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"Translational Neurosciences and Neurotechnologies"

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PSYCHOLOGICAL ISSUES IN TESTICULAR CANCER SURVIVORS: CORRELATION WITH PRIOR THERAPIES AND HORMONAL AGING

Scientific/Disciplinary Sector (SDS) MED/25

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ABSTRACT

Cancer survival research identifies a range of psychosocial issues and risk factors that affect cancer survivorship. In an observational study, we assessed the long-term psychological impact of stage I testicular cancer, the most common cancer in males aged 15 to 40 years, and correlations with hormonal levels. The results of our study showed the modest psychological long-term impact of stage I testicular cancer and no correlation with hormonal levels. The use of adjuvant chemotherapy did not hampered the quality of life and did not induce psychological sequalae. A high percentage of patients presented deficit in cognitive tests independently by the use of adjuvant chemotherapy. Our findings do not support the use of an extended follow-up for psychological issues in all stage I testicular cancer survivors, and adjuvant chemotherapy do not seem a risk factor.

1. INTRODUCTION AND RATIONALE

1.1 Testicular cancer

1.1.1 Testicular cancer epidemiology and risk factors

Testicular cancer (TC) is the most common solid tumor in males between the ages of 20 and 34 years (1), it accounts for approximately 1–1.5% of all cancers in men and its incidence is increasing worldwide (2-3). However, testicular cancer is a relatively rare disease considering the global cancer incidence, accounting for <1% of all male tumors and 5% of all urological malignancies (4). In the last decades, a statistically significant increase in testicular cancer incidence has been observed in many countries, among adolescents and young adult (AYA) males in 22 countries (South and North America, Asia, all parts of Europe, and Oceania) except for Africa (5).

Personal or family history of testicular cancer and/or cryptorchidism have been identified as risk factors for testicular germ cell tumours (1, 6) Some studies have suggested other risk factors such as high maternal hormone levels during pregnancy, pre-term birth and trauma (7).

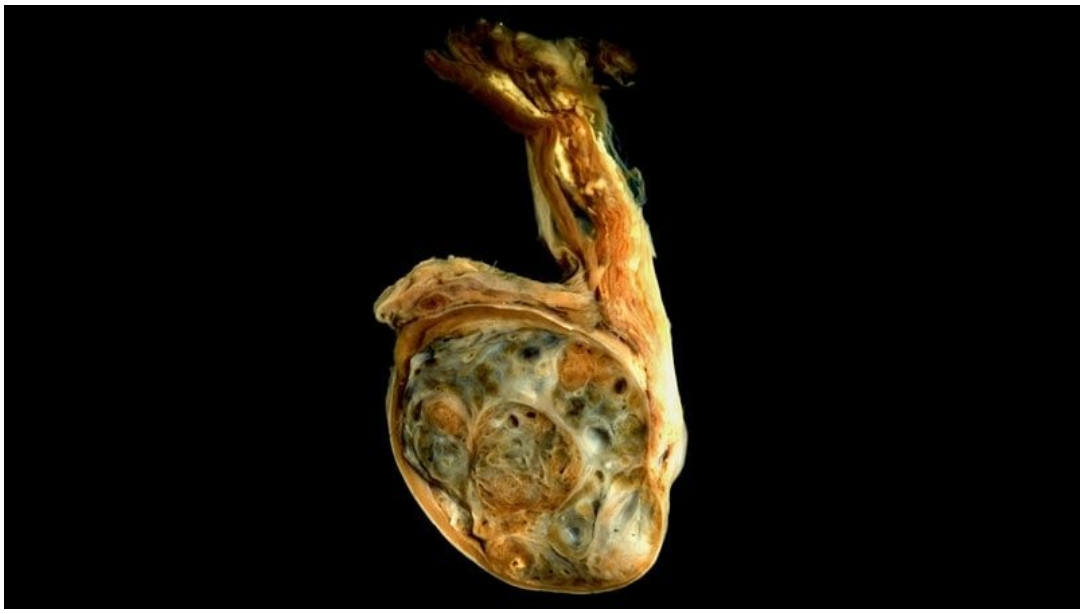
Recently a multicenter case-control analysis of men with or without TC provided first evidence for Checkpoint Kinase 2 (CHEK2) as a novel moderate-penetrance TC susceptibility gene, with potential utility for the clinical cancer-risk management of mutation carriers and their at-risk family members (8).

1.1.2 Testicular cancer diagnosis and treatment

TC can affect the tissues of one or both testicles, however commonly the tumor involves only one testicle, but men who have already had this tumor in the past have a higher risk of developing the same tumor in the other testicle. More than 90% of TC start in the germ cells, precursor cells of spermatozoa for which it is also called germ cell cancer. The remaining include stromal tumors such as Leydig cell and Sertoli cell tumors, as well as other more rare or poorly defined histologic types. Germ cell tumors (GCTs) of the testis are classified into two categories based on the presence of one or more histological types: seminoma (approximately 55%), nonseminoma (45%) (9).

Seminoma resemble primordial germ cells (PGCs) and non-seminoma, less common but more aggressive, often include multiple cell types, which is either undifferentiated (embryonal carcinoma) or differentiated (exhibiting a degree of embryonic (teratoma) or extra-embryonic (yolk sac - choriocarcinoma patterning) (10, 11). In figure 1 a picture of a section of a TC.

Figure 1 – Testicular cancer



In Table 1 the World Health Organization (WHO) classification of the most common histological types of TC (12).

Table 1 – Classification of Testicular Tumors

Germ cell tumors (95% of all testicular cancers)
Derived from germ cell neoplasia in situ
Seminoma
Nonseminoma (nonseminomatous germ cell tumors)
Embryonal carcinoma
Yolk sac tumor (postpubertal)
Trophoblastic tumors (e.g., choriocarcinoma, placental site trophoblastic tumor)
Teratoma (postpubertal) with or without malignant transformation
Mixed and unclassified germ cell tumors
Not derived from germ cell neoplasia in situ
Spermatocytic tumor
Teratoma (prepubertal)
Yolk sac tumor (prepubertal)
Sex cord–stromal tumors (< 5% of all testicular cancers)
Leydig cell tumor
Sertoli cell tumor
Granulosa cell tumor
Mixed and unclassified sex cord–stromal tumors
Mixed germ cell and stromal tumors (proportion of all testicular cancers not well defined)
Gonadoblastoma
Miscellaneous tumors (proportion of all testicular cancers not well defined)
Ovarian epithelial-type tumors
Hemangioma
Hematolymphoid tumors
Tumors of the collecting duct and rete testis (adenocarcinoma)

In the active phase of disease, clinical characteristics include a painless or painful testicular nodule, mass, enlargement or induration with a consequent testicular discomfort or swelling (1).

Cure depends on many factors: an early diagnosis, the correct use of diagnosis tools, appropriate treatments and specialized expertise for patients with advanced disease. Regarding patients with low-stage disease, clinical intervention aims at reducing treatment-related long-term toxicities and avoiding secondary cancers (6).

Cure rates for clinical stage I tumors approach 100% and even in cases of metastatic disease very high rates of long-term overall survival are reported when treated with appropriate chemotherapy (13). Radical inguinal orchiectomy, which involves removal of the testicle and ligation of the spermatic cord at the inguinal ring, is the primary treatment for any malignant tumor found on surgical exploration of a testicular mass (14).

Simultaneous implantation of testicular prosthesis is considered during orchiectomy if desired by the patient (15, 16). Since it is not possible to know the exact impact of cancer therapy on fertility, the cryopreservation of sperm before therapy should be offered to patients of reproductive age before undergoing any therapeutic intervention (17, 18)

Patients are cured by unilateral or radical orchiectomy and when the pathological diagnosis is defined (seminoma or non-seminoma), as well as the disease stage and the need for an additional treatment chemotherapy and/or radiotherapy; platinum-based chemotherapy regimens are the standard treatment because they allow to obtain complete responses, even in metastatic patients (19-21).

1.1.3 Testicular cancer survivorship

The excellent clinical outcome of TC patients is, however, associated with considerable short-term and long-term morbidity, including second malignant tumors, chronic fatigue, cardiovascular disease, neurotoxicity, nephrotoxicity, pulmonary toxicity, hypogonadism, decreased fertility, and psychosocial problems (22-23). Regarding sexual functioning, some issues (reduction or inhibition of libido) may be due to treatment-related somatic factors, among these fatigue, general malaise, hair loss, and excessive weight changes have a key role (23).

Because of the young age of patients at first diagnosis and the waited long-term survival, the study of TC survivorship has emerged as a valuable paradigm for AYA cancer survivorship research.

1.2 Cancer survivors

1.2.1 Cancer survivor complications

Several different definitions of cancer survivorship have been developed and used in the literature (24). The National Cancer Institute (NCI) defines a survivor as “one who remains alive and continues to function during and after overcoming a serious hardship or life-threatening disease” (www.cancer.gov/publications/dictionaries/cancer-terms/def/survivorship). It is, perhaps, more appropriate to refer more specifically to “cancer survivor” to describe any person who has been diagnosed with cancer who has completed treatment with curative-intent (with the exception of maintenance treatment) and is disease-free (no evidence of active cancer).

Cancer survivors, in general, appear to develop age-related diseases and phenotypes sooner than members of the general population. In particular, cancer survivorship can be affected by multiple medical conditions, often related to the late and long-term effects of cancer treatment as well as conditions related to premature aging (eg, fatigue, cognitive changes, decreased physical functioning). This is likely because damage to normal tissues from cancer therapies diminishes physiological reserve, accelerates processes typically associated with ageing or both (25).

1.2.2 Cancer survivors and hormonal and immunological aging

The possibility that some cancer treatments may accelerate the aging process is reported in the literature (26,27): cytotoxic chemotherapy has such effects on the hormonal and immune systems as to induce cellular senescence and accelerate molecular aging (28). This may have implications for the development of secondary medical conditions later in life, including the development of secondary malignancies, as the immune system plays a role in the development of cancer. The immunosenescence is defined as a decline in immune competence seen in old age and it is associated with a dramatic rise in morbidity and mortality from infectious disease (29, 30). Association between premature immunosenescence and poor cognitive function is reported (31-33).

TC survivors are also at risk to develop pre-mature reduced Leydig cell function and hypogonadism. They may therefore be predisposed for the syndrome of androgen deficiency of aging males (34). The results of a longitudinal study with a median follow-up of 10 years suggested that long-term TCSs presented treatment-related premature hormonal aging. Further deterioration of sex hormones probably

should be expected, putting TCSs at risk of metabolic problems, and reduced quality of life (QoL)(35).

Numerous studies have demonstrated associations between psychosocial stress and indices of poor health and evidence suggested that cellular aging at hormonal and immune system levels may be closely related to chronic stress and stress factors. (36). In a global view of cancer disease, other factors may also could be involved in the accelerate molecular aging as psychological implications of the disease and the traumatic nature of the stress experienced.

1.3 Quality of life issues and mental health

QoL is defined by the WHO as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". (https://www.who.int/tools/whoqol).

QoL is often affected by the cancer experience and can result influenced by many aspects: cancer type, the stage of disease and the severity of treatment cause different physical effects that consequently affect the subjective experience of cancer. For example, the more aggressive treatment the more the level of distress. Moreover, individual psychological factors (e.g., prior adjustment, history of losses, coping skills, emotional competence, disruption of life goals, and ability to modify life plans) as well as cultural, spiritual, and social factors of the cancer survivor influence the experience and the QoL of survivorship.

1.3.1 Testicular cancer and psychological impact

During the period of diagnosis and treatment, patients may experience psychological stress that affects the QoL(24). It depends on type and duration of treatments and consequently experience different physical and psychological loads. For example, chemotherapy was found to have side effects related to the cognitive function and seem to be associated with higher distress (37). Regarding the psychological impact of TC diagnosis, an association between distress and reduced QoL was found (38). In the process of diagnosis, the level of anxiety and depression can increase; in particular anxiety seems to be the most common issue for TC patients. Men who are single or unemployed appear most at risk of poorer psychological outcomes, which seem associated with impaired masculinity and sexual function (39).

In fact, TC includes a male organ that is highly associated with perceptions of masculinity, attractiveness and body image. In the cases of removal of a testicle, patients have to face a profound effect on his body image, that can influence also his personal values especially when there is a strong attention on the “perfect body” and a struggle for physical fitness (40).

Diagnosis of TC is a strong and upsetting event which involves not only the patient, but also the entire family system (41). Relatives, partners and close friends are exposed to important changes and different needs; in some cases, caregivers are not ready to take over this burden and can experience high level of stress (42). In couple relationships, both the patient and the partner have to deal with the possibility of treatment-related infertility and sexual difficulties in a period of life where these aspects are particularly important (43). A study showed that 41.2% of patients mentioned limited partner communication about sexual

problems (44). Albeit these difficulties, other investigations (45, 46) explained that only a minority of the couples experienced serious and long-lasting TC-induced disturbances in sexual and marital relationships; it can be explained because couples felt their relationship became more tightly bonded and stronger following the confrontation with TC.

Besides family context, TC patients seem to have less satisfactory social contacts and this can be explained by difficulties and inhibitions to talk openly about their disease (47). Rossen (48) underlined that some protective factors of good health-related QoL may include perceived attractiveness, retaining fertility, having a partner and children.

1.3.2 Testicular cancer survivors and quality of life

Therefore, a young age at diagnosis, a good excellent prognosis, physical, psychological and social well-being represent a significant indicator for follow-up and survivorship of men with TC. These aspects may be crucial after the active phase of disease, because cured patients may experience long-term negative effects and psychosocial distress according to the tumor and treatment burden (48).

TC survivors (TCSs) have an overall QoL that is not different from the level of the general population. But survivors have to live with some chronic side effects that have an influence on the QoL, like Raynaud Phenomena, peripheral neuropathy, fatigue, anxiety, cognitive impairment, sexual and fertility problems. The cancer-related fatigue is among the most frequent and distressing symptoms in TC

survivors (36, 49). Also long-term cognitive impairment can have serious implications on a TC survivor's life (50).

The typically young age at diagnosis, the existential challenge of receiving a life-threatening diagnosis and physical sequelae can interfere with psychological well-being and may give rise to increased levels of psychological distress (51). A review on psychological distress in TCSs, suggest that TCSs experience significantly more prevalent and severe anxiety than the general population (approximately 1 in 5 TC survivors) and fear of cancer recurrence is also common (nearly 1 in 3 TC survivors) (52). Most studies found depression was no more prevalent among TCSs than in the general population, although an Australian study did find higher rates of, and more severe, depression in TCSs than population norms (53). Patients affected by TC are then usually young males under 40 years, in a delicate period of life: in this central phase of life cycle men are still constructing their own personal identity and facing important life changes. The development of significant relationships, the will to start a family and long-term work goals often imply crucial worries (54-56). Moreover, in this life transition, patients can feel scared by the threat to existential continuity represented by cancer: normally, this life stage is not characterized by life-threatening illnesses or health concerns and death is a remote and unthinkable possibility (57).

1.3.3 Cancer-Specific Stress Disorder

Cancer is generally experienced as a threatening experience capable of generating symptoms of posttraumatic stress disorder (PTSD), such as hyper-activation, re-experimentation, and avoidance. Although only 5% to 15% of patients with cancer meet all criteria for a diagnosis of PTSD, up to 43% have

unpleasant intrusive thoughts, and 80% experience avoidance (58). PTSD was reported in 10.9 % of long-term TCSs at a mean of 11 years after diagnosis: 4.5 % with full PTSD and 6.4 % with Partial PTSD (59).

Moreover, TC involves sexual dimension and the traumatic experience of having this specific type of cancer may affect the sexuality of TCSs. Subjective aspects of sexual functioning such as sexual desire, sexual activity, and sexual satisfaction resulted deeply influenced (44). Thus, subjective perception of masculinity, sexual identity and body image may be subjected to changes because of the symbolic nature of the testes and cultural influences: its removal can have a severely traumatic effect and psychological consequences on the survivors. However, on the other hand, some investigations also show that the experience of cancer may also spark post-traumatic growth that includes new and positive perceptions of oneself, emotional growth, better relationships with others and greater appreciation of life (60, 61).

1.3.4. Psychological distress

Long term conditions can involve also psychological distress, in particular anxiety, depression, body image problems and aggressiveness. Survivors may experience constant preoccupation with illness, hypervigilance regarding minor symptoms, aches and pains, fears of disease recurrence or relapse (24).

Anxiety results to be a widely perceived problem in cancer survivors compared to healthy population (62). The most frequent symptoms of emotional distress in TC are tension, anxiety, restlessness, nervousness, and health worries (56). Increased levels of anxiety among TCSs are frequently associated with peripheral neuropathy, fear of recurrence, economic concerns, alcohol abuse, sexual

difficulties, younger age at diagnosis and a history of treatment for mental problems (63.). Studying the possible causes of the symptoms of anxiety that often are observed in follow-up visits, it resulted a feeling of unsafety and a paradoxical perceived loss of protection by medical providers due to decreased medical surveillance (55).

Regarding depression, the prevalence among long-term TCSs does not differ from that observed in the general population (64), but the overall scenario is somewhat unclear (65). Some investigations found a relevant frequency of self-reported depressive symptoms (56). Dahl and colleagues (63) reported that depression was prevalent in 9–11% of TC survivors up to 5 years after the end of treatment. Recently, a study reported anxiety in 6.1% of survivors and depression in 7.9% (51) with a significant association between higher anxiety, younger age at diagnosis and a shorter time since diagnosis. One frequent unmet need refers to existential concerns, that probably correlated to the young age of the TCSs and life phase of important personal achievements (growing family or career) (53).

1.3.5. Coping styles

Coping behavior in TCSs has been analyzed regarding both human relationships and work situations. Some authors (66) underlined that TCSs with more avoidance coping differed significantly from TCSs with more approach coping by showing more difficulties in paired relations and in paid work, more somatic and mental morbidity, more fatigue and poorer QoL and self-esteem. Avoidant coping is also associated with lower self-esteem, more depression and neuroticism. Also, Smith and collaborators (52) showed that passive strategies (i.e. avoidance of problems and concerns) or inadequate coping resources, such as low socio-economic status

and scarce social support, were associated with poorer outcomes and increased anxiety and fear of recurrence. Whereas a more active coping style, like actively addressing issues, and greater social support lead to better psychological outcomes for TCSs.

Regarding the employment rate, education and occupation modified the effect of cancer on the employment; in a Finnish study, it resulted a 9% lower employment rate than that of the cancer-free population (67). This difference may refer to the level of education: a higher level of education may preserve a greater chance of being employed after their cancer diagnosis compared to lower educational groups. Moreover, job type has an influence: because of physical issues due to disease and treatment, manual wis negatively associated with a return to work (68).

1.3.6. Cognitive functioning

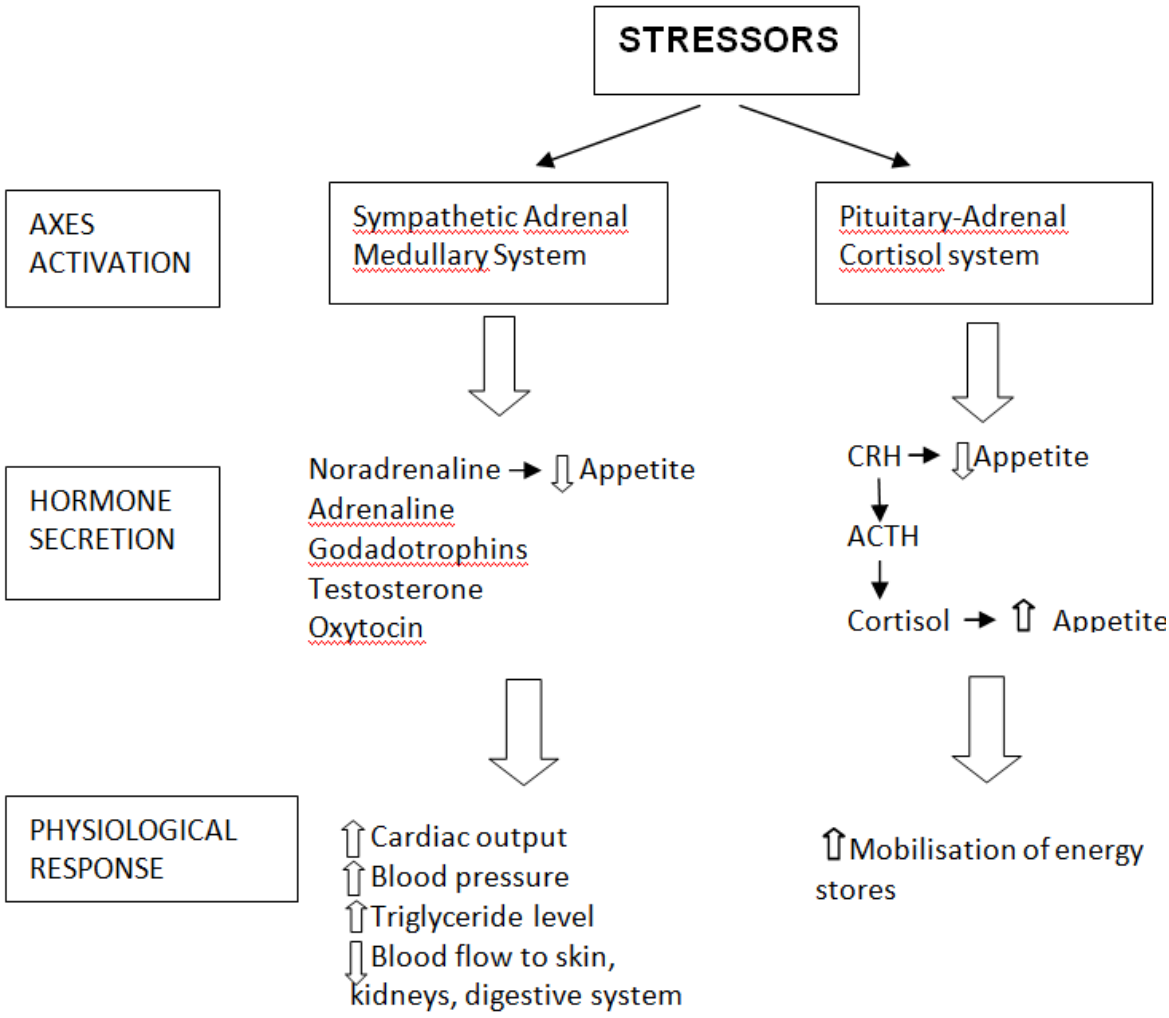
Investigations founded that cognitive functioning can be subjected to impairments after chemotherapy treatment (69, 70). Comparing psychosocial functioning, cognitive performance and brain (micro)structure following surgery and chemotherapy for TC, it resulted more memory problems in TCSs (71). Decline in learning and memory are reported particularly at later follow-up time points and in men receiving more chemotherapy (72). In a more specific way, a particular type of chemotherapy (platinum-based treatment) resulted correlated with paraesthesia, hypogonadism, hypercholesterolemia and hypertension (73), and also with memory problems and lower cognitive performance in TCSs (71). This condition is known as “chemo-brain” or “chemo-fog”, founded also in other tumor types. Cognitive difficulties in TCSs may manifest in terms of decreased

neuropsychological outcomes: in addition to verbal learning and memory (29–33% of TCSs), also visual learning and memory (14–28%), processing speed (8–24%), executive functioning (17%) and attention and working memory (4–15%) may have poor outcomes (50). Fung and colleagues (74) underlined the correlation between cognitive impairment and some psychological issues such as anxiety and depression and suggested that cognitive concerns may be managed by implementing effective coping strategies on specific stressors.

1.3.7. Stress and hormonal system

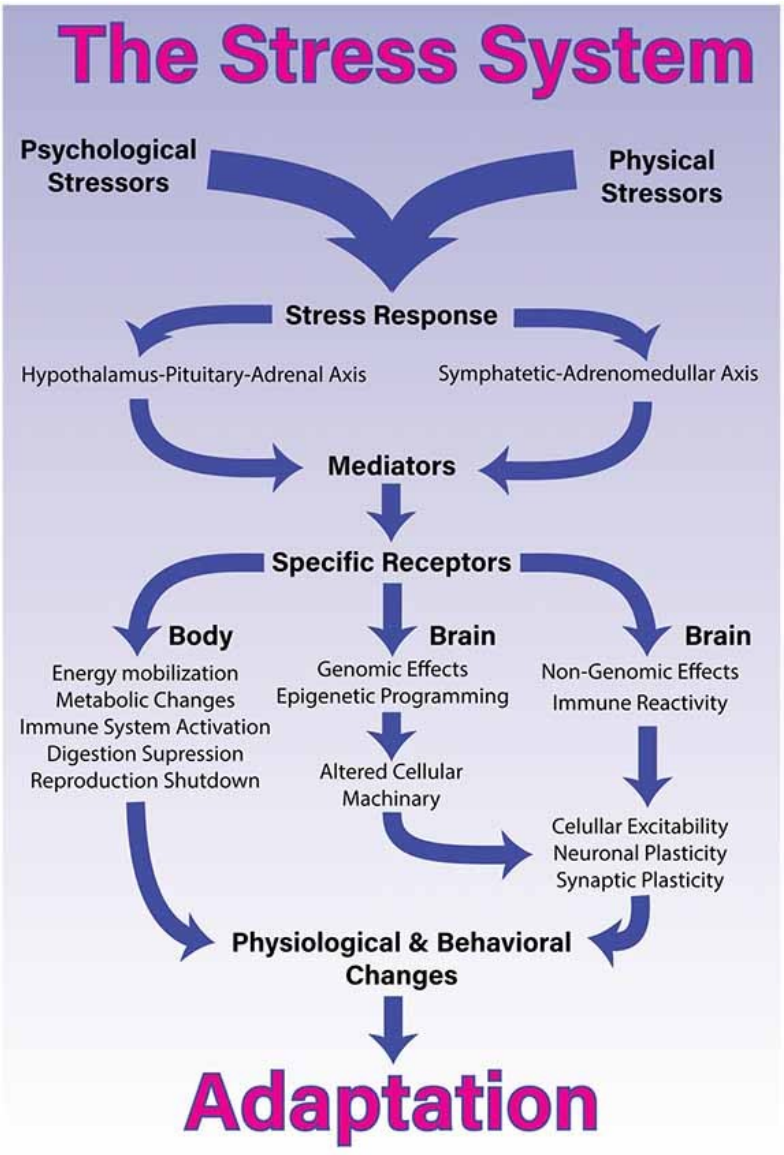
Stress is a condition characterized by a perceived discrepancy between information about a variable and criteria for eliciting adequate responses. Different stressors cause different types of activation of the sympathetic nervous, adreno-medullary hormonal and hypothalamic-pituitary-adrenocortical (75). Environmental events can trigger stress reactions in various degrees. In fact, stress can affect many aspects of physiology and levels of stress, emotional status, and coping strategies have different effects on health and disease. The stress system consists of brain elements whose main elements are the corticotropin-releasing hormone (CRH) and locus ceruleus (LC)-norepinephrine (NE)/autonomic systems, as well as their peripheral effectors, the pituitary-adrenal axis and the autonomic system, which play the role of coordinating the stress response

Figure 2 – The stress system



Activation of the stress system causes behavioral and physical changes that allow the organism to adapt.

Figure 3 – The stress system and adaptation



Stressful events and disorders such as depression may alter the balance among the central nervous, the hormonal systems and the immune system, however these effects need to be further investigated in TC survivors.

1.4 Rationale

The present study investigate hormonal senescence as a possible biological pathway linking psychological stress, cancer history and health of testicular cancer survivors.

This study would like to better address association of psychological issues and hormonal aging.

These results could contribute to improve the knowledge of this phenomenon in long-term survivors of TC. A better knowledge is useful to early recognize these problems and then better address the follow-up of these men, give them the opportunity for psychological support in selected cases.

It will be also useful to identify the group of patients who will have a high risk to develop hormonal senescence and their effects, eg hypogondism, to address therapeutic interventions.

For the health care system, it is relevant to have a contribution from this study in order to obtain a prevention of late psychological and/or metabolic complications in this young male patient population.

2. AIMS

2.1 Primary objective

The primary objective of the research was to explore the associations between psychological variables and markers of hormonal senescence in long-term survivors of TC treated or not with chemotherapy. The study aimed to assess the hormonal senescence phenotypic characteristics in TCSs and the relationships with the therapeutic pathway carried out and with psychological aspects of both distress and cognitive impairment.

2.2 Secondary objectives

Additional objectives of this study was to investigate features of hormonal senescence in long-term survivors of TC and to provide information about the prevalence of depression, anxiety, symptoms of posttraumatic stress, cognitive impairment and to explore health-related QOL in long-term survivors of TCSs.

3. MATERIALS AND METHODS

3.1 Study design

We performed a mono-center, observational (non-interventional), cross-sectional cohort study comprising three groups of TCSs based on treatment modality. TCSs were identified from the Institutional database at the IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori" di Meldola (Forlì-Cesena).

Patients participating in the trial were not be subjected to any invasive procedure that falls outside the clinical practice; in the same way, clinical variables that were collected for the study are those that are commonly collected by physician in daily clinical practice.

Study duration was planned in 18 months to enroll all patients. The subjects's participation was established to have only one face‑to‑face interview administered by psychologist and lasting approximately 1 hour. The original plans were to enrol 114 subjects evaluable. Recruitment was established to stop when approximately 114 evaluable subjects were enrolled. It was expected to approximately enrol 125 subjects to produce 114 evaluable cases (we considered nearly 10% of not evaluable cases). The study was conducted at one investigative site in IRCCS IRST Meldola (FC).

Despite these original plans, the delay in the initial approval of the formal protocol by Ethical Committee, and mainly the restrictions due the Covid pandemia strongly limited the enrollment. In particular, the stop to the access of patients to the hospital for large part of the period from March 2020 to December 2021.

The study was designed and conducted in accordance with the Declaration of Helsinki and approved by the bioethical local committee (see appendix B).

3.2. Study population

Male patients cured from TC. The study included testicular survivors followed up at the IRST IRCCS Ambulatorio “Liberi dal cancro”. All survivors who were disease-free at least 2 years from the completion of their last treatment were included.

TCSs: After 2 years of follow-up 70 to 99% of patients are considered cured according to the clinical stage and treatment received, so that they will not experience disease recurrence. In addition, after 2-3 years from treatment they could develop first signs or symptoms of late-effects of treatments.

The initial plans considered 114 evaluable patients from these cohorts:

- patients followed by surveillance only after orchiectomy,

- patients treated with 1 or 2 cycles of adjuvant chemotherapy after orchiectomy (19 with carboplatin and 19 with PEB, the combined treatment of cisplatin, etoposide, bleomycin),

- patients with advanced disease treated with at least 3-4 cycles of chemotherapy PEB (19 with PEB and 19 with PEB + other regimens including high-dose chemotherapy).

3.3 Inclusion/exclusion Criteria

Criteria for inclusion in the study were as follows: male subjects between 2 to 10 years after TC diagnosis, who have completed treatment and are regarded as complete responders. Furthermore patients must have met all of the following inclusion criteria to be eligible for participation in this study.

- Aged ≥ 18 years.

- Italian-speaking

- Participant willing and able to give informed consent.

Patients with any of the following were not eligible for participation in the study:

- Age < 18 years

- Inability to answer questionnaires (i.e due to mental impairment).

- Another malignancy.

3.4 Measures / Materials

Three lots of materials were produced for use in this study:

<u>Information sheet and informed consent form</u>

The information sheet and the informed consent form provided information in connection with the purpose and aim of the study, reasons for the patient being asked to participate, what participation would entail, confidentiality surrounding the information gathered, reassurance regarding the voluntary nature of the research and the lack of impact on their medical care, what they were required to do if they

wished to participate, a contact number for the principal researcher to enquire further about the project. All the participants provided written informed consent and General Authorisation to Process Personal Data. The generation of a personal security code warranted the data anonymity.

Case Report Form (CRF)

The CRF (Appendix C) was designed to collect socio-demographic and clinical data (paper form/electronic form), including elements of medical and psychological condition, both current and past.

Assessment battery

The study selected specific measures due to their relevance to cancer survivorship based on the literature and also the reported reliability and validity of the measure for the sample population. These measures covered a range of areas including QoL, cancer-specific stress, psychological distress (depression, anxiety, hostility, etc), coping styles (cognitive and behavioral attitudes towards cancer), fatigue embitterment, and cognitive impairment.

The questionnaires used in the study (Appendix D) are as follows:

Impact of Event Scale – Revised (IES-R) The psychological impact of TC was measured using the Italian version of the Impact of Event Scale-Revised (IES-R), a 22-item questionnaire assessing subjective distress caused by traumatic events (76, 77). Respondents were asked to indicate how much they were distressed or bothered during the past seven days by this specific stressful life event. The measure contains three subscales representative of the major symptom clusters of PTSD, according to DSM-IV of post-traumatic stress: intrusion, avoidance, and hyper-arousal (78).The intrusion subscale consists of 8 items (1, 2, 3, 6, 9, 14, 16,

20) and evaluates intrusive thoughts, nightmares, intrusive feelings, and imagery related to the event; the avoidance subscale consists of 8 items (5, 7, 8, 11, 12, 13, 17, 22), and evaluates numbing of responsiveness, effortful avoidance of feelings, situations, and ideas that serve as reminders of the traumatic event; the hyper-arousal subscale consists of 6 items subscale (4, 10, 15, 18, 19, 21) and evaluates anger, irritability, hypervigilance, heightened startle, physiological symptoms of hyper-arousal when thinking of the event. In the context of this study, participants were asked to relate to the TC (the single stressful life event). Each item was rated on a 5-point scale ranging from 0 ("not at all") to 4 ("extremely"). Hence, the IES-R provided a total score (ranging from 0 to 88) composed of three subscores. The psychological impact according to the total IES-R score was categorized as normal (0–23), mild (24–32), moderate (33–36), and severe (>37) (76). This instrument is not intended to be used to diagnose PTSD but rather to assess subjective distress and perhaps to identify individuals for a preliminary diagnosis of PTSD.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) The EORTCQLQ-C30, the most used tool for assessing QoL in cancer-specific patients (79), consists of 30 self-reported questions assessing different aspects of patient functioning, global health status, and cancer-related symptoms. More specifically, it is composed of five multi-item functional scales (role, physical, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), individual items concerning common symptoms in cancer patients (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties), and two global health and QoLitems. In each topic, four to seven Likert-type alternative responses are available. All of the multi-item scales and single-item measures range in a score

from 0 to 100, where a high score represents a higher response level. Thus, a high score for a functional scale implicates a healthy level of functioning, while a high score for a symptom scale represents a worse level of symptoms (80). The validated Italian version of the EORTC QLQ-C30 (81) was used in this study.

The European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire Testicular Cancer 26 (EORTC QLQ-TC26) questionnaire. It is a specific and supplementary module for the EORTC QLQ-C30 for the comprehensive assessment of TC-specific HRQOL in clinical trials and routine clinical practice (82). This instrument includes 26 items organised into 7 multi-item scales and 6 single items addressing: treatment side effects (8 items), treatment satisfaction (2 items), future perspective (2 items), work/education problems (single item), physical limitations (single item), infertility (single item), family problems (single item), sexual activity (2 items), sexual enjoyment (2 items), sexual problems (2 items), communication (2 items), body image problems (single item) and testicular implant satisfaction (single item). Answers are selected based upon patient-reported severity or intensity of TC-specific symptoms on a four-point Likert scale from ‘not at all’ to ‘very much’, with a reference frame of 1 week. The Italian version of the questionnaire was administered to the subjects enrolled in this study (83).

Brief Symptom Inventory-18 (BSI-18) The BSI-18 is a self-report symptom checklist measure consisting of 18 items taken from the original 53-item BSI (84). This instrument assesses current psychological distress with three subscales (each comprising six items): anxiety, depression and somatisation, as well as a global severity index (GSI) score. Study participants were asked to respond in

relation to how they had felt over the past 7 days and each item was rated on a 5-point Likert scale from 0 (not at all) to 4 (extremely) (85).

Raw scores are converted to standardized *T* scores which are characterized by a distribution with a mean of 50 and standard deviation (*SD*) of 10.

The test that will be administered is a revised version that adds 7 items concerning anger and irritability. According to the procedure of the BSI-18 manual (85) and following common practice for the BSI-18 in oncology (86, 87) for identifying respondents who have clinically significant symptom elevations is similar to the rule used with the BSI, with a respondent considered positive on the BSI-18 if the GSI T-score or any 2 subscale T-scores are 63 or greater.

Post Traumatic Embitterment Disorder (PTED) Scale is a self-rating questionnaire comprising 19 items and can be used to identify reactive embitterment, an emotional reaction to a negative life event associated with a feeling of being a "loser", of being victimized, of anger, or helplessness and hopelessness, and especially of phantasies of aggression or revenge (88). The scale starts with the statement "During the past months of this year there was a severe and negative life event" which is followed by single items like "that hurt my feelings and caused considerable embitterment," "that triggers feelings of satisfaction when I think that the responsible party has to live through a similar situation," or "that caused me to withdraw from friends and social activities."

Higher scores are indicative of PTED. Ratings are made on Likert scale from (0) not at all true toe (4) extremely true. The mean score of the PTED scale is used as a measure for the degree of embitterment. The PTED scale measures dimensional embitterment, that is, it can be used independently of 1 specific event, but as a screening of the general embitterment load that the person perceived due to

critical life events in recent months. The PTED scale can be used for embitterment as a dimensional phenomenon, but not as a tool for categorical diagnostic of an embitterment disorder 87). A mean total score of ⩾1.6 (total score above 30.4) suggests prolonged embitterment with strong clinical relevance. A mean total score of ⩾2.5 (total score above 47.5) indicates embitterment of clinically significant intensity (89).

Mini-Mental Adjustment to Cancer scale (Mini-MAC), in its validated version, was used to assess the patients' cognitive and behavioral attitudes towards cancer. The Mini-MAC is a 29-item self-report measure devised to evaluate the patient's coping styles, over the last 2 weeks, through five subscales: fighting spirit, hopelessness, anxious preoccupation, fatalism and avoidance (90, 91).

As already done in other studies (92), only two subscales were used in this study, specifically hopelessness-helplessness (H) and anxious preoccupation (AP), being key maladaptive coping strategies (90). Mini-MAC/H and Mini-MAC/AP both consist of 8 items (1–4 Likert scale: 1 = it definitely does not apply to me; 4 = it definitely applies to me) measuring the tendency to adopt a pessimistic and despairing attitude about the illness, and the tendency to feel worried and preoccupied about cancer, respectively.

Functional Assessment of Chronic Illness Therapy - fatigue (FACIT-fatigue) scale is an instrument designed to assess fatigue/ tiredness and its impact on daily activities and functioning in a number of chronic diseases (93). The scale consists of 13 items referring to the previous seven days. It is formatted for self-administration on one page and uses a five-point Likert-type scale ranging from "not at all" (scored 4) to "very much" (scored 0) with two items needing a reverse score. The final (raw) score ranges from 0 to 52, with higher scores representing

lower levels of fatigue, and lower scores more fatigue. For this purpose, Scores for negatively worded items are reversed, such that higher scores are better (i.e. less fatigue).

Screen for Cognitive Impairment in Psychiatry (SCIP), a simple and easy-to-administer instrument designed with the intention to assess cognitive impairment. The subtests within the SCIP quantify immediate and delayed verbal list learning, working memory, verbal fluency and psychomotor speed (94). The validated Italian version of the SCIP was administered (95). A total score for the SCIP is derived from the sum of fve domains scores: a score of 70 or greater has been found to correspond to normal cognitive functioning (96)

Montreal Cognitive Assessment (MoCA) is a brief cognitive screening instrument (thirty items) that measures the cognitive areas of executive functioning (eg, working memory, attentional and inhibitory control, problem solving, planning—cognitive control of behavior), attention and concentration (eg, ability to pay selective attention to something while ignoring other stimuli), language (eg, crystalized memory or memory of previously learned material), delayed recall (eg, short-term memory of newly learned material), abstraction (eg, isolating common features among dissimilar objects), and orientation (eg, knowledge of time, place, and context) (94). Scores were corrected for educational efects by giving one extra point to those with≤12 years of education (97). A cutoff score of 26 differentiate mild cognitive impairment (MCI) or dementia from normal (98).

3.5 Study procedures

3.5.1 Recruitment

During periodical meetings, the clinic's oncologists and nurses identified the potentially suitable patients who meet the inclusion criteria from medical records. The screening procedure aimed at confirming that inclusion criteria were met (3.3.1), and that none of the exclusion criteria were present (3.3.2). The nurses called potential patients by telephone to inform them of the study and asked them for their willingness to participate. The interested parties were notified of an appointment for oncologic examination, blood tests, and an interview with the psychologist. Once in the clinic, during the scheduled visit, the oncologist informed eligible patients about the possibility to participate in the study, provided them in a brief description and assessed their interest in participation. Patients who wished to participate were asked to sign a consent form.

The participants were asked to provided a blood sample and to complete socio-demographic, psychological and health questionnaires during a structured interview with the psychologist. There were no additional treatments, or laboratory collections required beyond those occurring within the course of normal care.

3.5.2 Clinical data collection

The following information was collected from all consenting patients after registration. The clinical data were extracted from the medical record or, in cases where the medical record data are not available, via patient self-report. The data should be noted on the CRF:

- medical history (e.g. date of tumor diagnosis, side, type of intervention, histology,

- concomitant medications

- laboratory exams

- any other parameter that have to be observed for the study

3.5.3 Assessment interview

The assessment interview was carried out in clinic, after the patient had seen the doctor or at a later date, on the date agreed by telephone. The interviews were took place in a private room and only the psychologist researcher and participant were present.

The first part of the interview was dedicated to the collection of the following information and data, then reported in the CRF:

- Socio-demographic data that include age, sex, level of education and employment status and living arrangements, etc. These data may be extracted from the medical file or obtained from the patient directly.

- Psychological data such as psychopathological episodes, stressful life events, psychotherapy or other psychological interventions carried out, etc.

The second part of the interview was dedicated to the administration of the psychological and quality of life questionnaires included in the assessment battery.

3.5.4 Clinical and laboratory data

At the time of the clinical visit, patients were undergone clinical evaluation with comorbidity assessment.

In addition, a blood sample was performed to investigate:

- medullary, liver and renal functions,

- tumor markers (Alphafetoprotein, betaHCG and LDH)

- evaluation of serum testosterone, LH (normal value <8,6), FSH (normal<12,3)

- other hormones as beta-estradiol, calcitonin, PTH

- assessment of metabolic disorders with glicemia, tryglicerids, cholesterol, and Vitamin D.

Peripheral blood mononuclear cells were isolated and collected for further analyses in the future.

3.6 Statistical considerations

3.6.1 Study design and objectives

This was an observational study in which the primary aims was to assess the psychological aspects of both distress and cognitive impairment in TCSs and to correlate with the therapeutic pathway carried out and with hormonal senescence phenotypic characteristics. Secondary objectives were to investigate features of

hormonal senescence in long-term survivors of TCSs and to provide information about depression, anxiety, symptoms of posttraumatic stress, cognitive impairment and health-related QOL in study population.

3.6.2 Population size and enrolment at the study protocol definition

In a prior our work (99), we have shown that post-traumatic stress syndrome (PTSD) characterized nearly 20% of TC survivors. In the original study design, we hypothized that PTSD was associated to 40% of patients in group 3 vs 10% in group 2 e 10% in group 1. As consequence, were necessary 38 patients per group (power 80%, type-I error 5%). 114 subjects evaluable, including 3 cohorts of subjects:

- group 1: 38 patients followed by surveillance only after orchiectomy,

- group 2: 38 patients treated with 1 or 2 cycles of adjuvant chemotherapy after orchiectomy (19 with carboplatin and 19 with PEB),

- group 3: 38 patients with advanced disease treated with at least 3-4 cycles of chemotherapy PEB (19 with PEB and 19 with PEB + other regimens including high-dose chemotherapy).

Enrollment period estimated: 15-18 months. Data analysis: 3 months

Total duration of the study: nearly 18 months.

IMPORTANT: However, due to COVID-19 pandemia, this recruitment was not respected and only a part of these patients were evaluable as reported in the Results.

3.6.3 Data analysis

The questionnaires were coded with an abbreviation that allows anonymity and were collected and inserted in a database for the subsequent statistical analysis.

The psychological and health questionnaires were represented by the calculation of partial and total scores and summarized by means and standard deviations, as reported in the scoring procedures of each questionnaire. The categorical socio-demographic and clinical variables were described by absolute and percentage frequencies while continuous variables were described by median, minimum and maximum values and interquartile range (IQR).

Multiple imputation method was applied in order to handle missing data (100). Differences in clinical outcomes between study groups were assessed with the Chi-square test for categorical variables and the Student's t-test for continuous variables.

All tests were two-sided at a significance level of 0.05. No interim analysis was planned and no multiplicity test correction was performed.

All statistical analyses were performed using SAS Statistical Software version 9.4 (SAS Institute, Cary, NC, USA).

4. RESULTS

COVID-19 pandemics in 2020-2022 strongly limited the accrual for this study. So overall 53 evaluable patients with stage I TC were recruited.

4.1 Patients- Standard Demographics

The subject group included 53 men, whose average age at the time of assessment was 44 years, range 26 to 65 years. Twenty-two received orchiectomy only, while 31 received orchiectomy and adjuvant chemotherapy consisting of 1 cycle of carboplatin AUC 7 in case of seminoma (n=31, 58.5%), and 1 cycle of PEB for nonseminoma (n=22, 41.5%). Other descriptive statistics that identify the subjects are included in Table 2A and 2B. No significant differences were reported between the group treated with surgery only and the group treated with adjuvant chemotherapy in terms of median age at diagnosis and at assessment, marital status, paternity, work and smoking habitude (Table 2A).

Table 1B describes the tumor characteristics at diagnosis and at relapse. All patients were stage I at diagnosis, nevertheless three patients experienced a tumor relapse during the follow-up, but at least three years before the assessment for the present study. As waited, adjuvant chemotherapy was given to more cases with pathological stage 2 (pT2) than pT1. Testosterone level was decreased in one case only, while an increase in LH and FSH was reported in 10 (19.2%) and 18 (34.6%) of cases, respectively (Table 2B).

Table 2A – Characteristics of patients (n=53)

	Overall (n=53)	Surgery only (n=22)	Adjuvant CT (n=31)	
	N (%)	N (%)	N (%)	p-value
Age (years) at date of assessment: median value (range, IQR)	44 (26-65, 37-48)	44 (26-65, 38-53)	43 (29-64, 36-47)	0.488
Age (years) at date of diagnosis: median value (range, IQR)	34 (19-57, 30-40)	34 (22-55, 28-43)	34 (19-57, 30-40)	0.823
Schooling years: median value (range, IQR)	18 (8-25, 13-18)	18 (8-25, 13-24)	17 (9-24, 13-18)	0.590
Marital status				
Unmarried	16 (30.2)	7 (31.8)	9 (29.0)	
Married	33 (62.3)	13 (59.1)	20 (64.5)	
Divorced	4 (7.5)	2 (9.1)	2 (6.5)	
Widower	0	0	0	0.899
Paternal status				
No	15 (28.3)	8 (36.4)	7 (22.6)	
Yes	38 (71.7)	14 (63.6)	24 (77.4)	0.272
median value	2	2	2	
(range, IQR)	(1-4, 1-2)	(1-4, 1-2)	(1-3, 1-2)	1.000
When had children				
Before diagnosis of TC	20 (55.6)	7 (50.0)	13 (59.1)	
After diagnosis of TC	14 (38.9)	7 (50.0)	7 (31.8)	
Before and after TC diagnosis	2 (5.5)	0	2 (9.1)	0.345
Unknown	2	0	2	
Profession				
Employed	49 (92.4)	20 (91.0)	29 (93.6)	
Unemployed	2 (3.8)	1 (4.5)	1 (3.2)	
Retired	2 (3.8)	1 (4.5)	1 (3.2)	
Student	0	0	0	
Unknown	0	0	0	0.938
Smoker				
No	40 (75.5)	17 (77.3)	23 (74.2)	
Yes	9 (17.0)	4 (18.2)	5 (16.1)	
Past smoker	4 (7.5)	1 (4.5)	3 (9.7)	0.780

Table 2B – Characteristics of patients (n=53)

	Overall (n=53)	Surgery only (n=22)	Adjuvant CT (n=31)	
	N (%)	**N (%)**	**N (%)**	**p-value**
Site of primary tumor				
Right testis	29 (54.7)	12 (54.5)	17 (54.8)	
Left testis	23 (43.4)	9 (40.9)	14 (45.2)	
Bilateral disease	1 (1.8)	1 (4.6)	0	0.481
T stage				
1	41 (77.4)	20 (90.9)	21 (67.7)	
2	12 (22.6)	2 (9.1)	10 (32.3)	
¾	0	0	0	0.093
Histology				
Seminoma	31 (58.5)	13 (59.1)	18 (58.1)	
Nonseminoma	22 (41.5)	9 (40.9)	13 (41.9)	
Site of relapse				0.067
Retroperitoneal nodes	2 (66.7)	2 (66.7)	0	
Lung and lymphnodes	1 (33.3)	1 (33.3)	0	
Treatment for relapse				-
Surgery	0	0	0	
Radiotherapy	0	0	0	
Chemoterapy	3 (100)	3 (100)	0	
Testosterone level				-
Normal	50 (96.2)	22 (100)	28 (93.3)	
Increased	1 (1.9)	0	1 (3.3)	
Decreased	1 (1.9)	0	1 (3.3)	
Unknown	1	0	1	
FSH level				-
Normal	34 (65.4)	13 (59.1)	21 (70.0)	
Increased	18 (34.6)	9 (40.9)	9 (30.0)	
Decreased	0	0	0	
Unknown	1	0	1	0.414
LH level				
Normal	42 (80.8)	18 (81.8)	24 (80.0)	
Increased	10 (19.2)	4 (18.2)	6 (20.0)	
Decreased	0	0	0	
Unknown	1	0	1	0.869

No major differences were observed in terms of comorbidities and medical therapy at the time of assessment, showing that the use of adjuvant chemotherapy was not associated with increased long-term side-effects and related treatments. Interestingly, there was no difference even in metabolic syndrome (diabetes, hypercholesterolemia, hypertension), which could be associated with prior chemotherapy (Table 3).

Table 3 – Comorbidities and pharmacological therapies.

	Overall (n=53)	**Surgery only (n=22)**	**Adjuvant CT (n=31)**	
	N (%)	**N (%)**	**N (%)**	**p-value**
Non-oncological diseases				
No	36 (67.9)	13 (59.1)	23 (74.2)	
Yes	17 (32.1)	9 (40.9)	8 (25.8)	0.246
Panic attacks	1	1	0	
Diabetes	2	2	0	
Ventricular extrasystole	1	0	1	
Favism	1	1	0	
Hypercolestherolemia	6	3	3	
Hypertension	4	1	3	
Allergic rhinitis	1	0	1	
Autoimmune thyroiditis	1	1	0	
Therapies				
No	44 (84.6)	17 (77.3)	27 (90.0)	
Yes	8 (15.4)	5 (22.7)	3 (10.0)	0.260
Almarytm	1	0	1	
Atenolole, ramipril	1	0	1	
Insuline	1	1	0	
Lisinopril	1	0	1	
Amlodipine, losartan	1	1	0	
Peridopline, simvastatine	1	1	0	
Pregabalin, venflaxine	1	1	0	
Simvastatine, bisoprolol, cardioaspirin, glicazide, pantoprazole	1	1	0	

Nearly one third (34%) of TCSs presented a history of psychopathological episodes in the anamnesis, apparently with a higher percentage in men treated with orchiectomy only (45%) vs adjuvant CT (25.8%), even if not statistically significant (p=0.137) (Table 4).

Table 4 Psychopathological history

	Overall (n=53)	Surgery only (n=22)	Adjuvant CT (n=31)	
	N (%)	N (%)	N (%)	p-value
Psychopathological episodes				
No	35 (66.0)	12 (54.5)	23 (74.2)	
Yes	18 (34.0)	10 (45.5)	8 (25.8)	0.137
Anxiety	8	4	4	
Depression	2	1	1	
Obsessive-compulsive symptoms	1	1	0	
Sleep disturbances	5	2	3	
Anxiety and depression	1	1	0	
Anxiety and sleep disturbances	1	0	1	
Obsessive-compulsive symptoms and sleep disturbances	1	1	0	
Alcohol or other drug dependence	0	0	0	
Temporal data in reference to cancer				
Before cancer	5 (27.8)	3 (30.0)	2 (25.0)	
During cancer	6 (33.2)	2 (20.0)	4 (50.0)	
After cancer	5 (27.8)	3 (30.0)	2 (25.0)	
Before, during and after cancer	1 (5.6)	1 (10.0)	0	
Before and after cancer	1 (5.6)	1 (10.0)	0	0.578
Duration of psychopathology				
<6 months	5 (27.8)	2 (20.0)	3 (37.5)	
6-12 months	3 (16.7)	2 (20.0)	1 (12.5)	
>12 months	10 (55.5)	6 (60.0)	4 (50.0)	0.698
Drug treatment				
No	16 (88.9)	9 (90.0)	7 (87.5)	
Yes	2 (11.1)	1 (10.0)	1 (12.5)	0.867
Psychological treatments				
No	49 (92.5)	19 (86.4)	30 (96.8)	
Yes	4 (7.5)	3 (13.6)	1 (3.2)	0.157

4.2 Questionnaire scores

Analysis of the questionnaires used indicated that a high percentage of TCSs presented deficit in cognitive tests. The psychological impact of TC, measured using the IES-R scale, revealed a sample mean score of 8.91 (SD, 8.95) that is a minimal impact (score: 0-23). Among IES-R, a marginal statistically significant difference was observed among the two cohorts treated with surgery only vs adjuvant chemotherapy following surgery (p =0.047), whereas no difference among cohorts was observed for Mini-MAC, PTED, MoCA, SCIP and FACIT-Fatigue (Table 5A).

Table 5A – Assessment of questionnaire scores according to the cohorts

	Overall (n=53)	**Surgery only (n=22)**	**Adjuvant CT (n=31)**	
	Mean value (SD)	**Mean value (SD)**	**Mean value (SD)**	**T-test p-value**
IES-R				
Avoidance sub scale	3.68 (3.59)	2.86 (2.83)	4.28 (3.99)	0.170
Intrusion sub scale	3.33 (3.55)	2.22 (2.56)	4.14 (3.97)	0.058
Hyperarousal sub scale	1.90 (3.45)	0.90 (1.30)	2.62 (4.29)	0.083
Total IES-R score	8.91 (8.95)	5.98 (5.05)	11.03 (10.52)	0.047
Mini-MAC				
Helpless_hopeless (H)	10.50 (3.48)	10.14 (3.21)	10.76 (3.70)	0.543
Anxious preoccupation	10.82 (4.07)	10.43 (3.74)	11.10 (4.35)	0.569
PTED (on total score)	14.22 (14.34)	15.14 (14.07)	13.55 (14.75)	0.703
PTED (on mean total score)	0.75 (0.75)	0.80 (0.74)	0.71 (0.78)	0.703
MoCA (corrected+1point if ≤12 y education)	26.10 (2.44)	25.76 (2.26)	26.36 (2.59)	0.404
SCIP				
Verbal learning	21.02 (3.41)	20.76 (3.82)	21.21 (3.12)	0.650
Working memory	20.29 (3.35)	20.10 (3.51)	20.43 (3.29)	0.735
Verbal fluency	16.00 (3.92)	15.14 (3.77)	16.64 (3.96)	0.187
Delayed recall	6.27 (2.16)	5.90 (2.68)	6.54 (1.67)	0.316
Psychomotor speed	9.82 (3.05)	9.86 (3.30)	9.79 (2.92)	0.936
Total SCIP score	73.39 (10.02)	71.76 (9.59)	74.61 (10.33)	0.330
FACIT-Fatigue	6.24 (5.93)	5.67 (4.53)	6.66 (6.82)	0.566

We evaluated both the EORTC QLQ-C30 and the new EORTC QLQ-TC26, a test dedicated to TCSs recently produced by EORTC. The EORTC QLQ-TC26 is a valid condition-specific questionnaire, supplementing the EORTC QLQ-C30, for the assessment of QoL in TCS, which explored symptom and functional scales, including topic specific for TC as sexual activity and enjoyment, and testicular implant satisfaction.

Most of the hypotheses on correlations between the QLQ-TC26 and the QLQ-C30 scales seems to be confirmed by our analysis. However, some differences should be considered, eg for “Family Problems” the QLQ-C30 scale measures actual impairment of social relations, whereas the QLQ-TC26 assesses patients’ concerns.

Table 5B shows mean values of EORTC QLQ-C30 and EORTC QLQ-TC26 scores for all scales and items. Most subjects reported no symptoms and a healthy level of functioning.

The results of the BSI-25 are shown in the same table, according to the two cohorts treated with surgery alone vs adjuvant chemotherapy after surgery. BSI-25 showed a small level of somatization, depression, anxiety and anger/irritability: subjects have not clinically significant symptom elevations.

Overall, the results of these questionnaires scores didn’t show statistically significant differences among different items (Table 5B).

Table 5B – Assessment of questionnaire score according to the cohorts

	Overall (n=53)	Surgery only (n=22)	Adjuvant CT (n=31)	
	Mean value (SD)	Mean value (SD)	Mean value (SD)	T-test p-value
EORTC QLQ-C30				
Global health status	79.67 (17.83)	84.92 (9.73)	75.86 (21.29)	0.076
Functional scales:				
Physical	97.07 (6.05)	97.14 (5.40)	97.01 (6.57)	0.940
Role	97.00 (8.71)	98.41 (5.01)	95.98 (10.59)	0.334
Emotional	81.33 (17.46)	81.75 (13.34)	81.03 (20.16)	0.889
Cognitive	93.33 (12.60)	93.65 (13.41)	93.10 (12.21)	0.881
Social	93.67 (14.63)	98.41 (7.27)	90.23 (17.55)	0.050
Symptom scales:				
Fatigue	15.33 (18.90)	14.81 (19.67)	15.71 (18.67)	0.871
Nausea and vomiting	1.00 (4.00)	0.79 (3.64)	1.15 (4.30)	0.760
Pain	3.33 (8.91)	2.38 (7.97)	4.02 (9.61)	0.526
Dyspnoea	4.67 (13.49)	3.17 (10.03)	5.75 (15.61)	0.511
Insomnia	15.33 (24.48)	12.70 (19.65)	17.24 (27.63)	0.523
Appetite loss	2.00 (8.00)	3.18 (10.03)	1.15 (6.19)	0.382
Constipation	6.00 (12.94)	6.35 (13.41)	5.75 (12.81)	0.873
Diarrhoea	6.00 (14.58)	6.35 (17.06)	5.75 (12.81)	0.887
Financial difficulties	2.67 (9.13)	1.59 (7.27)	3.45 (10.33)	0.483
EORTC QLQ-TC26*				
Functional scales:				
Treatment satisfaction	26.33 (28.19)	28.57 (30.80)	24.71 (26.58)	0.638
Future perspective	72.67 (22.78)	74.60 (18.72)	71.26 (25.55)	0.614
Communication	32.67 (20.19)	34.13 (13.41)	31.61 (24.13)	0.668
Sexual activity	32.00 (22.04)	27.78 (17.74)	35.06 (24.54)	0.253
Sexual enjoyment	54.96 (15.11)	53.33 (13.89)	56.17 (16.11)	0.530
Testicular implant satisfaction	21.99 (23.34)	23.33 (21.90)	20.99 (24.72)	0.737
Symptom scales:				
Treatment side effects	7.67 (8.88)	6.94 (7.38)	8.19 (9.93)	0.630
Job problems	8.67 (20.82)	3.17 (8.53)	12.64 (25.84)	0.113
Family problems	27.33 (29.88)	28.57 (28.45)	26.44 (31.34)	0.806
Infertility	35.33 (35.89)	39.69 (35.93)	32.18 (36.17)	0.472
Body image problems	20.00 (22.34)	25.40 (20.83)	16.10 (22.92)	0.148
Sexual problems	40.07 (16.55)	40.83 (17.50)	39.51 (16.11)	0.789
BSI-25				
Somatization	23.61 (8.29)	21.74 (7.64)	25.70 (8.97)	0.108
Depression	25.60 (8.05)	25.40 (7.64)	25.88 (8.44)	0.839
Anxiety	16.98 (9.72)	16.40 (7.63)	17.52 (11.77)	0.702
Anger and irritabilità	23.02 (10.79)	21.75 (6.55)	24.29 (15.10)	0.473

4.3 Hormonal levels and association with scores

Serum levels of LH e FSH and testosterone were assessed in all 53 cases, but laboratory results were not available for one case, so 52 patients are evaluable for the analysis of the results.

Testosterone levels resulted in the normal value in all cases but one, so only one case of hypogonadism was reported. Another case with a really small increase of the testosterone level over the upper normal level was considered clinically not significant. So we cannot analyze results according to hypogonadism.

LH resulted increased in 10 (19.2%) of 52 cases, FSH resulted increased in 18 (34.6%) of 52 cases. No difference were reported in LH and FSH levels according to the two cohorts (Table 6).

Table 6 – Assessment of LH and FSH according to the cohorts

	Overall (n=52)	**Surgery only (n=22)**	**Adjuvant CT (n=30)**	
	N (%)	**N (%)**	**N (%)**	**Chi-Square p-value**
LH				
Normal	42 (80.8)	18 (81.8)	24 (80.0)	
Increased	10 (19.2)	4 (18.2)	6 (20.0)	0.869
FSH				
Normal	34 (65.4)	13 (59.1)	21 (70.0)	
Increased	18 (34.6)	9 (40.9)	9 (30.0)	0.414
LH or FSH				
Normal	32 (61.5)	11 (50.0)	21 (70.0)	
Increased	20 (38.5)	11 (50.0)	9 (30.0)	0.143
LH and FSH				
Normal	44 (84.6)	20 (90.9)	24 (80.0)	
Increased	8 (15.4)	2 (9.1)	6 (20.0)	0.442

NB another case didn't have information on LH/FSH levels and was considered not evaluable for this table

We than evaluated in these 52 cases the association among hormonal levels and questionnaire scores. In the appendix, four supplementary tables describe these results.

Supplementary Table 1 shows results on questionnaire scores according to the increase or normal levels of FSH and LH, respectively. No difference was observed for Mini-MAC, PTED, MoCA, SCIP and FACIT-Fatigue (Supplementary Table 1A) and for EORTC QLQ-C30, the EORTC QLQ-TC26 and the BSI-25, except for increased family problems in cases with high FSH levels ($p = 0.02$) (Supplementary Table 1B).

Supplementary Table 2 shows results on questionnaire scores according to the normal levels of both FSH and LH versus increased FSH or LH or versus increased FSH and LH. In any case, no difference was observed for Mini-MAC, PTED, MoCA, SCIP and FACIT-Fatigue (Supplementary Table 2A) and for EORTC QLQ-C30, EORTC QLQ-TC26 and BSI-25 (Supplementary Table 2B).

Supplementary Table 3 shows results on questionnaire scores (IES-R, PTED, MoCA and SCIP) according to the increase or normal levels of FSH and LH, respectively; however, no difference was observed according to these cohorts for IES-R, PTED, MoCA and SCIP (Supplementary Table 3).

Supplementary Table 4 shows results on questionnaire scores (IES-R, PTED, MoCA and SCIP) according to the normal levels of both FSH and LH versus increased FSH or LH or versus increased FSH and LH; however, again no difference was observed according to these cohorts for IES-R, PTED, MoCA and SCIP (Supplementary Table 4).

5. DISCUSSION

The National Cancer Institute defines cancer survivors as anyone who has received a diagnosis of cancer, inclusive of those on treatment, through to the end of life (101). However, the high curability of TC makes it an ideal disease to study a young patient population with long life-expectancy and with a large population of long-term disease-free survivors, named long-term TC survivors. It is expected that TC will have a significant impact on the patient's physical, psychological and social well-being also because lived in a period of life, characterized by major life changes and specific developmental tasks (102).

Somatic issues reported by TC survivors regard fertility problems, fatigue, chronic peripheral neuropathy, hearing loss, Raynaud-like phenomenon, tinnitus, cardiovascular toxicity, decreased pulmonary function, hypertension, and hyperthyroidism and a higher risk of germ cell tumors development (64, 103, 104).

Furthermore, other studies showed that psychosocial problems caused by TC diagnosis and treatment have prolonged effects in survivors; anxiety, fertility distress, fear of recurrence are the most common(23, 54, 105).

Both somatic and psychological issues negatively influence overall life satisfaction and impact social contacts and family relationships (44).

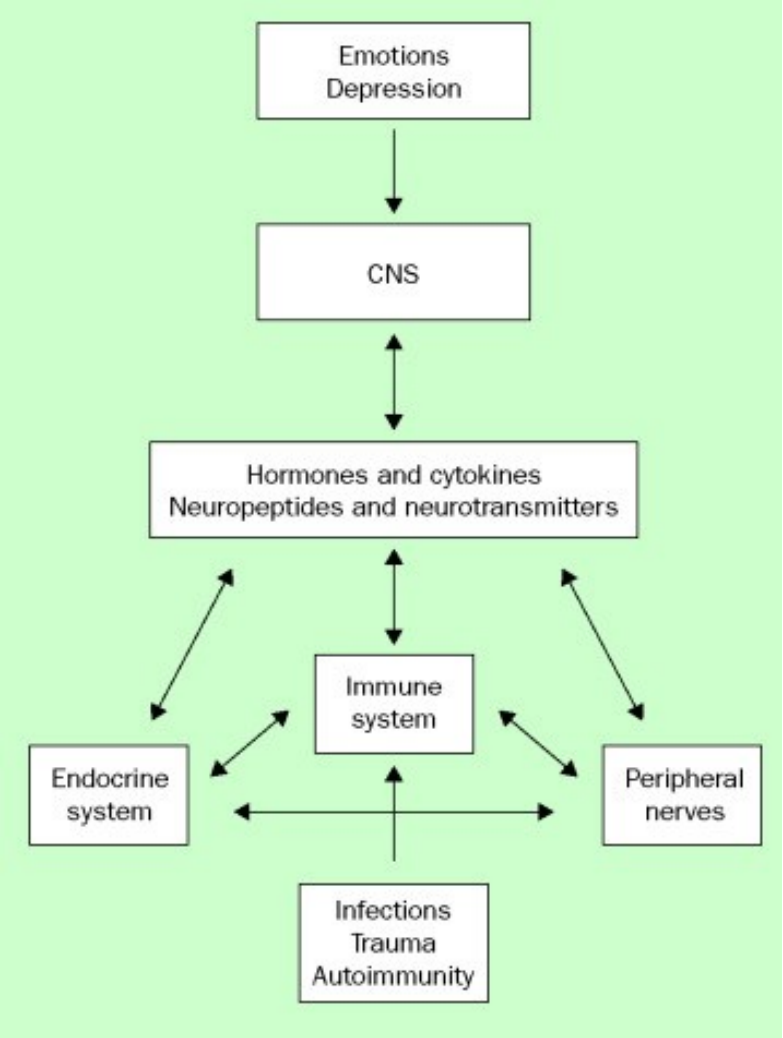
Considering the QoL of TCSs over time, unemployment status, having a chronic disease and negative life events seem to be important risk factors for an impaired functioning (57). Moreover, TC involves young men in a central phase of life cycle when their own personal and social identity is still being constructed; it often goes on interfering with the normal course of daily life months after healing (106). Physical and psychological consequences of treatment may force survivors to

change life plans made before cancer and to review short- and long-term goals (57).

Current stress research aims at understanding the mechanisms through which the stress-response is adaptive or becomes maladaptive and underlines a growing association of stress system and dysfunction, characterized by hormonal alterations (107). A study evaluated the effect of psychological stress on male fertility hormones and seminal quality in male partner of infertile couples. Measuring level of psychological stress, serum total testosterone, LH and FSH, it resulted that 27% had higher anxiety and depression score, lower serum total testosterone and higher serum FSH and LH compared to those having normal level of anxiety and depression (108). This can be explained by the fact that psychological stress primarily lowers serum total testosterone level with secondary rise in serum LH and FSH levels altering seminal quality. Another finding (showed a negative association between self-reported stress and semen quality underling that psychological stress can be a modifiable factor (109). Regarding cancer survivors, it resulted important the level of quality of life, especially in men who face prostate cancer. Song and collaborators (110) evaluated couples' QOL and showed that social support and cancer-related dyadic communication correlated negatively with couples' uncertainty, general symptoms, and patients' prostate cancer-related sexual and hormonal symptoms. Fewer problems in hormonal functions decrease level of stress, provide reassurance to couples and preserve their feelings of normalcy. Also in TC survivors, stressful life events and negative emotions such as anxiety and depression alter the interaction between the central nervous, the hormonal systems and the immune system (111). Moreover, cancer diagnosis and therapy may elicit both biological and psychological stress that, if prolonged over time, can trigger premature cellular aging and deterioration of

immune system in TC survivors, causing a major vulnerability to infections and autoimmune diseases (112). Figure 3 illustrates the interaction emotions/depression with hormonal and immune systems.

Figure 4 Emotions and hormonal and immune systems.



In our analysis, a high percentage of long-term TCSs presented deficit in cognitive tests independently by the use of adjuvant chemotherapy. Gritz et al (113) assessed testicular cancer survivors (seminoma and nonseminoma) who had received mixed treatments an average of 45 months earlier. Of these survivors,

14%-16% self-reported inability to concentrate, think clearly, and complete tasks 6 months following treatment, which was much more frequent than either before diagnosis or within the past month. Pedersen et al (114) reported results from a mixed sample that received either surgery alone (n=36) or surgery and chemotherapy (n=36) for advanced disease, chemotherapy and nonchemotherapy patients displayed similar performances on cognitive tests and no difference was reported in the proportion of cognitively impaired patients in the chemotherapy group (5.6%) compared to the nonchemotherapy group (8.3%) (p= 0.64). Schagen et al (115) reported cognitive dysfunction in 5.5% of testicular cancer survivors who were tested a median of 3 years after surgery and received no other adjuvant therapy. Cognitive impairment was not associated with fatigue or anxiety/depression. In another study, cognitive impairment was assessed in men with newly diagnosed TC were recruited after surgery and prior to adjuvant chemotherapy. Nearly 46% of patients had cognitive impairment, which was significantly higher than expected considering healthy population norms (116). The prevalence of cognitive impairment in men with newly diagnosed NSGCT was unexpectedly high before the receipt of adjuvant chemotherapy. The authors suggested to do efforts to track cognitive function over time and to develop effective interventions if warranted. Amidi et al (117) assessed sixty-six TC patients were compared with 25 healthy men on neuropsychological tests and a measure of cognitive complaints. Prevalence of CI among TC patients was 58%, significantly exceeding the frequency in healthy men ($p < 0.01$). Cognitive dysfunction experienced by individuals with cancer represents an important survivorship issue because of its potential to affect occupational, scholastic, and social activities, however, according to our results, it seems not conditioned by adjuvant chemotherapy (118).

In the present study, 52 patients were evaluable for the analysis of the results of serum levels of LH e FSH and testosterone, but only one case of hypogonadism with low testosterone levels was reported, whereas LH resulted increased in 10 (19.2%) of 52 cases and FSH resulted increased in 18 (34.6%) of 52 cases. We than evaluated in these 52 cases the association among hormonal levels and questionnaire scores. The four supplementary tables describe these results with no difference observed, except for an anecdotic increase in family problems in cases with high FSH levels ($p = 0.02$) (Supplementary Table 1B). Therefore no impact of LH or FSH on questionnaire scores can be concluded.

Our study is limited by its design lacking of a basal evaluation at the time of surgery. In addition a cohort of control with health men is also lacking. The study didn't provide data on other important laboratory examinations as those related to immune-surveillance. Another limitation of the analysis is that the two cohorts included patients treated initially with surgery only and those treated with surgery and adjuvant chemotherapy. However, three cases experienced relapse in the cohort with surgery only, whereas none in the cohort with adjuvant treatment, as waited for the prognosis of this patients and the impact of adjuvant chemotherapy. However the three relapsed patients received chemotherapy consisting of PEB for three cycle which could have an impact on questionnaire scores, even if we decided to consider the cohort based only on the first choice, that is adjuvant chemotherapy yes or not, to assess the impact of this choice in the long-term of TCSs. Limitations of the database included a selection bias dependent on the accuracy of data coding.

6. CONCLUSIONS

The results of our study confirmed the modest psychological impact of stage I TC, and even the use of adjuvant chemotherapy in these patients did not seem to hamper the QoL and did not induce psychological disorders in long-term TC survivors. No significant hypogonadism effect was reported and alterations in LH and/or FSH do not substantially correlate with psychological findings. Adjuvant chemotherapy in TC is confirmed to be safe and without significant consequences in the long-term including the psychological sphere.

Finally, our findings do not support in general in stage I TC survivors the use of an extended follow-up for psychological issues. Psychosocial support and compensatory interventions may be necessary in a subset of patients with especially disabling symptoms. Longitudinal studies that determine the impact of cognitive deficits, as well as predictive biomarkers, will be crucial. Larger trials with longer follow-up are needed for possible identification of subgroups of long-term TC survivors at higher risk of premature hormonal aging.

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Appendix A - Supplementary Tables (1-4)

Supplementary Table 1A –Questionaire assessment and association with LH and FSH levels

	LH normal (n=42)	LH increased (n=10)		FSH normal (n=34)	FSH increased (n=18)	
	Mean value (SD)	**Mean value (SD)**	**T-test p-value**	**Mean value (SD)**	**Mean value (SD)**	**T-test p-value**
IES-R						
Avoidance subscale	3.45 (3.73)	4.55 (3.24)	0.382	3.39 (3.98)	4.39 (2.87)	0.311
Intrusion sub scale	2.91 (2.80)	4.73 (5.46)	0.140	2.78 (2.77)	4.24 (4.62)	0.174
Hyperarousal subscale	1.55 (2.55)	3.18 (5.65)	0.175	1.55 (2.64)	2.56 (4.62)	0.335
Total IES-R score	7.91 (7.48)	12.45 (12.94)	0.144	7.62 (7.63)	11.18 (10.93)	0.187
Mini-MAC						
Helpless_hopeless (H)	10.26 (3.10)	11.45 (4.74)	0.327	10.06 (3.10)	11.33 (4.10)	0.226
Anxious preoccupation (AP)	10.61 (3.69)	11.36 (5.46)	0.595	10.23 (3.77)	11.72 (4.57)	0.222
PTED (assessed on total score)	13.61 (14.95)	16.91 (12.95)	0.510	13.45 (15.37)	15.89 (13.02)	0.575
PTED (assessed on mean total score)	0.72 (0.79)	0.89 (0.68)	0.510	0.71 (0.81)	0.84 (0.69)	0.575
MoCA corrected (+1 point if ≤12 y of education)	26.08 (2.35)	26.18 (2.86)	0.904	26.06 (2.41)	26.17 (2.57)	0.889
SCIP						
Verbal learning	20.97 (3.55)	21.18 (2.99)	0.860	21.35 (3.03)	20.44 (4.00)	0.373
Working memory	20.24 (3.42)	20.45 (3.27)	0.852	20.65 (3.32)	19.67 (3.41)	0.330
Verbal fluency	15.87 (3.78)	16.45 (4.52)	0.667	15.48 (3.92)	16.89 (3.85)	0.230
Delayed recall	6.21 (2.27)	6.45 (1.81)	0.745	6.61 (1.61)	5.67 (2.83)	0.141
Psychomotor speed	10.03 (3.04)	9.09 (3.14)	0.376	10.52 (3.24)	8.61 (2.30)	0.034
Total SCIP score	73.32 (10.28)	73.64 (9.52)	0.927	74.61 (9.85)	71.28 (10.22)	0.266
FACIT-Fatigue	6.29 (6.13)	6.36 (5.68)	0.971	6.29 (6.47)	6.33 (5.19)	0.981

Supplementary Table 1B – Questionaire assessment and association with LH and FSH levels

	Normal LH level (n=42)	Increased LH level (n=10)		Normal FSH level (n=34)	Increased FSH level (n=18)	
	Mean value (SD)	**Mean value (SD)**	**T-test p-value**	**Mean value (SD)**	**Mean value (SD)**	**T-test p-value**
EORTC QLQ-C30						
Global health status	80.04 (16.27)	76.52 (22.92)	0.567	80.38 (14.99)	77.31 (22.10)	0.566
Functional scales: Physical	96.14 (6.69)	100 (0)	0.064	96.56 (7.07)	97.78 (3.96)	0.506
Role	96.05 (8.93)	100 (0)	0.193	95.70 (10.51)	99.07 (3.93)	0.198
Emotional	81.58 (16.34)	79.55 (22.16)	0.739	81.99 (17.49)	79.63 (18.13)	0.655
Cognitive	92.98 (12.63)	93.94 (13.48)	0.828	93.55 (12.68)	92.59 (13.06)	0.802
Social	93.42 (15.76)	93.94 (11.24)	0.920	94.09 (15.84)	92.59 (13.06)	0.737
Symptom scales: Fatigue	14.33 (17.31)	20.20 (24.25)	0.371	15.05 (20.40)	16.67 (16.72)	0.777
Nausea and vomiting	1.32 (4.55)	0 (0)	0.346	1.08 (4.16)	0.93 (3.93)	0.902
Pain	3.95 (9.83)	1.52 (5.03)	0.435	4.30 (10.51)	1.85 (5.39)	0.363
Dyspnoea	4.39 (13.80)	6.06 (13.48)	0.723	5.38 (15.15)	3.70 (10.78)	0.683
Insomnia	13.16 (19.82)	24.24 (36.79)	0.192	12.90 (20.51)	20.37 (30.55)	0.311
Appetite loss	1.75 (7.54)	3.03 (10.05)	0.649	2.15 (8.32)	1.85 (7.86)	0.902
Constipation	7.02 (13.77)	3.03 (10.05)	0.377	6.45 (13.39)	5.56 (12.78)	0.819
Diarrhoea	7.02 (15.80)	3.03 (10.05)	0.434	6.45 (15.91)	5.56 (12.78)	0.840
Financial difficulties	2.63 (9.11)	3.03 (10.05)	0.901	3.23 (10.02)	1.85 (7.86)	0.620
EORTC QLQ-TC26*						
Functional scales: Treatment satisfaction	22.37 (27.48)	39.39 (29.13)	0.080	23.66 (29.43)	30.56 (26.97)	0.419
Future perspective	74.12 (17.63)	69.70 (36.38)	0.576	75.81 (19.17)	68.52 (27.94)	0.285
Communication	31.58 (18.90)	37.88 (24.82)	0.369	29.57 (18.61)	38.89 (22.14)	0.122
Sexual activity	30.26 (19.32)	34.85 (29.30)	0.542	31.18 (20.52)	31.48 (24.18)	0.963
Sexual enjoyment	52.70 (14.44)	64.81 (15.47)	0.031	53.76 (15.34)	57.78 (15.26)	0.409
Testicular implant satisfaction	20.72 (21.30)	29.63 (30.93)	0.310	21.51 (22.02)	24.44 (26.63)	0.694
Symptom scales: Treatment side effects	8.00 (8.35)	7.20 (11.04)	0.794	7.26 (7.83)	8.80 (10.68)	0.565
Job problems	8.77 (22.17)	9.09 (17.26)	0.965	5.38 (18.95)	14.81 (23.49)	0.131
Family problems	27.19 (26.68)	30.30 (40.70)	0.765	20.43 (23.85)	40.74 (35.34)	0.020
Infertility	35.96 (34.99)	30.30 (40.70)	0.651	32.26 (32.75)	38.89 (41.62)	0.540
Body image problems	19.30 (18.39)	24.24 (33.63)	0.524	16.13 (20.85)	27.78 (23.57)	0.079
Sexual problems	41.89 (16.49)	31.48 (15.47)	0.093	41.94 (16.59)	35.56 (16.51)	0.227

	Normal LH level (n=42)	Increased LH level (n=10)		Normal FSH level (n=34)	Increased FSH level (n=18)	
	Mean value (SD)	**Mean value (SD)**	**T-test p-value**	**Mean value (SD)**	**Mean value (SD)**	**T-test p-value**
BSI-25						
Somatization	23.81 (7.69)	25.11 (11.83)	0.665	23.58 (7.33)	25.01 (10.76)	0.582
Depression	23.32 (8.72)	22.76 (8.69)	0.852	23.10 (9.40)	23.35 (7.35)	0.923
Anxiety	18.41 (8.22)	19.43 (10.30)	0.732	18.81 (9.00)	18.33 (8.17)	0.852
Anger and irritability	24.74 (7.32)	27.26 (9.62)	0.355	24.97 (7.95)	25.89 (7.90)	0.697

Supplementary Table 2A – Questionaire assessment and association with increased LH or FSH levels and with increased LH and FSH levels

	Normal LH and FSH levels (n=32)	Increased LH or FSH levels (n=20)		Normal LH and FSH levels (n=44)	Increased LH and FSH levels (n=8)	
	Mean value (SD)	Mean value (SD)	T-test p-value	Mean value (SD)	Mean value (SD)	T-test p-value
IES-R						
Avoidance subscale	3.38 (4.10)	4.15 (2.83)	0.470	3.37 (3.66)	5.11 (3.30)	0.197
Intrusion subscale	2.77 (2.75)	4.11 (4.49)	0.200	2.91 (2.81)	5.11 (5.84)	0.097
Hyperarousal subscale	1.52 (2.68)	2.50 (4.42)	0.337	1.57 (2.53)	3.44 (6.21)	0.148
Total IES-R score	7.66 (7.73)	10.76 (10.60)	0.242	7.86 (7.42)	13.67 (13.84)	0.082
Mini-MAC						
Helpless_hopeless (H)	9.93 (3.12)	11.40 (3.94)	0.152	10.35 (3.08)	11.33 (5.20)	0.454
Anxious preoccupation (AP)	10.28 (3.88)	11.50 (4.41)	0.310	10.55 (3.62)	11.78 (5.97)	0.423
PTED (ossesse on total score)	12.90 (15.63)	16.45 (12.68)	0.404	14.00 (14.76)	15.89 (13.75)	0.727
PTED (assessed on mean total score)	0.68 (0.82)	0.87 (0.67)	0.404	0.74 (0.78)	0.84 (0.72)	0.727
MoCA corrected (+1 point if ≤12 years of education)	26.03 (2.46)	26.20 (2.48)	0.818	26.10 (2.32)	26.11 (3.10)	0.990
SCIP						
Verbal learning	21.34 (20.18)	20.55 (18.73)	0.428	21.00 (3.52)	21.11 (3.10)	0.931
Working memory	20.55 (3.38)	19.90 (3.37)	0.510	20.32 (3.38)	20.11 (3.41)	0.865
Verbal fluency	15.69 (3.79)	16.45 (4.15)	0.510	15.70 (3.89)	17.33 (3.97)	0.263
Delayed recall	6.62 (1.66)	5.75 (2.69)	0.167	6.22 (2.21)	6.44 (2.01)	0.786
Psychomotor speed	10.48 (3.26)	8.85 (2.50)	0.065	10.07 (3.04)	8.67 (3.00)	0.215
Total SCIP score	74.69 (9.72)	71.50 (10.38)	0.278	73.32 (10.34)	73.67 (8.96)	0.927
FACIT-Fatigue	6.10 (6.52)	6.60 (5.24)	0.778	6.42 (6.11)	5.78 (5.65)	0.772

Supplementary Table 2B – Questionaire assessment and association with increased LH or FSH levels and with increased LH and FSH levels

	Normal LH and FSH levels (n=32)	Increased LH or FSH levels (n=20)		Normal LH and FSH levels (n=44)	increased LH and FSH levels (n=8)	
	Mean value (SD)	**Mean value (SD)**	**T-test p-value**	**Mean value (SD)**	**Mean value (SD)**	**T-test p-value**
EORTC QLQ-C30						
Global health status	80.75 (15.29)	77.08 (21.09)	0.484	79.79 (16.00)	76.85 (25.27)	0.659
Functional scales: Physical	96.32 (7.26)	98.00 (3.81)	0.349	96.33 (6.57)	100 (0)	0.103
Role	95.40 (10.82)	99.17 (3.73)	0.142	96.25 (9.61)	100 (0)	0.252
Emotional	81.61 (17.73)	80.42 (17.79)	0.818	81.87 (16.22)	77.78 (23.57)	0.533
Cognitive	93.10 (13.00)	93.33 (12.57)	0.951	93.33 (12.40)	92.59 (14.70)	0.876
Social	93.68 (16.31)	93.33 (12.57)	0.937	93.75 (15.42)	92.59 (12.11)	0.834
Symptom scales: Fatigue	13.79 (18.46)	18.33 (19.84)	0.416	15.28 (18.94)	17.28 (20.12)	0.778
Nausea and vomiting	1.15 (4.30)	0.83 (3.73)	0.791	1.25 (4.45)	0 (0)	0.407
Pain	4.60 (10.82)	1.67 (5.13)	0.266	3.75 (9.61)	1.85 (5.56)	0.572
Dyspnoea	5.75 (15.61)	3.33 (10.26)	0.547	4.17 (13.48)	7.41 (14.70)	0.524
Insomnia	11.49 (18.42)	21.67 (31.11)	0.157	14.17 (21.20)	22.22 (37.27)	0.381
Appetite loss	2.30 (8.60)	1.67 (7.45)	0.791	1.67 (7.36)	3.70 (11.11)	0.500
Constipation	6.90 (13.74)	5.00 (12.21)	0.622	6.67 (13.50)	3.70 (11.11)	0.544
Diarrhoea	6.90 (16.38)	5.00 (12.21)	0.662	6.67 (15.47)	3.70 (11.11)	0.590
Financial difficulties	3.45 (10.33)	1.67 (7.45)	0.512	2.50 (8.89)	3.70 (11.11)	0.727
EORTC QLQ-TC26*						
Functional scales: Treatment satisfaction	22.99 (30.35)	30.83 (25.52)	0.348	22.92 (26.87)	40.74 (32.39)	0.090
Future perspective	74.71 (19.22)	70.83 (27.51)	0.563	75.00 (17.70)	64.81 (38.59)	0.229
Communication	29.31 (19.24)	38.33 (21.01)	0.127	31.67 (18.41)	38.89 (27.64)	0.339
Sexual activity	30.46 (20.93)	32.50 (23.24)	0.750	30.83 (19.08)	33.33 (32.27)	0.758
Sexual enjoyment	52.87 (15.47)	58.82 (14.57)	0.205	53.42 (14.40)	64.29 (17.82)	0.083
Testicular implant satisfaction	20.69 (22.56)	25.49 (25.08)	0.507	21.37 (20.92)	28.57 (35.63)	0.459
Symptom scales: Treatment side effects	7.76 (7.85)	7.92 (10.46)	0.952	7.60 (8.33)	8.80 (11.68)	0.721
Job problems	5.75 (19.56)	13.33 (22.69)	0.217	8.33 (21.68)	11.11 (18.63)	0.724
Family problems	21.84 (24.03)	36.67 (35.71)	0.088	25.83 (26.67)	37.04 (42.31)	0.315
Infertility	33.33 (33.33)	36.67 (40.32)	0.754	35.00 (34.55)	33.33 (44.10)	0.902
Body image problems	14.94 (19.08)	28.33 (24.84)	0.038	20.00 (19.68)	22.22 (33.33)	0.791
Sexual problems	42.53 (17.01)	35.29 (15.46)	0.157	41.45 (16.16)	30.95 (17.82)	0.126

	Normal LH and FSH levels (n=32)	Increased LH or FSH levels (n=20)		Normal LH and FSH levels (n=44)	increased LH and FSH levels (n=8)	
	Mean value (SD)	**Mean value (SD)**	**T-test p-value**	**Mean value (SD)**	**Mean value (SD)**	**T-test p-value**
BSI-25						
Somatization	23.89 (7.44)	24.41 (10.39)	0.837	23.57 (7.59)	26.46 (12.71)	0.371
Depression	23.28 (9.71)	23.06 (7.01)	0.933	23.17 (8.52)	23.26 (9.64)	0.979
Anxiety	18.89 (9.06)	18.27 (8.16)	0.806	18.37 (8.21)	19.82 (10.76)	0.654
Anger and irritabilità	24.88 (7.83)	25.93 (8.06)	0.649	24.82 (7.45)	27.47 (9.68)	0.367

Supplementary Table 3 – Questionaire assessment and association with LH and FSH levels

	Normal LH level (n=42)	Increased LH level (n=10)		Normal FSH level (n=34)	Increased FSH level (n=18)	
	N (%)	N (%)	Chi-Square p-value	N (%)	N (%)	Chi-Square p-value
IES-R						
Normal (0-23)	41 (97.6)	9 (90.0)		33 (97.1)	17 (94.4)	
Mild (24-32)	1 (2.4)	0		1 (2.9)	0	
Moderate (33-36)	0	0		0	0	
Severe (≥37)	0	1 (10.0)	0.106	0	1 (5.6)	0.297
Normal (0-23)	41 (97.6)	9 (90.0)		33 (97.1)	17 (94.4)	
Mild/Moderate/Severe (>23)	1 (2.4)	1 (10.0)	0.351	1 (2.9)	1 (5.6)	0.641
No Post-traumatic stress disorder(<33)	42 (100)	9 (90.0)		34 (100)	17 (94.4)	
Post-traumatic stress disorder (≥33)	0	1 (10.0)	0.192	0	1 (5.6)	0.346
PTED						
No clinically significant intensity of reactive embitterment (mean total score <2.5)	41 (97.6)	10 (100)		33 (97.1)	18 (100)	
Clinically significant intensity of reactive embitterment (mean total score ≥2.5)	1 (2.4)	0	0.622	1 (2.9)	0	0.462
No clinically significant intensity of reactive embitterment (mean total score <1.6)	35 (83.3)	9 (90.0)		29 (85.3)	15 (83.3)	
Clinically significant intensity of reactive embitterment (mean total score ≥1.6)	7 (16.7)	1 (10.0)	0.599	5 (14.7)	3 (16.7)	0.852
MoCA corrected						
Normal (≥26)	22 (52.4)	6 (60.0)		17 (50.0)	11 (61.1)	
Mild cognitive impairment/dementia (<26)	20 (47.6)	4 (40.0)	0.736	17 (50.0)	7 (38.9)	0.444
SCIP						
Normal cognitive functioning (≥70)	27 (64.3)	6 (60.0)		25 (73.5)	8 (44.4)	
Cognitive impairment (<70)	15 (35.7)	4 (40.0)	0.800	9 (26.5)	10 (55.6)	0.038

Supplementary Table 4 – Questionaire assessment and association with increased LH or FSH levels and with increased LH and FSH levels

	Normal LH and FSH levels (n=32)	Increased LH or FSH levels (n=20)		Normal LH and FSH levels (n=44)	increased LH and FSH levels (n=8)	
	N (%)	N (%)	Chi-Square p-value	N (%)	N (%)	Chi-Square p-value
IES-R						
Normal (0-23)	31 (96.9)	19 (95.0)		43 (97.7)	7 (87.5)	
Mild (24-32)	1 (3.1)	0		1 (2.3)	0	
Moderate (33-36)	0	0		0	0	
Severe (≥37)	0	1 (5.0)	0.328	0	1 (12.5)	0.056
Normal (0-23)	31 (96.9)	19 (95.0)		43 (97.7)	7 (87.5)	
Mild/Moderate/Severe (>23)	1 (3.1)	1 (5.0)	0.732	1 (2.3)	1 (12.5)	0.287
No post-traumatic stress disorder(<33)	32 (100)	19 (95.0)		44 (100)	7 (87.5)	
Post-traumatic stress disorder (≥33)	0	1 (5.0)	0.385	0	1 (12.5)	0.154
PTED						
No clinically significant intensity of reactive embitterment (mean total score <2.5)	31 (96.9)	20 (100)		43 (97.7)	8 (100)	
Clinically significant intensity of reactive embitterment (mean total score ≥2.5)	1 (3.1)	0	0.425	1 (2.3)	0	0.667
No clinically significant intensity of reactive embitterment (mean total score <1.6)	27 (84.4)	17 (85.0)		37 (84.1)	7 (87.5)	
Clinically significant intensity of reactive embitterment (mean total score ≥1.6)	5 (15.6)	3 (15.0)	0.952	7 (15.9)	1 (12.5)	0.806
MoCA corrected						
Normal (≥26)	16 (50.0)	12 (60.0)		23 (52.3)	5 (62.5)	
Mild cognitive impairment or dementia (<26)	16 (50.0)	8 (40.0)	0.482	21 (47.7)	3 (37.5)	0.711
SCIP						
Normal cognitive functioning (≥70)	24 (75.0)	9 (45.0)		28 (63.6)	5 (62.5)	
Cognitive impairment (<70)	8 (25.0)	11 (55.0)	0.029	16 (36.4)	3 (37.5)	0.951

APPENDIX B - ETHICAL ASPECTS

Local regulations/Declaration of Helsinki

The responsible Investigator will ensure that this study is conducted in compliance with the protocol, following the instructions and procedures described, adhering to the principles of Good Clinical Practice ICH Tripartite Guideline (December 2000) and in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964 and further amendments) or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

Independent Ethical Committee

The protocol, informed consent and any accompanying material provided to the patient will be submitted by the investigator to an Independent Ethical Committee for review. Approval from the committee must be obtained before starting the study. Any modifications made to the protocol, informed consent or material provided to the patient after receipt of the Ethics Committee approval must also be submitted by the investigator to the Committee in accordance with local procedures and regulatory requirements. The Independent Ethical Committee approval report must contain details of the trial (title, protocol number and version), documents evaluated (protocol, informed consent, accompanying material) and the date of the approval.

Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from each subject prior to entering the trial or, where relevant, prior to evaluating the subject's suitability for the study.

The informed consent document used by the Investigator for obtaining the subject's informed consent must be reviewed and approved by the Ethical Committee.

A copy of the patient's signed written consent will be kept by the center in the proper section of the Investigator Site File.

Patient data protection

The Informed Consent Form will incorporate wording that complies with relevant data protection and privacy legislation. In agreement with this wording, patients will authorize the collection, use and disclosure of their study data and samples by the Investigator and by those persons who need that information for the purposes of the study.

The Informed Consent Form will explain that the study data will be stored in a computer data base, maintaining confidentiality in accordance with national data legislation.

The Informed Consent Form will explain that the samples obtained by patients will be anonymized and stored in accordance with national data legislation. The Informed Consent Form will also explain that for data verification purposes, authorized representatives of Sponsor/Promoter, a regulatory authority, an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including patients' medical history.

Autorizzazione n. 9/2014

“Autorizzazione generale al trattamento dei dati personali effettuato per scopi di ricerca scientifica (11/12/2014)”

http://www.garanteprivacy.it/web/guest/home/docweb/-/docweb-display/export/3632879

Determination AIFA 20 March 2008

“Guideline for the classification and conduction of observational study”

https://www.agenziafarmaco.gov.it/ricclin/sites/default/files/files_wysiwyg/files/Normativa/DETERMINAZ_AIFA_20_Marzo_2008_ST_OSS.pdf

APPENDIX C - Case Report Form (CRF)

Codice soggetto _____ **Data valutazione** _____/_____/_____

Cognome: _____ **Nome:** _____

Data di nascita _____/_____/_____

Razza: ☐ Caucasica ☐ Altra _____

Tel_____

Scolarità (in anni) _____

Stato civile: ☐ celibe ☐ coniugato/convivente ☐ separato/divorziato ☐ vedovo ☐ non noto

Professione: ☐ occupato ☐ pensionato ☐ divorziato ☐ studente ☐ disoccupato ☐ non noto ☐ altro _____

Figli: ☐ si ☐ no se si, quanti? _____ ☐ prima della malattia ☐ dopo la malattia

Episodi psicopatologici ☐ SI ☐ NO

☐ disturbi d'ansia (ansia acuta tipo panico, fobie)

☐ depressione

☐ forme ossessive (ad es. bisogno di lavarsi ripetutamente le mani, ecc.)

☐ disturbi del sonno (non causati da dolore o altri problemi fisici)

☐ dipendenza da alcol/altre sostanze

☐ altro (specificare_____)

Episodio psicopatologico _____

☐ prima della malattia (specificare quanto tempo prima_____)

☐ durante la malattia

☐ dopo la malattia

Durata ☐ meno di 6 mesi ☐ superiore a 6 mesi meno di 1 anno ☐ più di un anno

Trattamento farmacologico effettuato ☐ SI ☐ NO

quale _____

Psicoterapia o interventi psicologici ☐ SI ☐ NO

Episodio psicopatologico _____

☐ prima della malattia (specificare quanto tempo prima_____)

☐ durante la malattia

☐ dopo la malattia

Durata ☐ meno di 6 mesi ☐ superiore a 6 mesi meno di 1 anno ☐ più di un anno

Trattamento farmacologico effettuato ☐ SI ☐ NO

quale _____

Psicoterapia o interventi psicologici ☐ SI ☐ NO

Episodio psicopatologico _____

☐ prima della malattia (specificare quanto tempo prima_____)

☐ durante la malattia

☐ dopo la malattia

Durata ☐ meno di 6 mesi ☐ superiore a 6 mesi meno di 1 anno ☐ più di un anno

Trattamento farmacologico effettuato ☐ SI ☐ NO

quale _____

Psicoterapia o interventi psicologici ☐ SI ☐ NO

Trattamento farmacologico in corso ☐ SI ☐ NO

quale_____

Psicoterapia o interventi psicologici in corso ☐ SI ☐ NO

Principali eventi stressanti precedenti ☐ SI ☐ NO

Evento 1: _____

☐ prima della malattia (specificare quanto tempo prima_____)

☐ durante la malattia

☐ dopo la malattia

Evento 2: _____

☐ prima della malattia (specificare quanto tempo prima_____)

☐ durante la malattia

☐ dopo la malattia

Evento 3: _____

☐ prima della malattia (specificare quanto tempo prima_____)

☐ durante la malattia

☐ dopo la malattia

Evento 4: _____

☐ prima della malattia (specificare quanto tempo prima_____)

☐ durante la malattia

☐ dopo la malattia

Evento 5: _____

☐ prima della malattia (specificare quanto tempo prima_____)

☐ durante la malattia

☐ dopo la malattia

Livello di consapevolezza della malattia

☐ Completamente consapevole della malattia (ad es. nomina la malattia in termini di tumore maligno, cancro, ecc.)

☐ Parzialmente consapevole (ad es. pensa e sospetta di avere avuto un tumore maligno ma non è certo completamente)

☐ Scarsamente consapevole (ad es. pensa di avere o avere avuto un tumore che avrebbe potuto diventare maligno ma non lo era ancora)

☐ Non consapevole (ad es. è sicuro di avere avuto una cisti o un tumore benigno senza rischi di malignità, pensa di fare solo controlli)

STORIA CLINICA

Età alla diagnosi _____ **Sede Tumore primitivo**: _____

Stadio: ☐ TNM classification: T(1-4):__ ; N(0-3):__ ; M(0-1):__
☐ Altra classificazione: _____

Sedi delle eventuali metastasi

Osso ☐ Fegato ☐ Parzialmente ☐ Polmone ☐ Cervello☐

Linfonodi torace/collo ☐ Linfonodi addominali☐ Tessuti molli ☐

Altro _____

Trattamento effettuato

☐ Intervento chirurgico _____e data: _____/_____/_____

☐ Radioterapia ☐ Chemioterapia ☐ Ormonoterapia

☐ Altro:_____

Data ultima terapia con cui acquisito remissione: _____/_____/_____
NB: riportare data intervento se intervento chirurgico radicale e altre terapie adiuvanti, se invece acquisito remissione completa dopo chemio +/- radio, riportare data ultima TAC dopo tali terapie

Recidiva: ☐ SI ☐ NO Data: _____/_____/_____

Sede della eventuale recidiva: _____

Terapia per recidiva:

Chemioterapia: ☐ SI ☐ NO Radioterapia: ☐ SI ☐ NO

Intervento chirurgico: ☐ SI ☐ NO Terapia ormonale: ☐ SI ☐ NO

Altro: _____

Data ultima terapia x recidiva con cui acquisito remissione: _____/_____/_____
NB: riportare data intervento se intervento chirurgico radicale e altre terapie adiuvanti, se invece acquisito remissione completa dopo chemio +/- radio, riportare data ultima TAC dopo tali terapie

Terapie effettuate

☐ solo sorveglianza dopo orchiectomia

☐ 1 o 2 cicli CT adiuvante dopo orchiectomia carboplatino o PEB

☐ malattia avanzata trattata con almeno 3-4 cicli di CT PEB (solo PEB o PEB+ CT alte dosi)

SITUAZIONE CLINICA ATTUALE

Patologie non oncologiche in atto (es cardiologiche, ipertensione, diabete, ecc.):

1) _____

Data/e di esordio_____/_____/_____

Se in trattamento farmacologico, quale/i_____

_____

2) _____

Data/e di esordio_____/_____/_____

Se in trattamento farmacologico, quale/i_____

_____

3) _____

Data/e di esordio_____/_____/_____

Se in trattamento farmacologico, quale/i_____

_____

Terapie mediche in corso ☐ SI ☐ NO

Quale/i_____

_____

_____

_____

_____

_____

APPENDIX D – Assessment battery

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori

IMPACT OF EVENT SCALE-REVISED

ISTITUTO SCIENTIFICO ROMAGNOLO PER LO STUDIO E LA CURA DEI TUMORI

Istruzioni per la compilazione del questionario: la lista che segue riguarda possibili stati d'animo che una persona può avere dopo un evento stressante. Legga per favore ogni frase e indichi, sulla relativa scala da 0 a 4, la risposta in relazione alle Sue reazioni, facendo riferimento alle **ultime 2 settimane, tenendo conto dei seguenti valori:**

0 = PER NULLA
1 = UN PO'
2 = MODERATAMENTE, ABBASTANZA
3 = MOLTO, UN BEL PO'
4 = ESTREMAMENTE, MOLTISSIMO

	Per niente	Un po'	Abbastanza	Molto	Moltissimo
1. Qualsiasi cosa mi ricordasse l'evento mi riportava a galla le emozioni provate	0	1	2	3	4
2. Ho avuto difficoltà a mantenere il sonno	0	1	2	3	4
3. Altre cose mi facevano pensare all'accaduto...	0	1	2	3	4
4. Mi sono sentito irritabile e arrabbiato	0	1	2	3	4
5. Evitavo di lasciarmi coinvolgere emotivamente quando ci pensavo e qualcuno o qualcosa me lo ricordava	0	1	2	3	4
6. Ci ho pensato anche senza volerlo	0	1	2	3	4
7. Mi sono sentito come se non fosse accaduto nulla o il fatto non fosse vero	0	1	2	3	4
8. Mi tenevo alla larga da qualunque cosa potesse ricordarmelo	0	1	2	3	4
9. All'improvviso mi venivano alla mente immagini dell'accaduto	0	1	2	3	4
10. Ero agitato e trasalivo facilmente	0	1	2	3	4
11. Ho cercato di non pensarci	0	1	2	3	4
12. Mi rendevo conto di avere ancora molte emozioni su quanto accaduto, ma cercavo di non affrontarle	0	1	2	3	4

IMPACT OF EVENT SCALE-REVISED

	Per niente	Un po'	Abbastanza	Molto	Moltissimo
13. Le mie emozioni sull'accaduto erano come ovattate	0	1	2	3	4
14. Mi trovavo ad agire o a sentire emozioni come se fossi tornato indietro al momento dell'accaduto	0	1	2	3	4
15. Ho avuto problemi ad addormentarmi	0	1	2	3	4
16. Avevo ondate di forti emozioni sull'accaduto ...	0	1	2	3	4
17. Ho cercato di cancellarlo dalla memoria	0	1	2	3	4
18. Avevo difficoltà a concentrarmi	0	1	2	3	4
19. Qualsiasi cosa che mi ricordasse quanto accaduto scatenava in me reazioni fisiche come sudorazione, problemi nel respirare, nausea, o batticuore	0	1	2	3	4
20. Facevo sogni su quanto accaduto	0	1	2	3	4
21. Mi sentivo vigile e come in guardia	0	1	2	3	4
22. Cercavo di non parlarne	0	1	2	3	4

EORTC QLQ-C30 (version 3.0)

Con questo questionario vorremmo sapere alcune cose su di Lei e sulla Sua salute. La preghiamo di rispondere a tutte le domande ponendo un cerchio attorno al numero che meglio corrisponde alla Sua risposta. Non esiste una risposta "giusta" o "sbagliata". Le Sue informazioni verranno tenute strettamente riservate.

Per favore scriva solo le iniziali del Suo nome e cognome: ____

Data di nascita (g, m, a): ____

La data di oggi (g, m, a): 31 ____

		No	Un po'	Parec-chio	Moltis-simo
1.	Ha difficoltà nel fare lavori faticosi, come sollevare una borsa della spesa pesante o una valigia?	1	2	3	4
2.	Ha difficoltà nel fare una lunga passeggiata?	1	2	3	4
3.	Ha difficoltà nel fare una breve passeggiata fuori casa?	1	2	3	4
4.	Ha bisogno di stare a letto o su una sedia durante il giorno?	1	2	3	4
5.	Ha bisogno di aiuto per mangiare, vestirsi, lavarsi o andare in bagno?	1	2	3	4

Durante gli ultimi sette giorni:		**No**	**Un po'**	**Parec-chio**	**Moltis-simo**
6.	Ha avuto limitazioni nel fare il Suo lavoro o i lavori di casa?	1	2	3	4
7.	Ha avuto limitazioni nel praticare i Suoi passatempi-hobby o altre attività di divertimento o svago?	1	2	3	4
8.	Le è mancato il fiato?	1	2	3	4
9.	Ha avuto dolore?	1	2	3	4
10.	Ha avuto bisogno di riposo?	1	2	3	4
11.	Ha avuto difficoltà a dormire?	1	2	3	4
12.	Ha sentito debolezza?	1	2	3	4
13.	Le è mancato l'appetito?	1	2	3	4
14.	Ha avuto un senso di nausea?	1	2	3	4
15.	Ha vomitato?	1	2	3	4

Continuare alla pagina successiva

Durante gli ultimi sette giorni:	**No**	**Un po'**	**Parec-chio**	**Moltis-simo**
16. Ha avuto problemi di stitichezza?	1	2	3	4
17. Ha avuto problemi di diarrea?	1	2	3	4
18. Ha sentito stanchezza?	1	2	3	4
19. Il dolore ha interferito con le Sue attività quotidiane?	1	2	3	4
20. Ha avuto difficoltà a concentrarsi su cose come leggere un giornale o guardare la televisione?	1	2	3	4
21. Si è sentito(a) teso(a)?	1	2	3	4
22. Ha avuto preoccupazioni?	1	2	3	4
23. Ha avuto manifestazioni di irritabilità?	1	2	3	4
24. Ha avvertito uno stato di depressione?	1	2	3	4
25. Ha avuto difficoltà a ricordare le cose?	1	2	3	4
26. Le Sue condizioni fisiche o il Suo trattamento medico hanno interferito con la Sua vita familiare?	1	2	3	4
27. Le Sue condizioni fisiche o il Suo trattamento medico hanno interferito con le Sue attività sociali?	1	2	3	4
28. Le Sue condizioni fisiche o il Suo trattamento medico Le hanno causato difficoltà finanziarie?	1	2	3	4

Per le seguenti domande ponga un cerchio intorno al numero da 1 a 7 che meglio corrisponde alla Sua risposta

29. Come valuterebbe in generale la Sua salute durante gli ultimi sette giorni?

1	2	3	4	5	6	7
Pessima						Ottima

30. Come valuterebbe in generale la Sua qualità di vita durante gli ultimi sette giorni?

1	2	3	4	5	6	7
Pessima						Ottima

EORTC QLQ-TC26

Talvolta i pazienti accusano i seguenti sintomi.

La preghiamo di indicare il grado in cui ha provato questi sintomi durante gli **ultimi sette giorni**.

		No	Un po'	Parecchio	Moltissimo
1.	Ha perso dei capelli?	1	2	3	4
2.	Ha riscontrato problemi nella percezione dei sapori e degli odori?	1	2	3	4
3.	Ha provato dolore nella regione dello stomaco?	1	2	3	4
4.	Ha avuto acidità gastrica?	1	2	3	4
5.	Ha avuto formicolio o intorpidimento delle dita delle mani o dei piedi?	1	2	3	4
6.	Ha avuto problemi di pelle (es. prurito, secchezza)?	1	2	3	4
7.	Le dita delle mani o dei piedi sono diventate pallide/fredde?	1	2	3	4
8.	Ha avuto problemi di udito?	1	2	3	4
9.	Può dirsi soddisfatto dell'assistenza ricevuta dal personale medico?	1	2	3	4
10.	Può dirsi soddisfatto delle informazioni ricevute sulla sua malattia?	1	2	3	4
11.	Si è sentito incerto riguardo al futuro?	1	2	3	4
12.	Si è preoccupato di una possibile ricomparsa della malattia?	1	2	3	4
13.	Ha avuto problemi sul lavoro o negli studi a causa della malattia o della terapia?	1	2	3	4
14.	La malattia o la terapia hanno limitato la sua attività fisica?	1	2	3	4
15.	Si è preoccupato per gli sconvolgimenti nella sua vita familiare?	1	2	3	4
16.	Ha mai temuto di non essere in grado di avere figli?	1	2	3	4
17.	Riesce a parlare della sua malattia con il partner o con la persona a lei più vicina?	1	2	3	4
18.	Si è sentito meno virile a causa della malattia o della terapia?	1	2	3	4
19.	Risponda alla domanda solo in caso di protesi testicolare: È soddisfatto della sua protesi testicolare?	1	2	3	4
20.	In che misura ha provato interesse per il sesso?	1	2	3	4
21.	In che misura è stato sessualmente attivo? (con o senza rapporti sessuali)?	1	2	3	4
	Risponda alle prossime domande solo in caso di attività sessuale				
22.	Riesce a parlare di sessualità con il partner o la persona a lei più vicina?	1	2	3	4
23.	Ha incontrato difficoltà a ottenere o mantenere un'erezione?	1	2	3	4
24.	Ha avuto problemi di eiaculazione?	1	2	3	4
25.	In che misura ha trovato il sesso piacevole?	1	2	3	4
26.	Il rapporto sessuale con il partner è stato soddisfacente?	1	2	3	4

BSI-18

ISTRUZIONI: Nella lista che segue sono elencati sintomi, disturbi o problemi che possono affliggere le persone. La legga attentamente e cerchi di ricordare se ne ha sofferto nell'**ULTIMA SETTIMANA, OGGI COMPRESO**, e con quale intensità, tenendo conto che:

0 = PER NIENTE **1 = UN PO'** **2 = ABBASTANZA** **3 = MOLTO** **4= MOLTISSIMO**

QUANTO HA SOFFERTO DI:

	Per niente	Un po'	Abbastanza	Molto	Moltissimo
1. Sensazione di svenimento o vertigini	0	1	2	3	4
2. Mancanza di interessi	0	1	2	3	4
3. Nervosismo o agitazione interna	0	1	2	3	4
4. Dolori al cuore o al petto	0	1	2	3	4
5. Sentirsi solo	0	1	2	3	4
6. Sentirsi teso e sulle spine	0	1	2	3	4
7. Senso di nausea e mal di stomaco	0	1	2	3	4
8. Sentirsi giù di morale	0	1	2	3	4
9. Paure improvvise senza ragione	0	1	2	3	4
10. Sentirsi senza fiato	0	1	2	3	4
11. Sentimenti di inutilità	0	1	2	3	4
12. Momenti di terrore o di panico	0	1	2	3	4
13. Intorpidimento o formicolio di alcune parti del corpo	0	1	2	3	4
14. Guardare al futuro senza speranza	0	1	2	3	4
15. Senso di irrequietezza tanto da non poter stare seduto	0	1	2	3	4
16. Senso di debolezza in qualche parte del corpo	0	1	2	3	4
17. Pensieri di morte o di morire	0	1	2	3	4
18. Senso di paura	0	1	2	3	4
19. Idee di togliersi la vita	0	1	2	3	4
20. Sentirsi facilmente infastidito o irritato	0	1	2	3	4
21. Scatti d'ira incontrollabili	0	1	2	3	4
22. Sentire l'impulso di colpire, ferire o far male a qualcuno	0	1	2	3	4
23. Sentire l'impulso di rompere gli oggetti	0	1	2	3	4
24. Ingaggiare frequenti discussioni	0	1	2	3	4
25. Sentirsi arrabbiato rispetto a molte cose	0	1	2	3	4

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori

PTED SELF-RATING SCALE

(Linden M. et al.)

ISTITUTO SCIENTIFICO ROMAGNOLO PER LO STUDIO E LA CURA DEI TUMORI

Istruzioni: legga le seguenti affermazioni e metta una crocetta nell'apposita griglia di risposta sul numero corrispondente alla risposta da lei scelta secondo la seguente scala:

0= assolutamente falso / 1= piuttosto falso/ 2= né vero né falso /3= piuttosto vero /4= assolutamente vero

Negli ultimi anni si è presentato un evento particolarmente grave e negativo …

1. che ha ferito i miei sentimenti e mi ha procurato amarezza	**0**	**1**	**2**	**3**	**4**
2. che ha portato a un significativo e persistente peggioramento del mio livello di benessere psicologico	**0**	**1**	**2**	**3**	**4**
3. che percepisco come ingiusto e scorretto.....	**0**	**1**	**2**	**3**	**4**
4. che mi fa pensare continuamente all'accaduto	**0**	**1**	**2**	**3**	**4**
5. che mi turba estremamente se mi capita di ripensarci	**0**	**1**	**2**	**3**	**4**
6. che mi provoca pensieri di tipo vendicativo	**0**	**1**	**2**	**3**	**4**
7. che mi fa sentire in colpa e mi fa provare rabbia verso me stesso	**0**	**1**	**2**	**3**	**4**
8. che mi dà la sensazione che è inutile sforzarsi per migliorare la situazione	**0**	**1**	**2**	**3**	**4**
9. che è alla base del mio frequente abbassamento dell'umore	**0**	**1**	**2**	**3**	**4**
10. che ha compromesso il mio generale benessere fisico	**0**	**1**	**2**	**3**	**4**
11. che mi porta ad evitare certe situazioni o persone per non pensarci e per non ricordare	**0**	**1**	**2**	**3**	**4**
12. che mi fa sentire impotente e disarmato	**0**	**1**	**2**	**3**	**4**
13. che mi procura soddisfazione se penso che la persona responsabile dovesse subire un torto simile	**0**	**1**	**2**	**3**	**4**
14. che mi ha portato a una considerevole perdita di forze e di risorse	**0**	**1**	**2**	**3**	**4**
15. che mi ha portato a essere più irritabile di prima	**0**	**1**	**2**	**3**	**4**
16. che mi ha portato a dovermi distrarre per avere un umore normale	**0**	**1**	**2**	**3**	**4**
17. che mi ha reso incapace di lavorare e/o dedicarmi alla famiglia come facevo prima	**0**	**1**	**2**	**3**	**4**
18. che mi ha portato a ritirarmi dalle attività sociali e dagli amici	**0**	**1**	**2**	**3**	**4**
19. che frequentemente mi evoca ricordi spiacevoli	**0**	**1**	**2**	**3**	**4**

MINI-MENTAL ADJUSTMENT – SHORT FORM

ISTRUZIONI: di seguito è riportata una serie di affermazioni riguardanti le possibili reazioni di fronte alla malattia. E' pregato di indicare, per ciascuna affermazione, il grado col quale Lei si sente d'accordo **IN QUESTO MOMENTO**, ponendo una crocetta in corrispondenza del numero per Lei più appropriato.
Se, per esempio, l'affermazione non corrisponde per niente al Suo modo di reagire, dovrà segnare il numero **1**, se l'affermazione corrisponde esattamente a come Lei reagisce, segnerà il numero **4**.
Per risposte intermedie potrà segnare il numero **2** o **3**. Faccia comunque riferimento allo schema qui riportato:

1 = COMPLETAMENTE IN DISACCORDO, NON È PER NULLA IL MIO CASO
2 = IN DISACCORDO, NON È' IL MIO CASO
3 = D'ACCORDO, È IL MIO CASO
4 = COMPLETAMENTE D'ACCORDO, È ESATTAMENTE IL MIO CASO

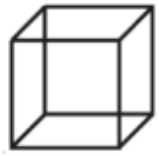
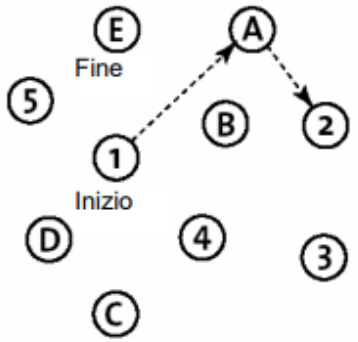
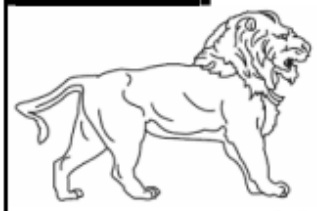
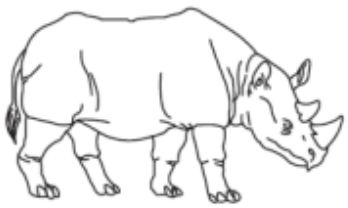
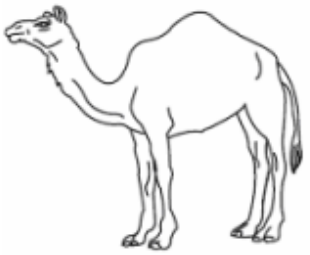
	1	2	3	4
1. Ho voglia di lasciar perdere tutto	☐	☐	☐	☐
2. Mi sento molto arrabbiato/a per quello che mi è capitato	☐	☐	☐	☐
3. Mi sento completamente perduto/a su cosa fare	☐	☐	☐	☐
4. Provo sensazioni terribili	☐	☐	☐	☐
5. Ho paura che il tumore ricompaia o si aggravi	☐	☐	☐	☐
6. Non riesco a controllare la situazione	☐	☐	☐	☐
7. Sono molto preoccupato/a	☐	☐	☐	☐
8. Non ho molta speranza per il futuro	☐	☐	☐	☐
9. Sento che non c'è nulla che posso fare per aiutarmi	☐	☐	☐	☐
10. .Mi pare che il mondo mi stia crollando addosso	☐	☐	☐	☐
11. Sento che la vita è senza speranza	☐	☐	☐	☐
12. Non riesco a far fronte alla situazione	☐	☐	☐	☐
13. Sono sconvolto da questa malattia	☐	☐	☐	☐
14. Mi è difficile credere che questo sia capitato a me	☐	☐	☐	☐
15. Mi sento molto in ansia per questa malattia	☐	☐	☐	☐
16. Sono spaventato/a	☐	☐	☐	☐

La preghiamo di indicare in quale misura queste affermazioni riflettono la sua esperienza nel corso dell'ultima settimana

	Per niente	Un po'	Abbastanza	Molto	Moltissimo
Mi sento affaticato/a	**0**	**1**	**2**	**3**	**4**
Mi sento molto indebolito/a	**0**	**1**	**2**	**3**	**4**
Mi sento svogliato/a.....	**0**	**1**	**2**	**3**	**4**
Mi sento stanco/a	**0**	**1**	**2**	**3**	**4**
Sono così stanco/a che ho difficoltà ad iniziare qualsiasi cosa	**0**	**1**	**2**	**3**	**4**
Sono così stanco/a che ho difficoltà a finire quello che ho iniziato	**0**	**1**	**2**	**3**	**4**
Ho energia	**0**	**1**	**2**	**3**	**4**
Riesco a svolgere le mie solite attività quotidiane (lavorare, fare la spesa, tempo libero...)	**0**	**1**	**2**	**3**	**4**
Ho bisogno di dormire durante il giorno	**0**	**1**	**2**	**3**	**4**
Sono troppo stanco/a per mangiare	**0**	**1**	**2**	**3**	**4**
Ho bisogno di aiuto nelle attività quotidiane	**0**	**1**	**2**	**3**	**4**
Mi sento frustrato/a perchè sono troppo stanco/a per fare le mie solite cose	**0**	**1**	**2**	**3**	**4**
Devo limitare le mie attività sociali a causa della stanchezza	**0**	**1**	**2**	**3**	**4**

MONTREAL COGNITIVE ASSESSMENT (MOCA)
- ITALIA -

NOME: _____
Scolarità: _____ Data di nascita: _____
Sesso: _____ DATA: _____

		PUNTI
VISUOSPAZIALE / ESECUTIVO	Copi Il cubo  Disegni un orologio (undici e dieci) (3 punti)	
 [ ] [ ]	[ ] Contorno [ ] Numeri [ ] Lancette	__/ 5
DENOMINAZIONE    [ ] [ ] [ ]		__/ 3
MEMORIA Leggere la lista di parole: il soggetto deve ripeterle. Fare le prime 2 prove di seguito e il " Richiamo " dopo 5 min.		0 punti

	Faccia	Velluto	Chiesa	Margherita	Rosso
1° prova					
2° prova					

ATTENZIONE	Leggere la serie di cifre (una cifra / sec.)	Il soggetto deve ripeterle [ ] 2 1 8 5 4 Il soggetto deve ripeterle in ordine inverso [ ] 7 4 2	__/ 2
Leggere la serie di lettere. Il soggetto deve dare un colpetto con la mano sul tavolo ad ogni lettera "A". **0 punti se ≥ 2 errori**		[ ] F B A C M N A A G H L B A F A H D E A A A G A M O F A A B	__/ 1
Sottrazione di 7 partendo da 100 per 5 volte		[ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65 4 o 5 sottrazioni corrette: **3 pt,** 2 o 3 corrette: **2 pt,** 1 corretta: **1 pt,** 0 corretta: **0 pt**	__/ 3
LINGUAGGIO	Ripeta: So solo che oggi dobbiamo aiutare Giovanni. Il gatto si nascondeva sempre sotto il divano quando c'erano cani nella stanza.	[ ] [ ]	__/ 2
Fluenza / In 1 minuto, nomini il maggior numero possibile di parole che iniziano con la lettera "**F**". [ ] __ (N ≥ 11 parole)			__/ 1
ASTRAZIONE	Similitudini tra per es. banana / arancio = frutti; [ ] treno / bicicletta [ ] orologio / righello		__/ 2

RICHIAMO DIFFERITO	Deve ricordarsi le parole **SENZA AIUTO**		**Faccia** [ ]	**Velluto** [ ]	**Chiesa** [ ]	**Margherita** [ ]	**Rosso** [ ]	Punti solo per ripetizione **SENZA AIUTO**
Opzionale	AIUTO	Categoria Seman.						
		Scelta multipla						

ORIENTAMENTO	[ ] Data [ ] Mese [ ] Anno [ ] Giorno [ ] Luogo [ ] Città	__/ 6

Versione 26 Luglio 2006
www.mocatest.org

Normale:
≥ 26 / 30

TOTALE __/30
Aggiungere 1 punto se ≤ 12 anni di istruzione

SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA
Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori

Screen for Cognitive Impairment in Psychiatry

Italian Version (SCIP-I) - Modulo 1

Scot E. Purdon, Giuseppe Guaiana & Giulia Balboni

ISTITUTO SCIENTIFICO ROMAGNOLO PER LO STUDIO E LA CURA DEI TUMORI

1. Test di Apprendimento di parole (Leggere la lista di parole con un intervallo di circa 3 secondi per parola. Valutare quante parole sono state ricordate. Ripetere la lista per altre due volte). Alla fine della terza prova informare il soggetto che gli verrà richiesto di ricordare la lista più tardi:

	Tamburo	Tenda	Campana	Caffé	Scuola	Padre	Luna	Giardino	Cappello	Contadino	Σ/10	
1												
2												
3												Σ/30 =

2. Test di Ripetizione delle Consonanti: Leggere ciascun gruppo di tre lettere. Il soggetto deve contare all'indietro partendo dal numero indicato nella colonna Inizio (#), per un numero di secondi indicato dalla colonna Ritardo, e successivamente ripetere le lettere. Qualsiasi ordine è corretto:

Stimolo	Inizio (#)	Ritardo	Risposta		Stimolo	Inizio (#)	Ritardo	Risposta	
Q-L-S					F-S-B	53	3		
H-R-T					R-C-N	46	9		
S-C-P	94	18			B-G-Q	117	18		
N-D-R	109	9			H-M-C	48	3		Σ/24 =

3. Test di Fluidità Verbale. 30 secondi per generare parole che cominciano con ciascuna lettera:

Stimolo	Risposta	
C		
L		Σ =

4. Apprendimento ritardato: chiedere al soggetto di ricordare le parole della prima prova. Non ripetere la lista.

	Tamburo	Tenda	Campana	Caffé	Scuola	Padre	Luna	Giardino	Cappello	Contadino	Σ/10	
4												t4/t3 *100=

----------PIEGARE QUI----------

5. Test di Velocità Visuomotoria: Dopo aver fatto fare pratica con gli items di prova, contare 30 secondi affinchè il partecipante completi i riquadri da sinistra a destra e dall'alto vero il basso.

A	V	C	U	G	I
. -	. . . -	- . - .	. . -	- - .	- . - -

Item di prova						Test			
G	U	C	I	A	V	C	A	G	
V	I	U	G	U	A	I	C	V	
A	C	I	G	U	V	C	I	V	
U	G	A	V	C	G	A	V	I	Σ/30

Iniziali Nome e Cognome del partecipante: _____ Genere: _____ Data di nascita (gg/mm/aa): _____
Data di somministrazione (gg/mm/aa): _____ Ora di somministrazione: _____
Livello di istruzione: _____ Esaminatore: _____
Città di residenza: _____ Università frequentata: _____

Abbreviations and acronyms

AYA Adolescents and young adults

BSI-18 Brief Symptom Inventory-18

CHEK2 Checkpoint Kinase 2

CRF Case Report Form

EORTC QLQ-C30 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30

FACIT Functional Assessment of Chronic Illness Therapy

GSI Global severity index

GCT Germ cell tumor

HRQOL Health-related quality of life

IES-R Impact of Event Scale – Revised

MCI mild cognitive impairment

Mini-MAC Mini-Mental Adjustment to Cancer scale

MoCA Montreal Cognitive Assessment

NCI National Cancer Institute

PEB combined treatment of cisplatin, etoposide, bleomycin

PTED Post Traumatic Embitterment Disorder

PTSD post-traumatic stress disorder

QoL Quality of life

SCIP Screen for Cognitive Impairment in Psychiatry

SD Standard deviation

TC Testicular cancer

TCS Testicular cancer survivor

WHO World Health Organization

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