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Reply: 'Comment on Prevalence of the metabolic syndrome and cardiovascular disease risk in chemotherapy-treated testicular germ cell tumour survivors'

P M Willemse[1], J Burggraaf[2], N A T Hamdy[3] and S Osanto[*,1]

[1]Department of Clinical Oncology, Leiden University Medical Center, Albinusdreef 2, 2333 Leiden, ZA, The Netherlands; [2]Centre for Human Drug Research, Zernikedreef 10, 2333 Leiden, CL, The Netherlands and [3]Department of Endocrinology and Metabolic Diseases, Leiden University Medical Center, Albinusdreef 2, 2333 Leiden, ZA, The Netherlands

We read with interest the Letter to the Editor by Singhera and Huddart (2013) and are pleased to respond to their comments.

Regarding their comments on missing data, the median follow-up time after completing treatment seems to have escaped their attention, as it was provided for all survivors and for separate treatment groups in Table 2 of our published article (Willemse *et al*, 2013).

We indeed had omitted to report on the actual number of survivors on antihypertensive, lipid modifying and/or antidiabetic medication, but did not exclude survivors on one or more of these medications from the analysis in calculating the 10-year risk of cardiovascular disease. In fact, the 36 survivors, with a median age of 50.7 years (range 29.5–69.5), who received cardiac-modifying medication had a Framingham Risk Score (FRS) and Systemic

*Correspondence: Professor S Osanto; E-mail: s.osanto@lumc.nl
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Coronary Risk Examination (SCORE) risk of 4.7% (interquartile range, IQR 0.8–2.7) and 7.9% (IQR 3.5–12.0), respectively, underscoring that Metabolic Syndrome (MetS) does indeed represent a risk factor for cardiovascular disease (CVD). Excluding these cardiac medication using survivors would decrease the 10-year FRS and SCORE risk to 2.2% (IQR 0.0–3.0) and 1.1% (IQR 0.1–1.1), respectively, in the remaining 215 patients, clearly demonstrating that the 'low FRS and SCORE risk' were not diluted due to the inclusion of survivors on anticardiac medication as suggested by the authors of the Letter. Although we assume that the definition for healthy controls as being subjects without any disease and receiving no treatment is globally accepted, we are happy to confirm that indeed none of the controls were on anticardiac medication.

As we acknowledged in our discussion that increased MetS prevalence in the survivors may not translate into increased 10-year FRS and SCORE predicted CVD risk because of short follow-up time and young survivors' age, we fail to understand the concerns expressed by Singhera and Huddart (2013) in their Letter. In addition, the calculated CVD risks are corroborated by our center's unpublished cardiovascular incidence data in testicular germ cell tumour (GCT) patients treated between 1977 and 2008. Of the 776 GCT patients included in the hospital's cancer registry during this 31-year period, 65 had died of testicular cancer, while 221 were discharged from follow-up. Of the remaining 490 survivors with a complete data set, 65 had died during follow-up: 3 of a myocardial infarction, 1 of a cerebrovascular event, 33 of second malignancies, 28 of other causes of death. Of the 425 patients currently alive and under regular follow-up, 5 had a non-fatal myocardial infarction, 4 had a non-fatal CVA, and 4 an acute coronary syndrome. Seventeen of 490 patients (3.5%) had thus a cardiovascular event at a median age of 51.4 years (23–67 year), 0.1–29 years (median 12.5 year) after their anticancer treatment. Fifteen of seventeen patients with a cardiovascular event had received combination chemotherapy in the past. This 'low' actual CVD incidence corresponds to the 'low' (3%) 10-year FRS cardiovascular risk estimate in the 251 patients reported in our article (Willemse *et al*, 2013).

We welcome the suggestion of undertaking a more pertinent lifetime risk rather than 10-year risk analysis, but are not aware of the existence of a validated predictive risk calculation model for the former. The alternative option recommended by Singhera and Huddart (2013) to use relative risk charts for counselling survivors regarding CVD risk (Graham *et al*, 2007) actually represents no alternative option to ours, as Graham *et al* (2007) also uses the SCORE risk used by us in determining CVD risk (Willemse *et al*, 2013). We do agree, however, that large-scale longitudinal cohort studies on CVD in cancer survivors should be of benefit as they would provide more accurate data on lifetime CVD risk in GCT survivors.

In keeping with the figure of 12–16% of GCT survivors with complete hypogonadism quoted by Huddart and Singhera (2013) in their Letter, 34 (12.9%) of our cohort of GCT survivors also had complete hypogonadism, whereas 42 survivors (15.9%) had partial hypogonadism.

Based on the biological activity of androgens in the male, the morbidity of low androgen levels and efficacy of testosterone in reducing MetS prevalence and CVD mortality (Rebuffe-Scrive *et al*, 1991; Marin *et al*, 1993; Anderson *et al*, 1996; Boyanov *et al*, 2003; Kapoor *et al*, 2006; Heufelder *et al*, 2009; Jones *et al*, 2011), we would strongly argue that there is no justifiable reason to withhold androgen replacement therapy from male GCT survivors with complete hypogonadism. While the results of randomised testosterone replacement trials in cancer survivors are eagerly awaited, the clock is ticking for GCT survivors who are at clear risk of developing significant morbidity related to long-term androgen deficiency.

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