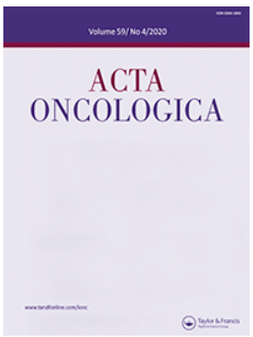

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ORIGINAL ARTICLE

Longitudinal kidney function outcome in aging testicular cancer survivors

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ABSTRACT

Purpose: Testicular cancer survivors (TCSs) have increased risk of reduced kidney function related to treatment burden, but longitudinal studies of renal outcome in aging TCSs have been lacking. This longitudinal study describes age- and treatment-related kidney function changes in TCSs compared to a comparison group from the general population.

Patients and methods: Estimated glomerular filtration rate (eGFR) was determined in blood samples from Norwegian TCSs (diagnosed 1980–1994) and surveyed median 11, 19 and 26 years since diagnosis (Survey1 [$N = 1273$], 2 [$N = 849$] and 3 [$N = 670$]) defining four treatment groups; Surgery only, Radiotherapy (RT) only, Cisplatin-based chemotherapy (CBCT) $\leq$850 mg and High CBCT/RT >850 mg cisplatin or any combination of CBCT with RT. A comparison group was constructed from similarly aged men who participated in a population-based health survey. By multiple linear regressions and generalized mixed models for repeated measurements, we studied difference in eGFR between TCSs and the comparison group for all TCSs combined and stratified by treatment modality.

Results: At Survey 1, the kidney function for the youngest TCSs combined versus the comparison group was significantly reduced by mean six units (mL/min/1.73 m^2) with further decline to mean 12 units at Survey 3. The kidney function was significantly reduced in all treatment groups with the largest differences emerging for TCSs from the High CBCT/RT Group, thus indicating a deteriorating impact of high cumulative doses of cisplatin.

Conclusion: Collated to the comparison group, the kidney function in TCSs became increasingly impaired during nearly three post-treatment decades, related to the treatment modality. Early detection and intervention of kidney dysfunction is important to reduce the risk of TCSs' long-term morbidity and mortality related to nephrotoxicity, such as cardio-vascular diseases.

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Introduction

Abdominal radiotherapy (RT) and primary retroperitoneal lymph node dissection (RPLND) have been effective treatments as adjuvant therapy or for low volume metastatic testicular cancer (TC). Both treatment modalities are decreasingly still in use [1–4].

However, these therapies used alone are less effective in advanced metastatic TC and have, since the late seventies been successfully replaced by or combined with cisplatin-based chemotherapy (CBCT) [5] alone or combined with RT. Thus, today's TC patients have five-year relative survival rate of 95% [6].

The success of TC treatment comes with the risk of treatment-related long-term adverse health outcomes [7–11], reduced kidney function being one of them. With a post-treatment life expectancy of 30–50 years, testicular cancer survivors (TCSs) represent an optimal group to study the impact of treatment on TCSs' kidney function during the aging process, with emphasis on CBCT and in comparison with the general population.

Currently, little is known about the development of the kidney function in TCSs > 10 years after treatment. Most reports on long-term nephrotoxicity in TCSs are cross-sectional studies [12,13] and the few longitudinal studies available lack comparison group from the general population [14,15]. As treatment is known to be nephrotoxic and longitudinal studies in aging TCSs were lacking, we initiated this study. Our aims were

1. to assess renal function in TCSs up to three decades after treatment and compared to findings from a comparison group from the general population.
2. to compare renal function in TCSs treated with different modalities.

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Supplemental data for this article can be accessed here.

Patients and methods

Patients

TCSs treated for unilateral testicular cancer between 1980 and 1994, were invited to participate in three surveys from 2000 to 2016; (Survey1 [S1: 2000]; Survey2 [S2: 2008]; Survey3 [S3: 2016]) [16,17]. Only those patients who had participated in the preceding survey were invited to the subsequent surveys. Each survey consisted of a mailed questionnaire, and if logistically possible, a clinical examination (including weight, height, waist circumference and blood pressure) and collection of blood samples. All patients had been treated at one of the four Norwegian University Hospitals. At S1, the patients attended the out-patient department of the responsible hospital, whereas the clinical examinations during S2 and S3 were performed at a cooperating general practitioner's office. The blood samples from S1 were analyzed at the laboratory of the respective University Hospital, whereas all samples for S2 and S3 were analyzed at the Department of Medical Biochemistry at the Oslo University Hospital (OUH).

The cohort of the current study included all TCSs attending the surveys and for whom glomerular filtration rate (GFR) could be calculated (Supplementary Figure 1).

Treatment

Since 1980 and up to 1994, the post-orchiectomy treatment for TC was dependent on histology and extent of the disease, consisted of no further treatment or RPLND ('Surgery'), RT, CBCT or a combination of these therapeutic modalities. For all patients with primarily metastatic non-seminomas or any patients with recurrent TC, CBCT has been the standard treatment, often combined with post-CBCT RPLND [18]. Up to about 1992 a diagnostic RPLND represented the routine therapy for patients with non-seminoma without radiographic suspicion of metastases at diagnosis [19]. In cases with histologically demonstrated lymph node metastases, RPLND was followed by two or three cycles of CBCT. Two or three additional cycles of CBCT were also given to patients in whom post-CBCT surgery revealed residual metastatic growth dependent on participation in international trials, carboplatin has been used in some patients instead of cisplatin.

The majority of CBCT cycles were given during the five days, applied with three weeks intervals and consisted of cisplatin, vinblastine and bleomycin or (since 1986) of cisplatin, etoposide and bleomycin (BEP) [20–23], with deviations from this routine in patients included into international protocols [24]. During the days of infusion, the patients were highly hydrated with frequent monitoring of their fluid balance, s-creatinine and s-Mg.

Patients with stage I or limited stage II seminoma received abdominal RT (30–36 Gy) to a dog-leg field or a target field restricted to the para-aortic area [25]. After application of 20 Gy, the para-aortic part of the target field was monitored as to the amount of included renal tissue. Individual lead blocks were constructed if more than 1/3 of one kidney was included into the para-aortic field, to be used during the subsequent RT fractions. Seminoma patients with extensive stage II or III received CBCT followed by abdominal RT or RPLND in case of residual lesions.

Based on these treatment principles, patients were divided into four groups according to total treatment burden: Group 1: Surgery only (orchiectomy with or without RPLND), Group 2: RT only, Group 3: CBCT (maximal cumulative total cisplatin dose $\leq$ 850 mg + surgery) and Group 4: High CBCT/RT (cumulative total cisplatin dose $>$ 850 mg or any CBCT in combination with RT).

Patients receiving carboplatin were placed in the corresponding chemotherapy group according to cumulative cisplatin equivalents administered after dividing the cumulative carboplatin dose by four [26].

The general population (comparison group)

Basis for the comparison groups were estimated GFR (eGFR) values from males ($N = 30{,}574$), divided into decadal age groups participating in a population-based health survey of the adult population in a county in mid-Norway, the HUNT2 survey (1995–1997) [27]. Demographics of the HUNT2 survey sample was similar to the distribution of such variables in the whole country and were generally found to be comparable, differing somewhat with regards to lower education level in the HUNT2 survey than in the Norwegian population as a whole [28]. Furthermore, standardized mortality rates were similar in the HUNT2 survey sample and the country as a whole.

Kidney function

Kidney function being the primary outcome is estimated by eGFR based on s-creatinine, age, gender and ethnicity (Supplementary Table 1), using the equation from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [29].

During the study period, methods for measuring s-creatinine have varied with different calibration recommendations for each assay type. Today's reference method for s-creatinine is isotope dilution-mass spectrometry [30]. We have adjusted earlier s-creatinine results of the TCSs and the comparison group according to the published recommendations to achieve results traceable to this method. The validity of our results is certified by laboratory-participation in an external quality control program (Lab Quality, Helsinki, Finland).

Based on Levin et al.'s [31] recommendations, our eGFR results were categorized ; 'Normal': eGFR $\geq$ 90 mL/min/1.73 m^2, 'mildly decreased': eGFR 60–89 mL/min/1.73 m^2 and 'decreased': eGFR $<$ 60 mL/min/1.73m^2.

Statistical analyses

Continuous data with skewed distributions were described with medians and ranges, normally distributed data with means and standard deviations. Categorical data were reported as numbers and percentages. To analyze differences in eGFR between TCSs and the comparison group for given

age groups, multiple linear regression models were fitted separately for each survey. The results were expressed as estimates of beta (*B*; the mean difference between the TCSs and the comparison group) with 95% confidence intervals. To analyze differences over time among the treatment groups, we fitted linear mixed models for repeated measures with unstructured covariance matrix to accommodate for the different time interval between the surveys and dependencies arising from the same patients being measured at three time points. The results were expressed as estimates of beta (the average difference between a given treatment group compared to the reference treatment group estimated for the whole duration of the follow up) with 95% confidence intervals.

All tests were two-sided. No correction for multiple testing was done as this study was considered exploratory. p Values $<.05$ were considered statistically significant. All analyses were conducted using SPSS version 23 (SPSS, Chicago, IL) and/or STATA version 14.2 (StataCorp, College Station, TX).

Ethical considerations

The present study was approved by the Committee for Medical Research Ethics of the Southern Health Region of Norway (2015/1264; S-98094; S-07305b).

Results

Patients and blood samples

Of the 1,813 invited TCSs, 1,436 participated in S1. In 1,273 of these, eGFR could be calculated with $N = 670$ also evaluable at S3 (Supplementary Figure 1). About half of the responders to S1 were diagnosed with seminoma and half had non-seminoma. Median age at diagnosis was 31 years with seminoma patients being slightly older (median 35 years) than those with non-seminoma (median age 28 years). At S3, TCSs had been followed for median 26 years (range 21–36 years) since diagnosis (Table 1), the interval between S1 and S3 being median 15 years. Initially non-metastatic disease was diagnosed in 71% of the patients. CBCT was administered to 39%, 42% received RT only and 19% surgery only. The treatment type distribution was similar at all three assessment time points (Table 1).

In total, $N = 897$ patients were represented by ≥ 2 eGFR values. No major treatment differences existed between responders with or without evaluable eGFR at S1 (Supplementary Table 2) [32]. Neither was there significant differences regarding medical variables or eGFR variables at S1 comparing TCSs with evaluable versus non-evaluable eGFR at S3 (Supplementary Table 2).

Kidney function

When stratified by age groups (age at Survey), the eGFR values for all TCSs combined were at each survey significantly lower than the comparison group, as is depicted in Figure 1. Moreover, the difference in mean eGFR values between the TCSs and the comparison group increased from S1 to S3.

Table 2 supports the findings from Figure 1 by listing differences in eGFR between TCSs and the comparison group separately for each of the three surveys and for different age categories analyzed by multiple linear regressions. At S1 the average difference between the comparison group and TCSs was greatest for the youngest patients (31–40 years; $B = 6.07$). At S3, the differences had doubled, thus being $B = 12.27$ for the TCSs aged 51 - 60 years at S3.

The effect of treatment modality on kidney function

Collated to the comparison subgroups of similar age, Figure 2 depicts the development of eGFR from S1–S3 for each treatment group. Both at S1 and S3 the differences in mean eGFR between TCSs and the comparison group, were statistically significant except for the surgery group at S1. These findings were supported by the age-adjusted generalized linear model (Supplementary Table 3) showing that the differences in eGFR between the TCSs and the comparison group increased from S1 to S3, the estimated mean difference in the High CBCT/RT Group ranging from 11.30 at S1 to 18.48 mL/min/1.73^2 at S3. Furthermore, the proportion of TCSs with decreased kidney function ($<$60 eGFR mL/min/1.73m^2) was the highest in this treatment group, ranging from 8% at S1 to 21% at S3. In total, $N = 22$ patients (of 897 TCSs with ≥ 2 blood samples) had ≥ 2 eGFR values $<$60 mL/min/1.73m^2. Interestingly, persistent eGFR $<$ 60 mL/min/1.73m^2 were observed for 1.1–2.4% of the TCSs after surgery, RT and CBCT with clear increase in the High CBCT/RT Group to 9.3%. At S3, mildly decreased kidney function (eGFR 60–89 mL/min/1.73m^2) was observed in 51% of all TCSs (Supplementary Table 3).

The effect of treatment modalities for the individual patient

Figure 3 depicts the longitudinal trajectories of eGFR for individual patients in the different treatment groups. The kidney function deteriorated at a similar rate for all treatment groups between S1 and S3. However, at all Surveys, the High CBCT/RT Group represented the TCSs with the lowest eGFR compared to the other groups. Using repeated measurements as described in the statistics section, considering the whole follow-up period (S1–S3), statistically significant differences emerged only between the Surgery Group and the High CBCT/RT Group. The latter group had on average 10 mL/min/1.73 m^2 lower eGFR than the Surgery Group (Supplementary Table 4). For the RT Group there was a trend toward a significant difference in average eGFR compared to the Surgery Group ($p = .07$).

Discussion

This longitudinal study covering nearly three decades since treatment, is the first to compare post-treatment kidney function in aging TCSs with the general population emphasizing CBCT. With a median follow-up time of 11 years at S1

Table 1. Pretreatment, treatment and follow-up characteristics.

Characteristics at Survey 1	Surgery only $N = 240$ (19%)	RT only $N = 537$ (42%)	CBCT $N = 346$ (27%)	High CBCT/RT $N = 150$ (12%)	Total $N = 1273$ (100%)
Age at diagnosis (years)	29[a] (16–64)[b]	35 (17–64)	28 (14–63)	29 (14–62)	31 (14–64)
Seminoma	9 (3.8%)	534 (99%)	40 (12%)	55 (37%)	638 (50%)
Non-seminoma	231 (96%)	3 (0.6%)	306 (88%)	95 (63%)	635 (50%)
Initial extent of disease					
Non-metastatic	240	509	128	19[c]	896 (70%)
Metastatic	N.A.	28	218	131	377 (30%)
Treatment					
Cum. cisplatin dose (mg)	N.A.	N.A.	740 (185–850)	985 (178–2455)	N.A.
Additional					
RT	N.A.		N.A.	53	53 (4%)
RPLND	67	N.A.	133	53	253 (20%)
Age at Survey 1	41 (24–73)	47 (28–75)	41 (22–73)	40 (24–72)	43 (22–75)
Observation time at Survey 1 (years)	12 (5–21)	11 (5–21)	12 (5–22)	10 (5–20)	11 (5–22)
Survey 2 participants	$N = 177$ (21%)	$N = 356$ (42%)	$N = 229$ (27%)	$N = 87$ (10%)	$N = 849$ (100%)
Age at Survey 2	49 (32–81)	55 (34–79)	49 (31–81)	49 (33–81)	51 (31–81)
Observation time at Survey 2 (years)	19 (13–27)	18 (13–28)	19 (13–27)	18 (13–27)	19 (13–28)
Survey 3 participants	$N = 138$ (21%)	$N = 269$ (40%)	$N = 191$ (29%)	$N = 72$ (11%)	$N = 670$ (100%)
Age at Survey 3	58 (40–78)	62 (42–87)	57 (38–89)	56 (42–80)	59 (38–89)
Observation time at Survey 3 (years)	27 (21–36)	26 (21–36)	28 (21–35)	25 (21–35)	26 (21–36)

[a]Median; [b]range; [c]Four of these patients had large body surface area which explains high cum. CBCT while the rest either relapsed or received intensive treatment that was standard for the period.
RT: Radiotherapy only; CBCT: cisplatin-based chemotherapy; High CBCT/RT: high cumulative CBCT >850mg or CBCT and RT; N.A: not applicable; RPLND: retroperitoneal Lymph Node dissection.

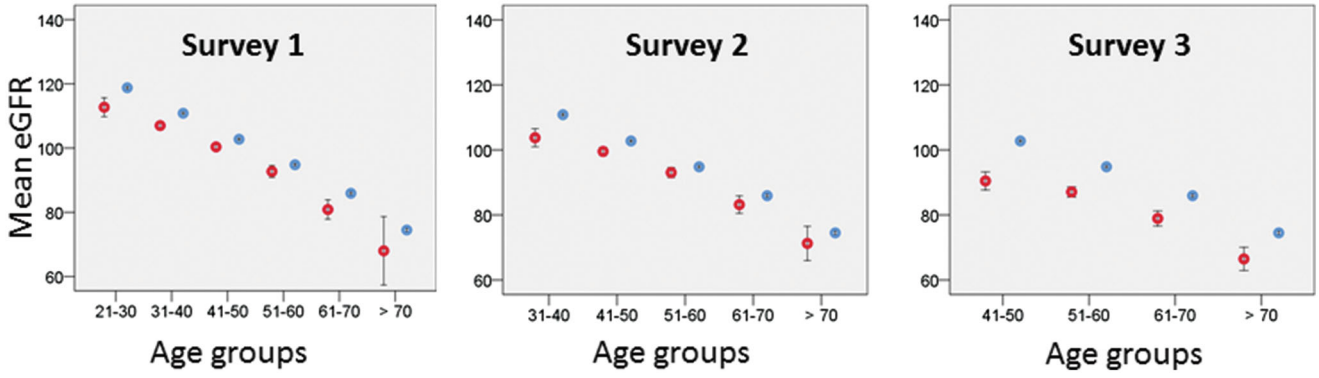

Figure 1. The development of mean eGFR with 95% confidence intervals in all testicular cancer survivors (red dots) compared to the comparison group (blue dots) divided into decadal age groups. Survey1: ∼2000; Survey2: ∼2008 and Survey3: ∼2016. Non-overlapping confidence intervals indicate statistical significance.

Table 2. eGFR differences at S1, S2 and S3 in TCSs versus comparison group, independent of treatment modality (generalized linear regression models stratified by each survey).

Age category (years)	S1		S2		S3	
	B[a]	95% CI	B	95% CI	B	95% CI
31–40	6.07	3.75; 8.39				
41–50	3.83	2.74; 4.92	7.09	4.81; 9.38		
51–60	2.38	1.37; 3.39	3.20	2.00; 4.40	12.27	10.20;14.35
61–70	2.08	0.58; 3.59	1.76	0.40; 3.11	7.73	6.39; 9.07
>70	0.93	−1.93; 3.79	0.07	−2.23; 2.38	4.90	3.06; 6.74

[a]Average difference.
95% CI: 95% confidence interval.

and having a comparison group from the general population, we document significantly reduced eGFR in TCSs having been treated with high CBCT (cumulative cisplatin exposure >850 mg) or with CBCT and RT, the differences being the largest in the youngest TCSs. During the period between S1 and S3 of median 15 years, reduction of eGFR had doubled. Also compared to the Surgery Group, all treatment modalities resulted in reduced renal function and subsequent similar decline, though the level of significance was only reached for the High CBCT/RT Group. Compared to the Surgery Group, inter-treatment analysis revealed significant decline of eGFR in TCSs with either a cumulative cisplatin dose >850 mg or those after combination of CBCT and RT ($p < .001$), also after RT alone eGFR declined ($p = .07$). A total of 60% of the TCSs had signs of at least mildly decreased kidney function (eGFR <90 mL/min/1.73 m^2) at S3. A new and unexpected finding is the decline of kidney function when compared to the comparison group in patients with surgery only. A total of 49% in the Surgery Group at S3 had eGFR < 90 mL/min/1.73m^2 which could influence on their risk of cardiovascular disease (CVD) [33].

Other groups have shown a 10–30% reduction in long-term eGFR after CBCT, though with a maximum of six years of follow-up and without a comparison group from the general population (Table 3) [35,39,43–47]. Our longitudinal study is in line with these mainly cross-sectional studies, showing persisting and slightly increasing post-treatment kidney function decline dependent on treatment burden. Cisplatin's dose-depended nephrotoxic effect during treatment is multifactorial and has been linked to tubular cell damage, inflammation and vascular injury, resulting in reduced GFR as confirmed by our study [48,49]. The long-term nephrotoxic effect of abdominal

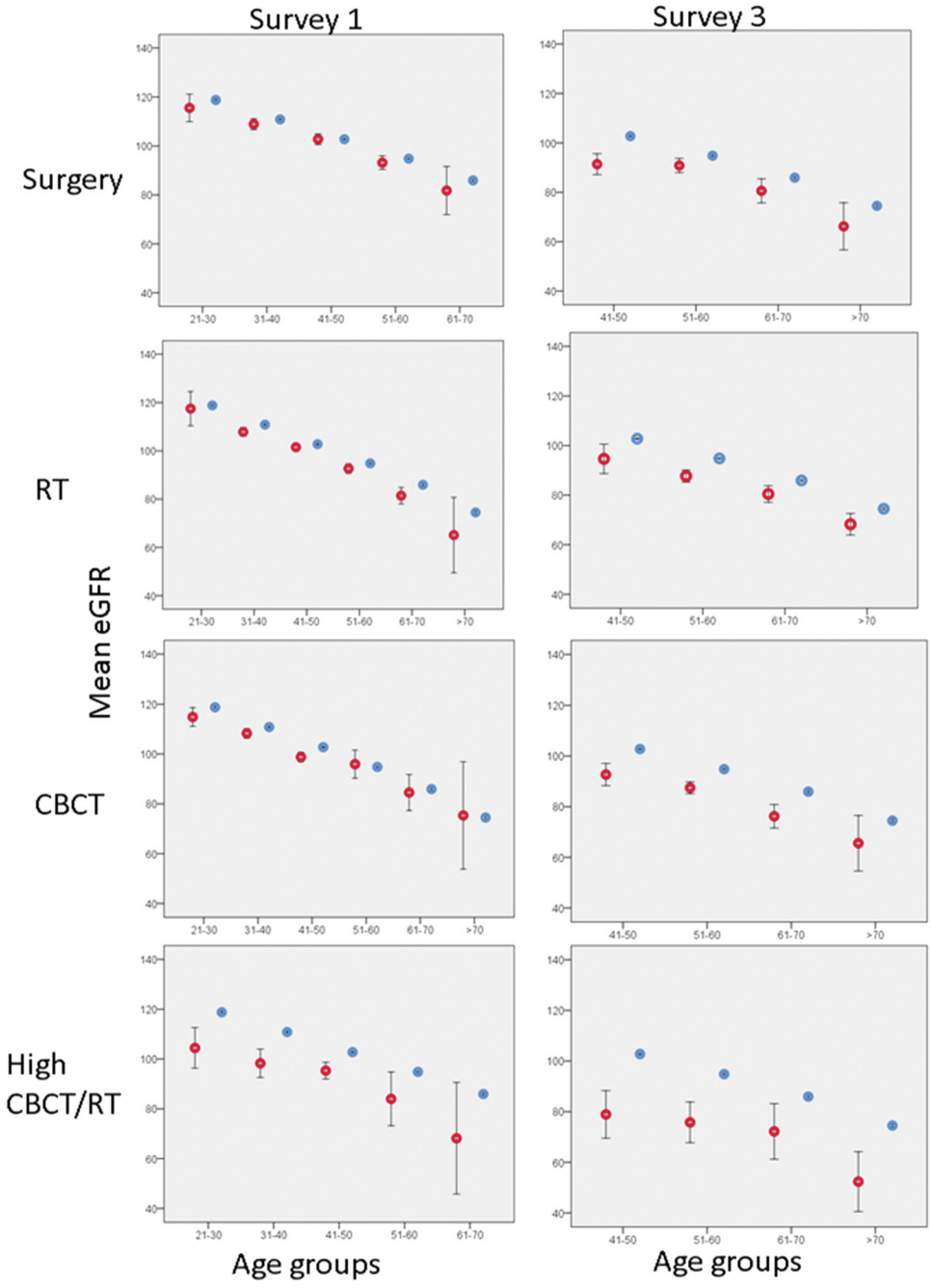

Figure 2. Development of mean eGFR with 95% confidence intervals in four different treatment groups of testicular cancer survivors (red dots) compared to the comparison group (blue dots), divided into decadal age groups. Non-overlapping confidence intervals indicate statistical significance. RT: Radiotherapy only; CBCT: cisplatin-based chemotherapy; High CBCT/RT: high cumulative CBCT >850mg or CBCT and RT.

RT in TCSs is less often described, and is, among other mechanisms related to atherosclerosis within the irradiated renal tissue [50,51]. The increased nephrotoxic effect in TCSs after CBCT plus RT can possibly be explained by long-term elevated levels of serum cisplatin during post-CBCT RT [52,53].

Already at S1, the youngest group in our cohort experienced the largest reduction in kidney function, with the greatest absolute decline during the follow-up. Non-seminoma histology and CBCT is over-represented in the youngest TCSs, thus explaining the poorer kidney function.

The finding of reduced kidney function at S3 in the Surgery versus the comparison group, declining from average 1.23 units at S1 to 5.18 at S3, is challenging [54]. We can only speculate whether post-RPLND fibrotic changes within the retroperitoneal space may lead to reduced blood flow to the peri- and intrarenal tissue thus being part of the explanation.

Kidney dysfunction and associated cardiovascular morbidity and mortality

The persistence of reduced GFR < 60 mL/min/1.73m^2 is one of several criteria of chronic kidney disease [55]. In only 2.5% of our patients, this eGFR reduction was observed at least twice, thus chronic kidney disease is only confirmed for a

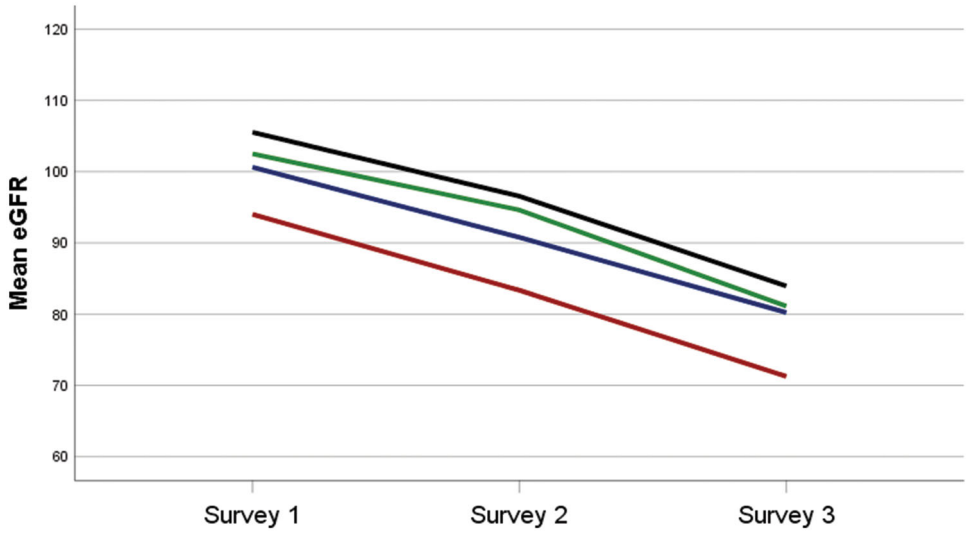

Figure 3. eGFR development from repeated measurements in individual testicular cancer survivors from Survey1 to Survey3 stratified by treatment groups. Black line depicts surgery only; green line depicts cisplatin-based chemotherapy (CBCT); blue line depicts Radiotherapy only (RT) and red line depicts high cumulative CBCT >850mg or CBCT and RT (High CBCT/RT).

Table 3. Previous reports on kidney function after radiotherapy and cisplatin-based chemotherapy for testicular cancer.

References	Patients (*N*)[a]	Treatment	Median follow-up (years)	Method	Kidney impairment eGFR change (median) or *N* (%)	Comparison group
Radiotherapy (RT)						
Kost et al. [34]	91[b] (45 TC)	31– 63 Gy	>1	^{99m}Tc-DMSA	*N* = 21 (23%)	No
Cisplatin-based chemotherapy (CBCT)						
Hansen et al. [35]	34	CBCT	5.4	Cr-EDTA	−12% eGFR	No
Moul et al. [36]	114	CBCT	5.8	S-creatinine	*N* = 11 (10%)	No
Stoter et al. [37]	57	CBCT	8	S-creatinine	*N* = 12 (21%)	No
Bissett et al. [38]	74 (15 also RT)	CBCT	4.3	CrCl	−22% eGFR	No
Boyer et al. [13]	28	CBCT	6.3	CrCl	*N* = 12 (43%)	No
Osanto et al. [39]	43	CBCT	4.1	CrCl	−15% (mean) eGFR	No
Inai et al. [15]	96	CBCT	5.8	MDRD	−23% eGFR	No
Suer et al. [40]	113	CBCT	4.8	MDRD	−26% eGFR	Yes (surgery)
Lauritsen et al. [14]	322	CBCT	Max. 5	Cr-EDTA	(−11, −26)% eGFR	No
CBCT and RT						
Fossa et al. [41]	18, 53	RT, CBCT ± RT	14	Hippuran clearance or ^{99m}DTPA	−8% (mean), −14% (mean) eGFR	Yes (surgery)
Cost et al. [42]	19, 81	RT, CBCT	1.9, 2.6	MDRD	+10%, −16% eGFR	Yes (surgery)

[a]Studies including < 25 pts with CBCT or < 10 pts with RT were excluded from the table; [b]Abdominal RT. TC: testicular cancer.

small proportion of patients in this study. However, at S3, eGFR < 60 mL/min/1.73 m^2 is observed in 9.6% of all the TCSs and 21% of the High CBCT/RT Group. Decreased kidney function seems thus prevalent in a substantial subset of TCSs. However, in general, we still consider the treatment-induced reduction of eGFR as slight or moderate, probably without clinically relevant risk for end-stage renal disease in the majority of TCSs. Further, today's reduction of CBCT to three cycles in good-risk metastatic patients, even more reduces the risk of clinically important renal dysfunction.

As mildly decreased kidney function (eGFR < 90 mL/min/1.73m^2) was such a frequent finding, we are concerned about the clinical implications related to possibly increased risk of CVD in this population. In studies in the general population, even mild renal dysfunction, especially if proteinuria is present [33,56,57] has been associated with increased risk of CVD, morbidity and mortality. Reduced renal function has rarely been addressed as a possible etiological factor for the well-known increased risk of CVD in TCSs. In our view, eGFR < 90 mL/min/1.73m^2 should in TCSs be evaluated as a risk factor for morbidity, in particular CVD.

In TCSs, studied maximally five years after treatment, Lauritsen et al. [14] described dose-dependent reduced renal function by 11–25% as compared to the pretreatment situation. However, the authors did not find any association between kidney function and major CVD morbidity or overall mortality up to median 15 years post diagnosis. In our view, post-treatment follow-up of 15 years may be un-sufficient to detect increased CVD mortality in TCSs not at least due to continuos improving treatments of CVD in general. For example, Kvammen et al. [58] document decline in relative survival first after 15–30 years. Furthermore, we cannot exclude that the elevated risk of hypertension in TCSs might be related to their mildly reduced kidney function. Based on

our findings, we therefore recommend including eGFR analyses, possibly combined with assessment of proteinuria in cases of eGFR < 90 mL/min/1.73m^2.

Our TCSs have received relatively 'old-fashioned' treatment compared to todays' standard treatment strategies with omission of RT and fewer CBCT cycles. Nevertheless, our findings are relevant for recurrent testicular cancer patients who often even today receive more than four cycles of CBCT and for any cancer survivors who have received high doses of cisplatin with or without RT. Our observation of the greatest kidney function impairment in the youngest TCSs should be of particular concern.

Limitations

Several limitations has to be considered: Even though medical characteristics seem similar in the three surveys between attendants and non-attendants, a gradual selection bias toward more healthy participants cannot be ruled out in this longitudinal study.

Kidney function in our study is evaluated by s-creatinine-based eGFR alone as documentation of albuminuria as an early finding in renal dysfunction was not available. The expensive and time-consuming direct measurement of GFR [59], the gold standard, is not feasible in large cohorts. eGFR calculations based on s-creatinine provide a straightforward approach in these situations [31]. The assays for determination of s-creatinine have changed several times during the observation period. We thus cannot exclude minor impact on the time-dependent variations of s-creatinine analyses, even though the impact on eGFR should be small [60].

The strength of our study is its longitudinal population-based design with detailed treatment information and a follow-up time of almost three post-treatment decades. The comparison to the general population represents a further advantage.

Conclusion

Compared with the general population, long-term TCSs are at risk of a slight, but persistently increasing renal impairment associated with treatment type and treatment intensity. Treatment with cumulative cisplatin doses >850 mg or the combination of cisplatin and RT, represent a particularly high risk. S-creatinine should be included in the routine tests recommended to all TCSs and all long-term cancer survivors after CBCT, with the aim of early detection of reduced renal function and prevention of CVD.

Acknowledgments

The authors wish to thank all the men in the cohort, without the good adherence to these studies, validity of our results would be limited. In addition, the patient's general practitioners have contributed with clinical information. Grethe Skjolde, Siri Lothe Hess and Vigdis Opperud have administered patient recruitment and bioengineers at OUH have analyzed blood samples in S3.

The comparison group: The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Center (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology NTNU), Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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