Appendix 5. Quality of life and long-term toxicities after cure of testicular cancer

The prognosis for testicular cancer (TC) is generally favourable, with high survival rates. Despite the excellent prognosis in TC survivors, reports of increased mortality rates from other causes, particularly secondary malignancies, are of concern [1]. Patients are typically diagnosed in their late teens to early 40s, and life expectancy after cure is extended over several decades [2]. Adherence to international guidelines can help minimize long-term toxicities associated with treatment.

The management of stage I TC remains controversial, with options including surveillance and adjuvant chemotherapy. The optimal approach to minimize long-term toxicities is uncertain, as both strategies have shown favourable outcomes in terms of mortality and late toxicities [3-5].

In contrast, after first-line chemotherapy, numerous side effects affecting nearly all organ systems as well as psychosocial problems have been described as summarised in the chapters below. For this reason during follow-up, TC patients should be screened and treated for known side effects as discussed below and interventions to modify risk factors should be encouraged. Specifically promoting a healthy lifestyle, mainly smoking cessation [6], as well as physical activity is important for long-term well-being and overall survival [7, 8]. Unemployment rates are higher in TC survivors, emphasizing the need for comprehensive support [9].

During follow-up, TC survivors should be screened and treated for known risk factors such as hypertension, hyperlipidaemia, and testosterone deficiency. Adverse health outcomes (AHOs) are more common in TC patients who received chemotherapy than those cured by surgery alone. Further, modifiable risk factors may contribute to AHOs, like hypertension and noise exposure to hearing impairment or smoking to Raynaud phenomenon [7]. Therefore, a healthy lifestyle should be promoted during the follow-up consultations. Adverse health outcomes are associated with unemployment, which is found clearly increased in TC survivors (TCSs) as compared to a male normative population [9]. When follow-up care concludes, providing TC survivors with a written cancer survivorship plan can address late toxic effects, lifestyle recommendations and recurrence risk, enhancing their long-term care and adherence [10-13].

Treatment of stage I TC is controversial, with some experts advocating surveillance for all, thereby avoiding unnecessary adjuvant chemotherapy [3], whereas others highlight the importance of patient autonomy and consider the prospect of avoiding salvage treatment with long-term toxicities appealing [318]. Unfortunately, it is not known which treatment spares most patients from long-term toxicities, which so far seem to be absent or mild after adjuvant chemotherapy. This observation is confirmed by the absence of excess mortality or late toxicities between stage I non-seminoma patients randomised to either primary RPLND or one cycle of adjuvant BEP [Bleomycin, etoposide, cisplatin] [4].

3.1 Second malignant neoplasms

3.1.1 Metachronous contralateral TC

Metachronous contralateral TC represents a particular second malignant neoplasms (SMN) as it consists of a germ-cell tumour (GCT), with a high likelihood of shared risk factors as the primary TC.

Further, cisplatin chemotherapy reduces the risk of a subsequent contralateral TC as compared to surgery only [14, 15]**.** Metachronous contralateral TCs may develop more than 20 years after the primary TC, and regular lifelong self-examination is recommended.

3.1.2 Second sold malignant neoplasms

Second malignant neoplasms of different histologic origin usually occur after the first ten years and are considered to be induced by chemo- and/or radiotherapy [11]. Testicular cancer is commonly diagnosed in adolescents and young adults (AYA), which have a higher absolute risk of developing a subsequent primary neoplasm than survivors of adult cancer [16]. In a comprehensive study on second cancers in AYA cancer survivors (aged 15-39 years at AYA cancer diagnosis), 24,309 TC survivors with 1,435 second cancers were registered as opposed to 808 expected second cancers, yielding a standardised incidence ratio of 1.8. The second cancer incidence increased with time resulting in remarkably high and accelerating 35-year cumulative incidence rate of 20% (95% CI: 18·9–21·5) [16].

The risk for solid SMN increases with younger age at radio- or chemotherapy [11]. Radiotherapy-related SMN are primarily localised within, or close to, the radiotherapy field (lung, colon, stomach, pancreas, bladder, and kidney) [11]. A remarkably clear radiation-dose relationship to gastric- and pancreatic cancer has been demonstrated [17].

Modern cisplatin-based chemotherapy has been found to be associated with a 40% increased risk of a solid SMN [18]. A relationship between cumulative dose of cisplatin and second SMN, especially in the GI tract, has been noted [19]. As few studies have observation times beyond 25 years, the cumulative incidence of SMN may be underestimated. An increase from 6.5% after 25 years to 20% after 35 years has been reported [16]. Second malignant neoplasms were identified in 9.4% of Swedish TC survivors, with half these cancers considered uncommon in men in their 40s [20]. Survival was 40% in TC survivors with a SMN as opposed to 80% in those without [20].

Among 24,900 US TC survivors (TCSs), one out of six (16.9%) developed a solid SMN after 30 years of observation time [21].

3.1.3 Hematologic second malignant neoplasms The European Society for Blood and Marrow Transplantation (EBMT) reported SMN in 59 of the 5,295 TC patients registered after receiving high-dose chemotherapy (HDCT) within a median follow-up of 3.8 years. Of them, 39% developed a hematologic SMN and 58% a solid SMN. Twenty-year cumulative incidence of solid and hematologic SMN was 4.2% and 1.4% respectively, with median overall survival (OS) shorter after diagnosis of hematologic vs. solid SMN (8.6 vs. 34.4. months). Age ≥ 40 years at the time of HDCT was significantly associated with hematologic, but not with solid SMNs [22].

In a series of 40,576 TCSs, the observed ratio for developing leukaemia, mostly acute myeloid (AML) and lymphoblastic leukaemia was 2.6 [23]. Among 24,900 US TCSs, the risk of developing leukaemia, mostly AML, after chemotherapy was 2.7 fold increased [21]. The risk of AML seems to be related to both the dose of cisplatin and etoposide. Doses of etoposide exceeding 2 g/m^2 have been shown to increase the subsequent risk of AML [24]. The majority of TC patients receive much lower doses of etoposide than this so that the absolute risk of AML after three to four courses of BEP is very low. In patients requiring HDCT with cumulative etoposide doses exceeding this threshold, fewer than 1.5% have been reported to develop AML. There is a cumulative dose disease risk relationship with cisplatin

and AML. Chemotherapy-induced leukaemia is usually diagnosed within the first ten years after treatment for TC and has a poor-prognosis [25].

*3.3 **Infections***

Chemotherapy-treated TCSs have a higher risk of dying from infections than the general population (standard mortality ratio 2.35-2.48, 95%; CI: 1.70-3.5) [1, 26]. This is possibly due to long-term bone marrow suppression, as well as complications of subsequent salvage treatment (which was not reliably registered). Alternatively, extensive or subsequent surgical treatment may be contributory. Furthermore, asymptomatic pulmonary fibrosis by mediastinal radiotherapy and/or bleomycin may render TCSs vulnerable to respiratory infections long after treatment.

*3.4 **Pulmonary complications***

The TCSs who received high cumulative cisplatin doses and/or pulmonary surgery, have a poorer pulmonary function than those cured with surgery alone [27]. Intriguingly, long-term pulmonary complications were associated with the cumulative cisplatin doses but not with the dose of bleomycin [27]. The data contrasts with a meta-analysis on chemotherapy for TC including 6,498 patients showing a significant effect of bleomycin administration on all-grade pulmonary toxicity [28]. A Danish cohort of 565 TC survivors found pulmonary function recovered with repeated assessments over five years in almost all patients [29]. Pulmonary function was not associated with reduced renal function, age, tobacco-smoking, and cumulative chemotherapy, but rather pulmonary embolism, lung surgery, and poor IGCCCG risk group [29]. In 234 good risk TCSs patients the inclusion of bleomycin did not seem to influence pulmonary morbidity, operative difficulty, or non-pulmonary post-operative complications after post-chemotherapy retroperitoneal lymph node dissection (RPLND) [30].

A Canadian study on 212 TC patients receiving bleomycin-containing chemotherapy revealed bleomycin-induced pneumonitis (BIP) in 73 patients (34%) with the majority of these (75%) asymptomatic [31]. Granulocyte colony stimulating factor use was not associated with increased risk of BIP in multivariable analyses nor was it associated with increased severity of symptomatic BIP. There was a non-statistically significant trend towards greater risk of BIP in patients that developed renal impairment during chemotherapy treatment [31].

*3.5 **Cardiovascular toxicity***

Thromboembolic events (mostly venous) occur more frequently in GCT patients receiving chemotherapy than in other young male adults treated with chemotherapy for other cancers [32]. (See Appendix 2 Prevention of thromboembolism events during chemotherapy 2023).

Older studies have reported a higher mortality rate from cardiovascular disease (CVD) in TCSs compared to the general population [33-35], however a recent Norwegian study did not find any increased CVD mortality risk [1]. There is a clear link between chemotherapy and CVD morbidity, regardless of the specific chemotherapy regimen used (BEP x 3 vs. EP x 4). This increased CVD risk can be attributed to the presence of undetected cardiovascular risk factors among many TCSs, including dyslipidemia in 86% of cases, hypertension in 50%, and metabolic syndrome in 35% [33, 36-38]. Notably, TCSs with lower educational levels and less physical activity have a higher risk of developing CVD [39]. However, after undergoing surgery, there is no evidence of an increased risk of CVD [40, 41].

Metabolic syndrome, which encompasses hypertension, obesity, and hypercholesterolemia, is a significant risk factor for CVD. Its prevalence increases with the intensity of treatment for testicular cancer [35, 42, 43]. Hypogonadism, a common consequence of testicular cancer treatment, increases the risk of insulin resistance, which is closely associated with metabolic syndrome and CVD. However, most associations between testicular cancer treatment and metabolic parameters become statistically insignificant after adjusting for hypogonadism, suggesting that hypogonadism may mediate several toxicities typically attributed to the treatment itself [44] . Additionally, the presence of residual serum platinum in the bloodstream may induce endothelial stress, potentially leading to hypertension [45]. Furthermore, exposure to circulating platinum is associated with paraesthesia, hypogonadism, hypercholesterolemia, and major vascular events [46].

Regular physical activity reduces the risk of metabolic syndrome and CVD. A twelve-week high-intensity aerobic interval training (HIIT) program has been shown to improve cardiorespiratory fitness, various CVD risk factors, and surrogate markers of mortality in TCSs compared to standard care with no supervised training [47]. However, HIIT during cisplatin chemotherapy may pose risks. A planned study involving 94 patients was terminated prematurely after recruiting nineteen patients due to severe CVD complications observed in three out of nine patients undergoing HIIT [48]. Two patients developed pulmonary embolisms (one on day seven and the other on day nine of the second cycle of BEP), while the remaining patient experienced a myocardial infarction (on day seven of the third cycle of BEP). Although firm conclusions cannot be drawn from such a small sample size, the incidence of CVD events exceeded the expected 5% risk of thromboembolic complications during or shortly after cisplatin chemotherapy. Therefore, the authors discourage the implementation of HIIT during cisplatin chemotherapy for testicular cancer.

3.6 ***Neurotoxicity including Raynaud, paresthesia, ototoxicity***

A comprehensive clinical and genome-wide analysis of severe cisplatin-induced neurotoxicity's has revealed a correlation between neurotoxicity, ototoxicity, and Raynaud phenomena in TCSs [49]. Cisplatin leads to a dose dependent neurotoxicity [50] and for this reason cisplatin associaed neurotoxicity could be limited by using 3 x BEP instead of 4 x EP [49].

Raynaud-like phenomena associated with chemotherapy were reported before the introduction of cisplatin and are typically attributed to bleomycin [51, 52]. Cisplatin is believed to contribute to cold-induced vasospasms [53].

Cisplatin induces symmetric, dose-dependent sensory paraesthesia in a distal, length-dependent glove and stocking distribution. This symptom affects 29% of testicular cancer survivors (TCSs) who received cisplatin chemotherapy, compared to 10% after orchidectomy alone [35, 54]. The frequency of this paraesthesia increases to 46% with five or more cycles of treatment. Paclitaxel-induced acute neuropathy manifests as an acute pain syndrome that typically develops within three to seven days after administration. Platinum remains measurable in the serum of TCSs for many years following its application, and the intensity of paraesthesia is more strongly associated with serum platinum levels than with the cumulative dose of cisplatin administered [45]. TCSs who experience a larger decline in circulating residual serum platinum during follow-up are at a reduced risk of worsening tinnitus or hand paraesthesia [55].

3.7 **Ototoxicity**

Cisplatin-induced ototoxicity, including tinnitus and hearing loss and differs between patient-reported and audiometrically-defined HL but is reported by 68% and 59% of patients of which 10% require a hearing aid, and is dependent on the number of given chemotherapy cycles [54, 56, 57]. It particularly affects frequencies of 4,000 Hz and higher and is caused by damage to the outer hair cells in the inner ear [35]. Encouragingly, hearing impairment does not significantly deteriorate after the first decade following chemotherapy, and normal speech perception tests conducted 30 years after treatment indicate limited clinical relevance of high-frequency hearing loss [58, 59]. A significant association has been demonstrated between Glutathione S-transferases (GST) genotypes and the risk of cisplatin-induced ototoxicity [60, 61].

3.8 ***Cognitive function***

There are concerns that chemotherapy may reduce the cognitive function leading to "chemo-brain." Amidi *et al.*, could show an alteration of brain structural networks after cisplatin-based chemotherapy for TC [62]. Impaired brain networks may underlie poorer performance over time on both specific and non-specific cognitive functions in TC survivors following chemotherapy.

3.9 ***Nephrotoxicity***

Cisplatin-based chemotherapy may lead to long-term renal dysfunction in 20-30% of TCSs [41, 42, 46]. In TC patients, reduced renal excretion of cisplatin and bleomycin might increase the risk of other toxicities, e.g., bleomycin-related pneumonitis [63, 64]. A comprehensive assessment of 1,206 Danish TCSs, however, did not reveal a significant association between chemotherapy-induced impaired renal function and other toxicities [34]. Renal recovery was poor after five or more cycles of BEP as compared to after BEP x 3 [43]. The estimation of glomerular filtration rate (eGFR) depends on whether creatinine or cystatin is applied, with the latter substance leading to an overestimation of eGFR in cisplatin treated TCSs, whereas this discrepancy was not found in patients with chronic kidney failure due to medical disease [65]. Genomic markers are related to the risk of cisplatin-induced nephrotoxicity [66]. How these results will impact selection and/or modification of chemotherapy remains to be seen.

3.10 ***Hypogonadism***

Testicular endocrine dysfunction comprises insufficient testosterone production and/or compensatory increased luteinizing hormone (LH) levels. Subnormal testosterone levels have been reported in TCSs treated with chemotherapy, when compared to those treated with surgery only or the general population [35, 63, 67, 68]. Compensated Leydig cell dysfunction in TCSs (testosterone within normal limits & increased LH values) was not associated with symptoms of depression, anxiety, sexual dysfunction, fatigue or impaired overall self-evaluated QoL [69], such that testosterone substitution seems not to be indicated in these patients [70].

Hypogonadism increases the risk of insulin resistance and hence the risk of metabolic syndrome, which, in turn, might lead to CVD in the long term [44]. Wiechno *et al*., showed a decline in testosterone and an increase in LH and follicle-stimulating hormone (FSH) within one year after treatment for unilateral TC [71]. Although there are clear indications of hypogonadism-related complications, and despite an established association between low testosterone and metabolic

syndrome, no clear association between Leydig cell dysfunction and the risk of metabolic syndrome during a median ten-year follow-up could be established [72].

An RCT demonstrated a benefit of testosterone replacement therapy in young male survivors of testicular cancer, lymphoma, and leukaemia aged 25–50 years who had low morning serum testosterone. Under the six months of replacement therapy, cancer survivors that received testosterone experienced a decrease in trunk fat mass and whole-body fat mass and an increase in lean body mass, but no effect on reported physical functioning or other quality of life (QoL) scores when compared to those that received a placebo gel [73]. The absence of improved QoL and the issue of rendering TCSs sub- or infertile by testosterone replacement therapy is the reason why the TC panel does not recommend this strategy until more compelling endpoints are reported. An ongoing Danish RCT might yield new level 1 evidence [74].

Erectile dysfunction (OR: 4.2) has been significantly associated with chemotherapy in a recent multicentre study [35]. Of 481 North American TCSs treated with modern cisplatin chemotherapy, 38% were hypogonadal (defined as on testosterone substitution or serum testosterone level ≤ 3.0 ng/mL) [75]. Hypogonadism was associated with the number of adverse health outcomes and its risk increased with age and obesity [76].

3.11 ***Fatigue***

Chronic fatigue (CF) is described as a subjective feeling of emotional, physical and/or cognitive tiredness that is not relieved by rest and persists for more than six months. Significantly higher levels of C-reactive protein and interleukin-1 receptor antagonist are measured in TCSs with CF [76]. Also, a significantly higher frequency of CF (16%) was reported in a cross-sectional Norwegian study of long-term TCSs at a median of twelve years after treatment for TC when compared with the age-matched Norwegian population (10%) [77]. Of note, the prevalence of CF increased from 15-27% during a ten-year period in long-term TCSs [78].

3.12 ***Bone health***

Patients treated with chemotherapy have an increased risk of osteoporosis [79].

3.13 ***Quality of life***

Quality of life is transiently reduced by chemotherapy, during which patients experience a loss of appetite, increased fatigue, increased dyspnoea and reduced social- and physical function [77]. When comparing three or four cycles of BEP in good-risk patients, all outcomes favour treatment with three courses [80]. After one and two years, one-third of patients reported an improvement in global QoL after chemotherapy, while one fifth of patients reported deterioration, with no difference between treatment groups. After adjuvant treatment of non-seminoma stage I patients, there was no difference in short-term or long-term (five years) QoL between RPLND, or one course of BEP [81].

3.14 **Mental health**

Anxiety, depression, fear of cancer recurrence (FCR), and distress significantly impact the health-related quality of life (HRQoL) of testicular cancer survivors (TCSs) [82]. Clinically significant anxiety is reported in approximately one out of five TCSs [83], and distress in one out of seven, while depression prevalence varies. Fear of recurrence is reported by about one-third of TCSs. Factors such as single

status, unemployment, low socio-economic status, comorbidities, worse symptoms/side effects, and passive coping strategies contribute to poorer psychological outcomes, including increased levels of anxiety [82, 84, 85]. Approximately 11% of TCSs experience a traumatic diagnosis leading to long-term post-traumatic stress disorder and reduced quality of life [86]. Assessing stress symptoms during follow-up visits is recommended to identify TCSs in need of support [87] and to offer an intervention [88]. Testicular cancer survivors who developed bilateral cancer showed higher anxiety levels but similar overall quality of life compared to survivors of unilateral cancer [6].

Erectile dysfunction is reported in men who underwent radiotherapy, BEP chemotherapy with surgical resection, or multiple lines of treatment. Sexual satisfaction is affected differently among these groups [6]. A large cohort study found that testicular cancer survivors have a higher prevalence of stress compared to the reference population, which can increase the risk of suicide [87, 89].

3.15 **Impact on fertility and fertility-associated issues**

Sperm abnormalities and Leydig cell dysfunction are frequently found in patients with TCs prior to orchidectomy [90, 91]. Up to 24% of TC patients are azoospermic and almost 50% have abnormal sperm counts (oligozo-ospemic) before treatment [91].

Treatment for TC, including orchidectomy, may have a negative impact on reproductive function [92]. Both chemotherapy and radiation treatment (RT) can impair fertility. Long-term infertility is rare after RT and dose-cumulative-dependent with chemotherapy [93-95]. Spermatogenesis usually recovers one to four years after chemotherapy [96]. Adjuvant treatment for CS1 (BEP [Bleomycin, etoposide, cisplatin] x1; Carbo x1) does not appear to significantly affect testicular function compared to surveillance, with full recovery after one year [97].

All patients should be offered semen preservation as the most effective strategy for fertility preservation. This should be offered before orchidectomy when feasible, maximizing the chances of fertilisation, and avoiding the risk of a non-functioning remaining testicle. If not arranged before orchidectomy, it should be undertaken prior to chemotherapy or RT [93-95, 98, 99].

Chemotherapy and RT are both teratogenic. Therefore, contraception must be used during treatment and for at least six months after its completion [100].

For further information regarding management of hypogonadism and sub-fertility the reader is referred to the EAU Guidelines on Sexual Reproductive Health [101].

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