Testicular cancer, testosterone deficiency and the metabolic syndrome.

A BSSM position statement on the patient pathway and follow up.

Testicular cancer (TC) is the most common malignancy in young men, with around 18 000 new diagnoses in Europe each year.[1] While this disease often used to have a lethal outcome, with the main aim being to increase the chance of survival,[2] improved treatments have now resulted in cure rates close to 100% in stage I disease and over 80% in metastatic cases.[2]

However, studies have shown that TC survivors are at increased risk of long-term side effects from the treatment:

- Testosterone deficiency (TD)[4]
- Metabolic syndrome (MetS)[5]
- Decreased fertility
- Pulmonary toxicity
- Nephrotoxicity
- Neurotoxicity
- Psychosocial problems[6]

The main treatments for TC are surgery (orchidectomy), radiotherapy (RT) and chemotherapy. Orchidectomy is the first step for all TCs, regardless of stage. If the cancer is detected early, orchidectomy may be the only treatment required. In more advanced stages, orchidectomy is usually followed by RT or chemotherapy (typically platinum/platin-based).

TD causes significant physical and psychological effects, which can compromise a man's general wellbeing, sexuality and fertility.[7,8] TD has also been strongly associated with MetS,[9] and increased CV and all-cause mortality.[10-14] Primary TD, characterised by low testosterone and high luteinising hormone (LH) levels, has been reported to affect around 20% of TC survivors after orchidectomy, with or without chemotherapy.[15]

A systematic review and meta-analysis of 12 studies[4] evaluated the risk of TD in TC survivors based on three different treatment combinations: Orchidectomy plus standard chemotherapy (defined as four cycles of platin-based chemotherapy), orchiectomy plus non-conventional chemotherapy (defined as platin-based combination chemotherapy with double dose cisplatin, >4 cycles of platin-based combination chemotherapy, or both chemotherapy and infra-diaphragmatic RT), and orchidectomy plus infra-diaphragmatic RT

The odds ratios for TD were 1.8 in subjects treated with orchidectomy plus standard chemotherapy compared with orchidectomy alone, 3.1 in subjects treated with orchiectomy plus non-conventional chemotherapy compared with orchidectomy alone, and 1.6 in patients treated with orchidectomy plus infra-diaphragmatic RT compared with orchidectomy alone.[4]

As compared to TC survivors with normal testosterone levels, those with TD were more likely to take medications for:[16]

- Dyslipidaemia (20% versus 6%, $p<0.001$)
- Erectile dysfunction (20% versus 12%, $p=0.02$)

- Hypertension (19% versus 11%; p=0.01)
- Anxiety or depression (15% versus 10%, p=0.06)
- Diabetes (6% versus 3%, p=0.07)

Metabolic syndrome following testicular cancer is a clustering of risk factors for CVD and type 2 diabetes mellitus (T2DM). These include abdominal obesity, raised blood pressure, dyslipidaemia (raised triglycerides and lowered HDL cholesterol), and raised blood glucose.

Patients with MetS are twice as likely to develop CVD over the next 5 to 10 years as those without it, and their lifetime risk will be greater still. MetS also confers a five-fold increase in the risk of T2DM.[17]

The causes of TD in the presence of TC include: Cancer-related damage to the testicular cells that are responsible for the production of testosterone, orchidectomy, chemotherapy/RT-related damage to the remaining testicular tissue and hormonal abnormalities resulting from cancer-related stress.

Orchidectomy, of course, immediately halves the number of Leydig cells, which produce testosterone in the presence of LH.[15] Residual Leydig function may be reduced by RT and/or chemotherapy, the testicles are highly radiosensitive and may be damaged be direct or scattered radiation from adjacent tissues, with the degree of damage dependent on the dose. The degree of gonadal damage resulting from chemotherapy will depend on the type/s used and cumulative dose/s.[18] The risk of TD appears to be greatest in the most heavily treated patients.[4]

Stress increases cortisol production and may decrease testosterone levels,[19] with secondary increases in serum LH and FSH levels.[20] Increased cortisol and decreased testosterone may, in turn, contribute to increased stress.[19]

An increased risk of accelerated hormonal ageing has been reported in TC survivors over the long term (ie 20 years after TC treatment).[21] However Leydig cell function may recover more than two years after TC treatment,[15] emphasising the importance of regular follow-up and monitoring either in primary or secondary care.

For those with sexual problems or psychological issues, including stress, psycho-sexual counselling may be helpful.

The ongoing Platinum study[22] evaluated clinical and genetic MetS risk factors in North American TC survivors (mean age 38.1 years), using matched controls from the National Health and Nutrition Examination Survey. TC survivors were significantly more likely than controls to have:[22]

- Hypertension (43.2% versus 30.7%; p<0.001)
- Elevated LDL cholesterol levels (17.7% versus 9.3%; p<0.001)
- Elevated total cholesterol levels (26.3% versus 11.1%; p<0.001)
- BMI ≥25kg/m2 (75.1% versus 69.1%; p=0.04)

BUT they were less likely to have abdominal obesity (28.2% versus 40.1%; p<0.001) or decreased HDL-C levels (23.7% versus 34.8%; p<0.001).[22]

Because TC survivors appear to be at increased risk of TD, MetS and CVD,[4,5] careful follow up and monitoring is important for the early detection and timely treatment of TD and CV risk factors to

help reduce CVD risk. The relatively high prevalence of Leydig cell dysfunction in TC survivors, implies that hormonal status should be regularly assessed.[6] This may also help identify men at high risk of MetS and CVD.[2] Testosterone replacement therapy should be considered in the presence of biochemical evidence of TD and persistent clinical symptoms.

A recent 6-month double-blind randomised placebo-controlled trial using testosterone replacement in young male cancer survivors has been published.[23] It included 136 participants, 42.6% were aged 25–37 years, 57.4% were aged 38–50 years, 88% had testicular cancer, 10% had lymphoma, matched for body mass index [BMI]). Participants were randomised 1:1 to receive testosterone (Testosterone 2% gel) or placebo for 26 weeks.

The study demonstrated that in young adult male cancer survivors with low and low-normal fasting morning total testosterone 7–12 nmol/l, testosterone treatment is associated with improvement in adverse body composition, and the reduction in trunk fat mass with testosterone treatment is potentially more beneficial in those with an increased trunk fat mass.[23]

Follow up

Annual follow-up for these men would therefore seem appropriate, including CVD risk factor screening and measurement of BP, waist circumference, height, weight and BMI, HBA1c, renal function and testosterone + SHBG levels.

Healthy lifestyle advice should include the importance of smoking cessation, regular physical activity and the consumption of a healthy, balanced diet.

It's worth bearing in mind though, that current MetS criteria was originally developed for the general population, so it may not cover the full spectrum of metabolic abnormities seen in TC survivors.[22]

The fact that cisplatin may remain detectable in plasma up to 20 years after chemotherapy for TC,[5,24] and may still be partially reactive,[5,25] highlights the risk of long-term toxicity and the importance of extended follow up in these patients, to monitor possible adverse effects.

In TC survivors, long-term, persistent treatment-related side effects are associated with both impaired physical and mental quality of life.[3] If patients are warned about the potential long-term toxicity of their cancer therapy, it may facilitate early identification and reporting of any treatment-associated health problems, and help prevent TD, MetS and CVD from occurring.

The follow up should also include vigilance for the other long-term effects of TC treatment, which include decreased fertility, sexual dysfunction, pulmonary toxicity, nephrotoxicity, neurotoxicity and psychosocial problems. Their incidence and time of onset will vary according to treatment type and intensity.[6]

Annual follow-up:

CVD risk factor screening, BP, lipids QRisk3

Waist circumference

Height, weight and BMI

HBA1c

Renal function

Testosterone + SHBG

Healthy lifestyle advice should include the importance of smoking cessation, regular physical activity and the consumption of a healthy, balanced diet.

Vigilance for the other long-term effects of TC treatment

Decreased fertility

Pulmonary toxicity

Nephrotoxicity

Neurotoxicity

Sexual dysfunction

Psychosocial problems, anxiety and depression

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