1 cycle (66%)	12	5.0	8.0	3 MM, 3 prostatic cancer

F/U follow-up; MM malignant melanoma

et al. 2015). In all, the available evidence for a carcinogenic effect of carboplatin treatment is limited. However, based on the present results, a pathogenetic association cannot entirely be ruled out. Further studies are, therefore, needed to clarify this relationship.

No increased rates of arterial hypertension and major cardiovascular events relating to carboplatin treatment were noted in our patient population which is consistent with previously reported data (Reiter et al. 2001; Powles et al. 2008; Terbuch et al. 2017) and with results from cross-sectional national evaluations (Neuhauser et al. 2017).

Hypogonadism was found in 13.2% of the carboplatin cases which is lower than the rate of 24% as previously reported (Pühse et al. 2011) but higher than the hypogonadism rate of 7.5% reported in patients on surveillance (Bandak et al. 2016). Thus, a possibly decreased Leydig cell function subsequent to carboplatin therapy requires further validation.

Only 5.9% of our carboplatin patients reported infertility mirroring the 9% rate observed in an Austrian series (Nöst et al. 1998). These data suggest that there is obviously no major impact on fertility from adjuvant carboplatin therapy (Reiter et al. 1998).

Regarding overall treatment satisfaction, surveillance patients reported significantly higher rates of treatment tolerance (81.9%) than those treated with carboplatin (71.2%). Our results show that the patients' perception of the treatment received was generally favourable for all modalities, with surveillance ranking highest. This result may be important for care-givers´ decision-making thereby respecting patient autonomy, as recently called for in a joint statement from several European Oncological Societies (Oldenburg et al. 2015).

There are several limitations regarding the methodology of our study. While the sample size seems appropriate, the retrospective study design opens the possibility of selection bias. It cannot be ruled out that higher toxicity rates would have been found if a major proportion of the patients lost to F/U could have been included in the analysis.

Major drawbacks to the study include the fact that 17% of the originally identified patients were lost to F/U, and that 30% did not respond to the questionnaire. We cannot rule out that health-related reasons, or even death, kept these patients from answering. However, based on the well-known low rate of overall mortality among seminoma patients (Berghen et al. 2019), we may assume that the systematic error resulting from the non-responders would be still acceptable. Another drawback is that 10% of participants had an F/U of less than 2 years. Additionally, the three treatment subgroups were quite dissimilar in size, because preferences for the different management strategies significantly changed during the study period. Moreover, comparisons between groups were hindered, as there were only a few events reported for each of the items addressed. Statistical problems may likewise arise from the divergent observation times of the subgroups. Our calculation of the expected numbers of SMNs may involve inaccuracies, as the computation relies on assumptions and extrapolations based on the cancer incidence tables of the RKI. Finally, most of the data are derived from patients' answers to a questionnaire; thus, misinterpretation must also be considered.

In conclusion, carboplatin therapy is highly rated in terms of patient satisfaction, but surveillance strategies had even better scores on tolerance. With respect to the long-term toxicity profile, we observed a 2.4-fold higher than expected rate of second malignancies and a 13.2% rate of hypogonadism—as opposed to a reported rate of 7.5% among surveillance patients. These results are clearly worthy of consideration by clinicians administering this drug to seminoma patients. Due to limitations in the present study, these results require further evaluation, and thus, the long-term toxicity profile of carboplatin remains to be fully determined.

Acknowledgements Dr. Raphael Ikogho assisted in the collection and interpretation of patient clinical data. Prof. Andreas Stang, director of the Center of Clinical Epidemiology, Institute of Medical Informatics, Biometry and Epidemiology (IMIBE), provided valuable advice in calculating the expected numbers of subsequent malignant neoplasms. Profs. Guido Sauter and Thomas Loening and their staffs provided the

histological diagnoses of the patients. Dr. Daniela Dinger provided valuable advice in the design and management of the study.

Funding The present study did not receive any funding.

Compliance with ethical standards

Conflict of interest None of the authors declare any conflicts of interest related to the present report.

Ethical approval The present study received approval from the ethical committee of the Ärztekammer Hamburg (PV5025/2015). All procedures performed in this study were in accordance with the ethical standards of the institutional research committees and with the 1964 Helsinki Declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in this study.

References

Albers P, Albrecht W, Algaba F, Bokemeyer C, Cohn-Cedermark G, Fizazi K, Horwich A, Laguna MP, Nicolai N, Oldenburg J (2015) Guidelines on testicular cancer: 2015 update. Eur Urol 68:1054–1068

Aparicio J, Maroto P, García del Muro X, Sánchez-Muñoz A, Gumà J, Margelí M, Sáenz A, Sagastibelza N, Castellano D, Arranz JA, Hervás D, Bastús R, Fernández-Aramburo A, Sastre J, Terrasa J, López-Brea M, Dorca J, Almenar D, Carles J, Hernández A, Germà JR (2014) Prognostic factors for relapse in stage I seminoma: a new nomogram derived from three consecutive, risk-adapted studies from the Spanish Germ Cell Cancer Group (SGCCG). Ann Oncol 25:2173–2178

Bandak M, Jørgensen N, Juul A, Vogelius IR, Lauritsen J, Kier MG, Mortensen MS, Glovinski P, Daugaard G (2016) Testosterone deficiency in testicular cancer survivors—a systematic review and meta-analysis. Andrology 4(3):382–388

Berghen C, Albersen M, Blanchard P, Bossi A, Briganti A, Cozzarini C, Decaestecker K, Fonteyne V, Haustermans K, Joniau S, Lim Joon D, Khoo V, Nguyen PL, Ost P, Villeirs G, Vulsteke C, Zietman A, De Meerleer G (2019) Readressing the rationale of irradiation in Stage I seminoma guidelines: a critical essay. BJU Int 124(1):35–39

Brown WM, Doll R (1965) Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis. Br Med J 2(5474):1327–1332

Chau C, Cathomas R, Wheater M, Klingbiel D, Fehr M, Bennett J, Markham H, Lee C, Crabb SJ, Geldart T (2015) Treatment outcome and patterns of relapse following adjuvant carboplatin for stage I testicular seminomatous germ cell tumour: Results from a 17 year UK experience. Ann Oncol 26(9):1865–1870

Dieckmann K-P, Brüggeboes B, Pichlmeier U, Küster J, Müllerleile U, Bartels H (2000) Adjuvant treatment of clinical stage I seminoma: is a single course of carboplatin sufficient? Urology 55:102–106

Dieckmann KP, Dralle-Filiz I, Heinzelbecker J, Matthies C, Bedke J, Ellinger J, Sommer J, Haben B, Souchon R, Anheuser P, Pichlmeier U (2016) Seminoma clinical stage 1—patterns of care in Germany. Urol Int 96(4):390–398

Dieckmann KP, Richter-Simonsen H, Kulejewski M, Ikogho R, Zecha H, Anheuser P, Pichlmeier U (2018) Testicular germ-cell tumours: a descriptive analysis of clinical characteristics at first presentation. Urol Int 100(4):409–419

Fung C, Fossa SD, Milano MT, Oldenburg J, Travis LB (2013) Solid tumors after chemotherapy or surgery for testicular nonseminoma: a Population-Based Study. J Clin Oncol 31(30):3807–3814

Groot HJ, Lubberts S, de Wit R, Witjes JA, Kerst JM, de Jong IJ, Groenewegen G, van den Eertwegh AJM, Poortmans PM, Klümpen HJ, van den Berg HA, Smilde TJ, Vanneste BGL, Aarts MJ, Incrocci L, van den Bergh ACM, Jóźwiak K, van den Belt-Dusebout AW, Horenblas S, Gietema JA, van Leeuwen FE, Schaapveld M (2018) Risk of solid cancer after treatment of testicular germ cell cancer in the platinum era. J Clin Oncol 36(24):2504–2513

Hartmann M, Krege S, Souchon R, De Santis M, Gillessen S, Cathomas R (2011) Nachsorge von Patienten mit Hodentumoren. Interdisziplinäre evidenzbasierte Empfehlungen. [Follow-up of testicular germ cell cancer patients: Interdisciplinary evidence-based recommendations]. Urologe A 50(7):830–835

Hay JH, Duncan W, Kerr GR (1984) Subsequent malignancies in patients irradiated for testicular tumours. Br J Radiol 57:597–602

Horwich A, Alsanjari N, Hern RA, Nicholls J, Dearnaley DP, Fisher C (1992) Surveillance following orchidectomy for stage I testicular seminoma. Br J Cancer 65:775–778

Horwich A, Fossa SD, Huddart R, Dearnaley DP, Stenning S, Aresu M, Bliss JM, Hall E (2014) Second cancer risk and mortality in men treated with radiotherapy for stage I seminoma. Br J Cancer 110:256–263

Kier MG, Hansen MK, Lauritsen J, Mortensen MS, Bandak M, Agerbaek M, Holm NV, Dalton SO, Andersen KK, Johansen C, Daugaard G (2016) Second malignant neoplasms and cause of death in patients with germ cell cancer: a Danish Nationwide Cohort Study. JAMA Oncol 2(12):1624–1627

Lewinshtein D, Gulati R, Nelson PS, Porter CR (2012) Incidence of second malignancies after external beam radiotherapy for clinical stage I testicular seminoma. BJU Int 109(5):706–712

Mortensen MS, Lauritsen J, Gundgaard MG, Agerbæk M, Holm NV, Christensen IJ, von der Maase H, Daugaard G (2014) A nationwide cohort study of stage I seminoma patients followed on a surveillance program. Eur Urol 66:1172–1178

Neuhauser H, Kuhnert R, Born S (2017) 12 Monats Prävalenz von Bluthochdruck in Deutschland. J Health Monitoring 2(1):57–63. https://doi.org/10.17886/RKI-GBE-2017-008

Nöst G, Lipsky H, Würnschimmel E (1998) Carboplatinmonotherapie im klinischen Stadium I des Seminoms. Eine akzeptable Alternative? Urologe A 37:629–634

Oldenburg J, Aparicio J, Beyer J, Cohn-Cedermark G, Cullen M, Gilligan T, De Giorgi U, De Santis M, de Wit R, Fosså SD, Germà-Lluch JR, Gillessen S, Haugnes HS, Honecker F, Horwich A, Lorch A, Ondruscaron D, Rosti G, Stephenson A, Tandstad T (2015) Personalizing, not patronizing: the case for patient autonomy by unbiased presentation of management options in stage I testicular cancer. Ann Oncol 26:833–838

Oliver RT, Mason MD, Mead GM, von der Maase H, Rustin GJ, Joffe JK, de Wit R, Aass N, Graham JD, Coleman R, Kirk SJ, Stenning SP, Collaborators MTcatE (2005) Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomised trial. Lancet 366:293–300

Oliver RT, Mead GM, Rustin GJ, Joffe JK, Aass N, Coleman R, Gabe R, Pollock P, Stenning SP (2011) Randomized trial of carboplatin versus radiotherapy for stage I seminoma: mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). J Clin Oncol 29(8):957–962

Patel HD, Srivastava A, Alam R, Joice GA, Schwen ZR, Semerjian A, Allaf ME, Pierorazio PM (2017) Radiotherapy for stage I and II testicular seminomas: secondary malignancies and survival. Urol Oncol 35:606.e1–606.e7

Powles T, Robinson D, Shamash J, Moller H, Tranter N, Oliver T (2008) The long-term risks of adjuvant carboplatin treatment for stage I seminoma of the testis. Ann Oncol 19:443–447

Pühse G, Secker A, Kemper S, Hertle L, Kliesch S (2011) Testosterone deficiency in testicular germ-cell cancer patients is not influenced by oncological treatment. Int J Androl 34(5 Pt 2):e351–e357

Rajpert-De Meyts E, McGlynn KA, Okamoto K, Jewett MA, Bokemeyer C (2016) Testicular germ cell tumours. Lancet 387(10029):1762–1774

Reiter WJ, Kratzik C, Brodowicz T, Haitel A, Pokorny A, Zielinski CC, Marberger M (1998) Sperm analysis and serum follicle-stimulating hormone levels before and after adjuvant single-agent carboplatin therapy for clinical stage I seminoma. Urology 52:117–119

Reiter WJ, Brodowicz T, Alavi S, Zielinski CC, Kozak W, Maier U, Nöst G, Lipsky H, Marberger M, Kratzik C (2001) Twelve-year experience with two courses of adjuvant single-agent carboplatin therapy for clinical stage I seminoma. J Clin Oncol 19:101–104

Robert Koch Institut, Gesellschaft der epidemiologischen Krebsregister in Deutschland (2015) Krebs in Deutschland 2011/12, 10. Ausgabe. Robert Koch Institut, Berlin. https://doi.org/10.17886/rkipubl-2015-004

Ruf CG, Isbarn H, Wagner W, Fisch M, Matthies C, Dieckmann KP (2014) Changes in epidemiologic features of testicular germ cell cancer: age at diagnosis and relative frequency of seminoma are constantly and significantly increasing. Urol Oncol 32(1):33.e1–33.e6

Steiner H, Scheiber K, Berger AP, Rein P, Hobisch A, Aufderklamm J, Pilloni S, Stoehr B, Aigner F, Fritzer A, Zangerl F (2011) Retrospective multicentre study of carboplatin monotherapy for clinical stage I seminoma. BJU Int 107(7):1074–1079

Terbuch A, Posch F, Annerer LM, Bauernhofer T, Pichler M, Szkandera J, Hutterer GC, Pummer K, Partl R, Kapp KS, Stöger H, Gerger A, Stotz M (2017) Long-term cardiovascular complications in stage I seminoma patients. Clin Transl Oncol 9(11):1400–1408

Travis LB, Fossa SD, Schonfeld SJ, McMaster ML, Lynch CF, Storm H, Hall P, Holowaty E, Andersen A, Pukkala E, Andersson M, Kaijser M, Gospodarowicz M, Joensuu T, Cohen RJ, Boice JDJ, Dores GM, Gilbert ES (2005) Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. J Natl Cancer Inst 97:1354–1365

van den Belt-Dusebout AW, de Wit R, Gietema JA, Horenblas S, Louwman MW, Ribot JG, Hoekstra HJ, Ouwens GM, Aleman BM, van Leeuwen FE (2007) Treatment-specific risks of second malignancies and cardiovascular disease in 5-year survivors of testicular cancer. J Clin Oncol 25:4370–4378

Zengerling F, Müller J, Schrader AJ, Schrader M (2013) Clinical stage I seminoma: is surveillance a new therapy standard? [Article in German]. Urologe A 52(9):1265–1269