

# Health-related quality of life and psychosocial implications in testicular cancer survivors. A literature review

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**Abstract. – OBJECTIVE:** In this review, we focused our attention on Quality of Life (QoL) of testicular cancer survivors (TCSs), in general and in the most relevant areas. Several key findings have been highlighted in our review.

**MATERIALS AND METHODS:** PubMed, MEDLINE and PsycINFO databases were consulted to find published studies, from 1980 to May 2017, that met our inclusion criteria.

**RESULTS:** The majority of studies investigated older adult TCSs, while few studies on adolescent and young adult patients were available. Many studies indicate that health-related QoL (HRQoL) is similar among the TCSs and the general population. Even if QoL deteriorates so clear at the time of diagnosis and throughout treatment, afterward returns to normal levels, as defined by the matched controls. However, there are numerous chronic conditions consequent to diagnosis and treatment of testicular cancer that plague survivors and affect QoL, like Raynaud-like phenomena, peripheral neuropathy, fatigue, anxiety, sexual, fertility and body image problems. Even if these problems can have no effects on the measures of global QoL, they have an impact on the quality of life. Differences between TCSs with and without a partner bring to different outcomes in the adjustments to cancer.

**CONCLUSIONS:** It is necessary to identify TCSs with higher risks of poorer QoL outcomes, to focus interventions on the areas with the greatest impairments. Further researches should consider the effects of testicular cancer on the impaired areas, collecting more data to

better identify survivor's needs and consequent interventions, with a special focus on adolescent and young adult TCSs.

Other works are requested on therapies, preventive and ameliorative, to reduce chronic side effects of testicular cancer treatment.

*Key Words:*

Health-related quality of Life, Psychosocial issues, Testicular cancer survivors, Urologic oncology.

## Introduction

### *Testis Germ Cell Tumors (TGCT)*

Malignant germ cell tumors arise from germ cells, which are involved in the formation of sperm in males and ova in females. Testicular cancer (TC) is a neoplasm that mainly affects young men between 15 and 40 years, with an incidence rate of generally at 1%. Although this is a relatively rare cancer, the trend of incidence is growing in Western countries<sup>1</sup>. TC is divided in two types: seminoma (SGCT), with a higher incidence in males between 30 and 35 years of age and more treatable than nonseminoma (NSGCT), which has a higher incidence among young adults aged between 25 and 29 years, and discloses more aggressive features.

Spermatocytic seminoma is an uncommon variant of classic seminoma, responsible of 0.61%

of germ cell tumors, that affects individuals older than 60 years. An interesting characteristic is that it is not able to metastasize, except when there are sarcomatous changes<sup>2,3</sup>.

The main risk factors reported were: familiar history on TC, the exposure to substances that have an effect on the endocrine levels, infertility (infertile males have three times the risk to be affected by a TC), and smoking (that double the risk of a TC)<sup>4</sup>.

The unilateral orchiectomy is the mainstay treatment of TC and produces the histological diagnosis of seminoma and non-seminoma. Elective treatments for high recurrence risk tumors after orchiectomy are cisplatin-based polychemotherapy<sup>5</sup> and resection of residual retroperitoneal tumor mass (RRRTM). Adenomatoid tumors (ATs) are a kind of uncommon benign tumor that usually arises in the paratesticular area. This kind of tumor produce the same clinical signs of the others tumors but, in this case, orchiectomy is not necessary. A proper diagnosis avoids an unnecessary, invasive treatment<sup>6</sup>.

Earlier diagnosis and progress in treatments have extended the life expectancy of cancer survivors. On the other side, surgery, radiation, and chemotherapies can have an impact on the functionality of the organs<sup>7</sup>. Nutritional science has a growing role in the therapeutic path, as it can produce relevant changes in the hormonal levels and the other functional parameters<sup>8</sup>.

Therefore, an increasing number of testicular cancer survivors (TCSs) addresses survivorship-related issues. The key question is how the experience of diagnosis, treatment, side effects and consequences of testicular cancer make the quality of life (QoL) of TCSs different than comparative men without cancer. In the medical tradition, QoL is the expression of the subjective experience of complete physical, social and mental health, often referred to as health-related QoL. QoL is regularly defined by a number of domains, composed mainly by physical functioning, physical symptoms, emotional functioning, cognitive functioning, role functioning, well-being and social functioning, sexual functioning, and existential problems<sup>9</sup>.

In this review, we have considered the most relevant domains in quality of life of TCSs, to present a synthesis of existing literature about the effect of testicular cancer on several domains, including emotional functioning and mental health, cognitive functioning, social functioning, senti-

mental relationships, body image, sexual functioning, and fertility. Our review considered older adult, adolescent and young adult testicular cancer survivors.

## Materials and Methods

### Search Strategy

PubMed, MEDLINE, and PsycINFO databases were consulted to find published studies that met inclusion criteria of our review. The MeSH (medical subject headings) terms used for the search were as follows: "Quality of life" and "Testicular cancer", "Testicular cancer survivors", together with phrases identifying the population of interest (older adult, young adults, adolescents). To encompass a wide range of QoL outcomes of these patients, we also used the following terms: "depression", "anxiety", "distress", "marital functioning", "relationships", "sexuality", "body image", "fertility", "social functioning", "work-related problems", "cognitive functioning". We summarized the most relevant literature on QoL between TCSs from 1980 to May 2017.

### Inclusion, Exclusion Criteria and Data Extraction

Selection criteria were: (1) papers published in English from 1980 to May 2017, (2) studies on patients with TC who were in remission, (3) studies on physical, psychological, and social well-being, (4) papers were subgroups of testicular cancer survivors could be identified, (5) analysis of qualitative or quantitative data regarding the effect of TC on romantic and sexual relationships, body image, or fertility, (6) papers including adolescents and young adults. Reviews on TCSs have not been included as the original cited articles were already present.

Methodological aspects were not used as inclusion criteria since the objective was to do an inventory of the literature on the QoL of testicular cancer survivors. Studies that had methodological shortcomings, such as small sample sizes, were considered.

We excluded any studies that did not include testicular cancer survivors, those that did not assess HRQoL outcomes or that did not assess specific HRQoL domains.

The data extraction sheet identifies the research objective, methodology used, and HRQoL issues assessed using formal measurement tools or using interviews.

As these studies used a broad variety of methodologies and research questions, this review was necessarily descriptive.

## Results

Figure 1 shows the flowchart of the systematic review process followed. The initial search found a total of 150 publications, mainly in PubMed, MEDLINE, and PsycINFO. Duplicated references, conference abstracts, papers that not met inclusion criteria, and non-original researches had been discarded. After this selection, 77 papers were reviewed, with 54 papers that fulfilled the identified inclusion criteria. The selected studies are shown in Table I.

### Study Objectives

The studies considered HRQoL of TCSs in general and in the most relevant areas, with a particular interest to seven core domains in quality of life of TCSs. The presentation of the findings is organized analyzing general QoL and the

following domains: emotional functioning and mental health (studies on anxiety, depression and fatigue); studies on cognitive functioning; studies on social functioning; the relationship with partner; studies on changes in body image; studies on sexual functioning; studies on fertility problems.

General QoL instruments like Short Form-36 (SF-36)<sup>10</sup>, and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire<sup>11</sup>, analyze most of the listed domains, while other tools specific for the disease consider more specific functioning issues and side effects.

### Studies on Health-Related QoL

Even if many studies have evaluated QoL in survivors of testicular cancer, few significant and reliable measures of the QoL were available.

A study of a Norwegian group in 2005 used the Impact of Event Scale and the 36-item Short Form Survey to make a comparison of 1.409 TCSs with 2.678 men<sup>12</sup>. There were no relevant differences in QoL in patients after eleven years median follow-up. A TC treatment caused only

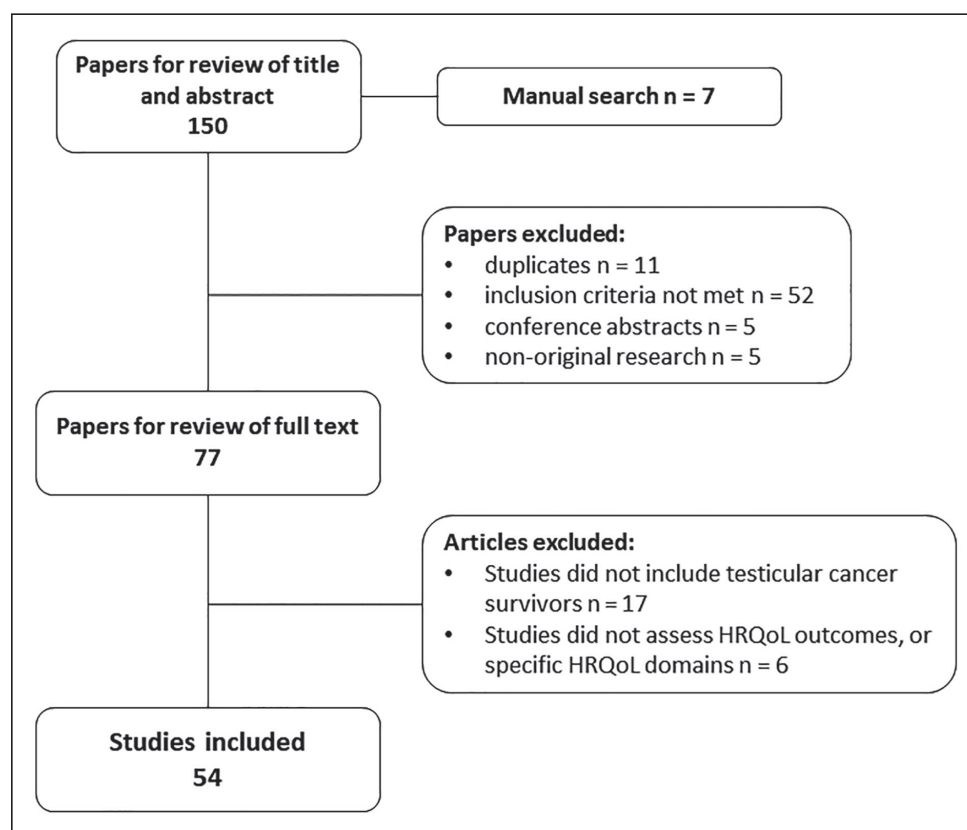


Figure 1. Flowchart of process of systematic literature search.

**Table I.** Studies on Quality of Life in general of TCSs and in its several domains.

Author (s) and Ref	Year	Sample	Objective	Methods/Measurement instruments
Alacacioglu et al <sup>20</sup>	2014	41	To investigate anxiety, depression and sexual satisfaction levels of TCSs	Quantitative surveys: HADS (Hospital Anxiety and Depression Scale), GRISS (Golombok-Rust Inventory of Sexual Satisfaction) and EORTC-30 (European Organization for Research on Treatment of Cancer Questionnaires Quality of Life-C30)
Arai et al <sup>60</sup>	1996	83	To investigate psychosocial aspects of TCSs	Quantitative surveys: SWL (Satisfaction with Life Scale).
Blackmore <sup>61</sup>	1988	16	To explore sexual life in TCSs	Quantitative surveys: questionnaire modified from the DSFI (Derogatis Sexual Functioning Inventory)
Brodsky <sup>50</sup>	1995	11	To examine changes in self because of the experience of TC	Qualitative interview with open-ended questions
Brodsky <sup>51</sup>	1999	11	To assess the experience of TCSs	Qualitative interview with open-ended questions
Brydoy et al <sup>77</sup>	2005	1.433	To assess post-treatment paternity of TCSs	Quantitative surveys: questionnaire not reported in publication and Laboratory Tests
Caffo, Amichetti <sup>62</sup>	1999	98	To explore sexual life in TCSs	Quantitative surveys: UCLA/RAND sexual module and the Groningen sexual questionnaire
Carpentier et al <sup>57</sup>	2011	21	To explore perceptions of masculinity and self-image in AYA TCSs	Semi-structured qualitative interview with open-ended questions
Chapple, McPherson <sup>66</sup>	2004	45	To understand reasons for and against seeking prosthesis	Qualitative interview with open-ended questions
Dahl et al <sup>73</sup>	2007	1.084	To explore sexual function in TCSs	Quantitative surveys: BSFI (Brief Male Sexual Function Inventory)
Dahl et al <sup>23</sup>	2005	1.408	To assess anxiety and depression in TCSs	Quantitative surveys: HADS
Fegg et al <sup>46</sup>	2003	341	To assess QoL, psychosocial dimensions and subjective QL in TCSs	Quantitative surveys: QLS (Questions on Life Satisfaction)
Fleer et al <sup>24</sup>	2006	350	To assess cancer-related stress symptoms in TCSs	Quantitative surveys: IES (Impact of Events Scale). Qualitative, open-ended interviews with a subsample of 30
Fleer et al <sup>14</sup>	2006	354	To assess QoL in TCSs	Quantitative surveys: SF-36 (Medical Outcome Study 36- item Short Form Health Survey)
Fossa et al <sup>22</sup>	2003	791	To assess anxiety, depression and Fatigue in TCSs	Quantitative surveys: HADS; FQ (Fatigue Questionnaire)
Fossa et al <sup>35</sup>	2003	666	To describe QoL in TCSs	Quantitative surveys: EORTC QLQ C-30 + TC module
Foster et al <sup>81</sup>	1994	51	To examine fertility in TCSs	Quantitative surveys: questionnaire not reported in publication and Laboratory Tests
Girasolet al <sup>84</sup>	2006	129	To assess frequency of sperm banking and describe differences between men choosing to bank sperm or not	Quantitative surveys: questionnaire not reported in publication

*Table continued*

**Table 1 (Continued).** Studies on Quality of Life in general of TCSs and in its several domains.

Author (s) and Ref	Year	Sample	Objective	Methods/Measurement instruments
Gritz, et al <sup>48</sup>	1989	88	To assess psychosocial sequelae in TCSs and their partners	Quantitative surveys: questionnaires not reported in publication. Qualitative interviews
Grov et al <sup>17</sup>	2009	1.428	To examine associations between neuroticism and mental and somatic morbidity and lifestyle issues in TCSs	Quantitative surveys: EPQ-18 (Eysenck Personality Questionnaire); BSFI; HADS; SF-36; FQ; IES
Hartmann et al <sup>76</sup>	1999	58	To examine types and occurrences of sexual dysfunction and fertility distress in TCSs	Quantitative surveys: questionnaire not reported in publication
Herr et al <sup>82</sup>	1998	105	To assess post-treatment paternity of TCSs	Quantitative surveys: questionnaire not reported in publication and Laboratory Tests. Qualitative telephone interview
Huddart et al <sup>68</sup>	2005	680	To examine fertility and sexual function in TCSs	Quantitative surveys: EORTC QLQ C-30 + TC module
Incrocci et al <sup>63</sup>	2002	123	To assess treatment outcome, body image, and changes in sexuality in TCSs	Quantitative surveys: questionnaire adapted from a standard questionnaire
Joly et al <sup>10</sup>	2002	190	To assess QoL and social problems in TCSs	Quantitative surveys: EORTC QLQ C-30; SF-36
Jonker-Pool et al <sup>74</sup>	2004	314	To assess the need for information and support in TCSs	Quantitative surveys: questionnaire adapted from a study among women with gynecological tumors
Kassa et al <sup>41</sup>	1991	149	To assess of psychosocial well-being in TCSs	Quantitative surveys: HSCL (Hopkin Symptom Checklist)
Kim at al <sup>85</sup>	2010	246	To examine fertility, sexual functioning, and general QoL among TCSs	Quantitative surveys: questionnaire not reported in publication
Kim et al <sup>15</sup>	2011	256	To assess of QoL in TCSs	Quantitative surveys: SF-36
Levison <sup>83</sup>	1986	46	To examine occurrences of sexual dysfunction and fertility in TCSs	Quantitative surveys: Laboratory Tests
Liguori et al <sup>79</sup>	2008	30	To examine semen quality in TCSs	Quantitative surveys: Laboratory Tests
Mykletun et al <sup>12</sup>	2005	1.409	To assess of QoL in TCSs	Quantitative surveys: IES and SF-36
Moynihan <sup>40</sup>	1987	102	To assess of psychosocial problems in TCSs	Quantitative surveys: PSE (Present State Examination)
Orre et al <sup>27</sup>	2008	1.431	To assess of Fatigue in TCSs	Quantitative surveys: FQ (Fatigue Questionnaire)
Ozen et al <sup>54</sup>	1998	140	To assess sexual and professional performance of TCSs	Quantitative survey: GHQ-28 (General Health Questionnaire-28). Qualitative interview
Paderson et al <sup>37</sup>	2009	72	To assess cognitive function in TCSs	Neuropsychological tests
Rossen et al <sup>15</sup>	2009	401	To assess QoL, depression and Fatigue in TCSs	Quantitative surveys: EORTC-30; BDI-II (Beck Depression Inventory-II); MFI (Multidimensional Fatigue Inventory-20)

Table continued

**Table 1 (Continued).** Studies on Quality of Life in general of TCSs and in its several domains.

Author (s) and Ref	Year	Sample	Objective	Methods/Measurement instruments
Rossen et al <sup>75</sup>	2012	401	To assess sexuality and body image in TCS	Qualitative interview: Six questions from the EORTC QLQ-PR25 (for prostate cancer)
Rudberg et al <sup>45</sup>	2000	277	To assess health-related QoL in TCSs	Quantitative surveys: SWEDQUAL (Swedish Health Related Quality of Life Questionnaire)
Rudberg et al <sup>59</sup>	2002	669	To assess frequency of physical and psychologic symptoms in TCSs	Quantitative surveys: GQL (Gothenburg Quality of Life Instrument) only symptom checklist
Schagen et al <sup>38</sup>	2008	182	To assess cognitive functioning in relation to emotional distress and fatigue in TCSs	Quantitative surveys: EORTC-30; HSCL; MFI-20 (multi-dimensional fatigue inventory); neuropsychological tests
Sheppard and Wylie <sup>52</sup>	2001	27	To assess sexual difficulties in TCSs	Quantitative surveys: GRISS; EORTC-30. Qualitative interviews with a subsample of 7
Schover et al <sup>47</sup>	1985	121	To assess sexual functioning and marital relationship in TCSs	Quantitative surveys: questionnaire not reported in publication
Skaali et al <sup>26</sup>	2009	1.336	To explore fear of recurrence in TCSs	Quantitative surveys: HADS; FQ; SF-36; EPQ-18; Rosenberg Self-Esteem Scale (RSES). Psychiatric Interview
Skaali et al <sup>39</sup>	2011	122	To assess cognitive problems in TCSs	Quantitative surveys: IES; FQ; Qualitative Interview. Neuropsychological test
Skoogh et al <sup>19</sup>	2013	974	To investigate the psychological needs of TCSs	Quantitative surveys: a study-specific questionnaire
Skoogh et al <sup>36</sup>	2012	960	To assess cognitive function in TCSs and specific activities and behavior in every day life	Quantitative surveys: a study-specific questionnaire
Smith et al <sup>18</sup>	2013	244	To identify the supportive care needs in TCSs	Quantitative surveys: CaSUN (Supportive care needs), DASS21 (Depression Anxiety Stress Scale 21); SF-36v2
Smith AB et al <sup>25</sup>	2016	244	To assess psychological distress; health-related quality of life; coping; social support, and unmet needs in TCSs	Quantitative surveys: DASS21; SF-36v2; EORTC QLQ-TC26 (TC- module HRQoL); MAC (Mental Adjustment to Cancer Scale), DUFSS (Functional Social Support Questionnaire), and CaSUN
Spermon et al <sup>78</sup>	2003	226	To assess prevalence of fertility/infertility in men before and after TC	Quantitative surveys: a study-specific questionnaire

*Table continued*

a variance from 0.3% to 0.7% in QoL measures. There were some differences in survivors, compared to controls: less vitality, a poorer social function, and increased body pain. However, they were considered not significant. Patients treated only with orchiectomy have less relevant side effect than those treated with radiotherapy, chemotherapy or retroperitoneal lymph node dissection (RPLND). The most common side

effects reported were gastrointestinal and sexual ones, and were strongly related to a worse quality of life.

Also, a French study<sup>13</sup> of 2002 on 71 TCSs and 119 controls with 11 years follow-up indicate no differences in QoL and professional or familial life. TCSs have reported more erectile problems, less pleasure and less sexual desire than controls.

**Table 1 (Continued).** Studies on Quality of Life in general of TCSs and in its several domains.

Author (s) and Ref	Year	Sample	Objective	Methods/Measurement instruments
Tinkler et al <sup>65</sup>	1992	155	To assess sexual function in TCSs	Quantitative surveys: a study-specific questionnaire
Tuinman et al <sup>55</sup>	2005	259	To compare marital and sexual satisfaction of TCSs and their spouses to a reference group, and to compare marital and sexual satisfaction of couples partnered during TC to couples partnered after TC	Quantitative surveys: MMQ (Maudsley Marital Questionnaire)
Tuinmann et al <sup>53</sup>	2006	129	To assess self-esteem, social support, and mental health in TCSs, on the basis of relationship status	Quantitative surveys: SSL (Social Support List), RSES, and SF-36 (subscale mental health)
Tuinmann et al <sup>56</sup>	2010	93	To assess sexual functioning during the first year after TC and examine the effect of relationship status and depressive symptoms on sexual functioning	Quantitative surveys: IIEF (International Index of Erectile Function) and CES-D (Center for Epidemiological Studies Depression Scale)

The biggest difference was that 31% of the cases, when compared to the 2% of controls, reported more problems to get loans from banks.

QoL is not related to the treatment (chemotherapy, RPLND, and radiotherapy). There is a strong correlation between fatigue and low QoL scores in symptoms and functional scale, and both are related to a diminished sexual life.

In a study on 354 TCSs in the Netherlands, Fleer et al<sup>14</sup> reported that survivors had a quality of life similar to the component of a reference group. It is not a surprise that unemployed men who had a chronic disease have a higher risk of impaired functioning.

Other two studies have reached similar conclusions: Kim et al<sup>15</sup> released a case-control study comparing 246 TCSs and 236 controls among the men of the U.S. armed forces. This study reported similar global QoL levels in cases and controls, even if highlighted some physical limitations and long-lasting effects on the health in the cases. In the same study, there were reported lower scores on the physical component associated with chemotherapy, including measures of physical role and physical functioning, and a lower self-reported social functioning.

Rossen et al<sup>16</sup> on 401 Danes TCSs underlined that previous chemotherapy treatment was related to Raynaud-like phenomena, ototoxicity, and peripheral neuropathy. However, QoL among the survivors was identical with QoL of the same age men in the general population.

These studies show that global QoL is similar in TCSs and general population and that there are TCSs subgroups where there is a direct relation between the disease and the therapy with the scores in the quality of life.

A Norwegian study on 1.428 testicular cancer survivors reported that neurosis was associated with several complaints of QoL, including sexual problems, neurotoxic side effects (hearing impairment, peripheral neuropathy, Raynaud's Phenomenon), and reduced physical function<sup>17</sup>.

Many studies are based on relatively small samples<sup>13</sup>, and low statistical power may explain the lack of reported differences. Other studies have a short follow-up time, and so the influence of long-term effects of therapy on quality of life could be lost.

Another way to look at the question of QoL is from the point of view of needs assessment: in 2013, an Australian study reported that 66% of 244 TCSs had several unmet supportive care

needs<sup>18</sup>. The most relevant were life stress and relationship problems. In this study was not present a control group.

A Sweden group studied 974 TCSs with an average 11-years follow-up: over the 60% of TCSs have had no sufficient counseling on how to react to crisis linked to their diagnosis of cancer<sup>19</sup>. These studies provide also information on the actual needs of survivors.

### ***Emotional Functioning and Mental Health: Studies on Anxiety, Depression, and Fatigue***

Diagnosis and treatment of cancer can be psychologically traumatic. Some studies have analyzed the risk of an increased level of anxiety or depression in the survivors of testicular cancer<sup>16,20-23</sup>.

A 2003 study of a Norwegian group on 791 TCSs highlighted lower levels of depression, but higher rate of anxiety and chronic fatigue, according to the Hospital Anxiety and Depression Scale (HADS), in TCSs compared to the general population<sup>22</sup>.

The same group, with an expanded survivors number, has been object of a follow-up study that investigated 1.408 TCSs, reporting a higher rate of anxiety disorder (19% vs. 13.5%,  $p < 0.001$ ) and no difference in depression (9.7% vs. 10.1%,  $p = 0.56$ )<sup>23</sup>. The work reported an increased risk of anxiety associated with factors like youth, economic problems, alcohol abuse, sexual problems, fear of relapse, mental illness, peripheral neuropathy. Anxiety treatments might alleviate some of these problems, and it is possible that the treatment of these problems may reduce anxiety of TCSs.

TCSs, as the general population, can have relevant pretreatment problems, like economic worries, unemployment, relational and sexual problems, mental disorders, or physical illnesses. It can be a common mistake to attribute these problems in TCSs to treatments and side effects, rather than to the common condition of younger men in society. But the influence of pretreatment problems on adaptation after treatment is not well known, as there are not enough well sized prospective studies<sup>21</sup>.

In 2006 Fleer et al<sup>24</sup> analyzed the cancer-related stress symptoms in TCSs, to identify the relationships of cancer-related stress symptoms with cancer related and socio-demographic variables, and to find relations among subjective and objective aspects of cancer diagnosis and treatment

with the post-cancer phenomena. In this study were involved 354 TCSs that filled in the Impact Event Scale (IES). Some of these TCSs were also interviewed.

Cancer-related stress symptoms were experienced by the 13% of TCSs. Higher levels of stress were reported by the less educated and the unemployed ones: cancer-related variables didn't seem relevant. The interviews indicated that the subjective perceptions of the TCSs of the disease impact on the current and future life were strongly related to the stress symptoms of cancer, more than the real medical situation.

In 2016 Smith et al<sup>25</sup> highlighted an increase in anxiety and depression levels in 244 TCSs, with about a 20% that experience a moderate to severe level increase. They reported also a decrease in the mental domains of HRQoL: mainly for psychosocial aspects and for the fear of recurrence, rather than for the physical aspects of the treatment or of the disease.

Some studies highlighted possible factors that can contribute to emotional problems in the survivors of testicular cancer. Skaali et al<sup>26</sup> studied the fear of recurrence in 1.336 TCSs at an average time after diagnosis of 11 years: the 24% of TCSs indicated a moderate worry of recurrence in the week before the survey, the 7% a high level of apprehension. This fear is positively related to fatigue and stress, and negatively related to self-esteem and QoL.

Survivors of testicular cancer have an increased incidence of chronic fatigue syndrome. A study of a Norwegian group on 1.431 TCSs and 1.080 male controls confirmed a higher rate of fatigue in TCSs (17.1% vs. 9.7%)<sup>27</sup>. The study reported also that fatigue was related to somatic and psychological problems, and to a lower quality of life.

A French study of 71 TCSs reported a different result: similar levels of fatigue in survivors and the same age control group. But we have to highlight that this study has a small group of survivors, and adopt only one kind of fatigue measurement<sup>13</sup>.

There is not a full comprehension of the cause of the fatigue in testis cancer survivors, and there is no clear relation to the kind of treatment.

Some factors can play a role in the fatigue of the TCSs: cardiac dysfunction, hypothyroidism, anemia, renal failure, substance abuse, relapsed testicular cancer, secondary tumors, depression or other mental illness. For this reason, it is essential to assess the etiology of fatigue<sup>28</sup>.



A moderate fatigue reduction in cancer survivors was also highlighted in randomized controlled trials of psychosocial treatments, including cognitive-behavioral therapy and educational programs to manage and reduce fatigue. Some evidence indicates that mind-body interventions can produce a decrease in cancer-related fatigue<sup>29-33</sup>.

### ***Studies on Cognitive Functioning***

There has been increasing attention to cognitive mental disorders after chemotherapy in patients with cancer<sup>34</sup>. Few researches<sup>35-39</sup> have studied cognitive function in TCSs in the range from 1 to 11 years after the treatment. About 20% of TCSs of the European studies<sup>35</sup> reported a decrease in cognitive function 2 years after 4 cycles of PEB (bleomycin, etoposide, and cisplatin). No research has reported permanent decrease of neuropsychological performance. Cognitive issues have been correlated to fatigue and emotional distress.

Other prospective studies are highly necessary for better evaluating the changes of cognitive functions in TCSs.

### ***Studies on Social Functioning***

It is very important for TCSs to have a normal education and working life after treatment, but just a few researches have addressed this problem. Fleer et al<sup>14</sup> underlined that employment is very important for the quality of life in TCSs. Studies show that mostly all of TCSs still work<sup>40</sup>. Studies of Kaasa et al<sup>41</sup> indicate a greater job satisfaction in TCSs than in a matched-age population sample.

The unemployment rate for TCSs in the United States was similar to that one for men of the general population<sup>42</sup>.

There was not enough data on the workability ten or more years after diagnosis of testicular cancer.

A good social support has a relevant positive impact on the life of the cancer patients<sup>43</sup>: a good network of relatives and friends is an important support in the therapeutic path<sup>44</sup>. There seems to be a small change in the relation with friends and social contacts<sup>45</sup>, although a study from Germany reported that TCSs have fewer friends and acquaintances compared to normal controls<sup>46</sup>.

### ***The Relationship With the Partner***

Changes in roles of these young couples can lead to conflicts. The wife can shift from potential sexual partner, mother and career woman to nurse.

TCSs may change their role in the family, losing the capability to provide economically to the family and the role in the decisions, and may downshift into an adolescent role or even childish<sup>47</sup>. In the few studies on wives, a majority reported no change in their sexual satisfaction<sup>48</sup>. Wives are focused on preserving the capability of having kids, especially if the couple have no children yet.

Moynihan<sup>40</sup> reported that 22% of the partners had psychiatric morbidity, especially anxiety and fertility concerns, while Tuinman et al<sup>49</sup> showed that spouses who had established a relationship before testicular cancer had improved QoL, compared to the reference group in the general population, and lowered the levels of response to stress. This result was in contrast with lower levels of QoL and the higher stress in spouses who had established their relation with the TCSs after treatment.

There are just three researches<sup>50-52</sup> that have specifically evaluated the subject of romantic relationships in survivors of testicular cancer, although the survivors' average age was between 32-35 years.

However, it is clear that TCSs that were romantically involved, when received the diagnosis, had a better emotional and physical adaptation to cancer, and in many cases, they have tightened the relationship with their partners<sup>50,52</sup>. In the same way, man that had a relationship at the time of cancer diagnosis and treatment reported higher levels of self-esteem, better support from family and a better mental health of those who did not have a sentimental relationship during the diagnosis<sup>53</sup>.

Even if studies highlighted that is better to have a relationship at the moment of the diagnosis of testicular cancer, other researches indicated that the diagnosis can intensify the pre-existing conflicts with the partner, or can even create new ones, bringing sometimes to the end of the relationship<sup>47,52</sup>. After the treatment, 51.5% of TCSs and 55.9% of their wives reported the emerging of problems like fear of speaking of cancer, the possibility of relapse, financial worries. Survivors felt they can't talk about these issues with their spouses, and this indicates that relationship issues centered on the difficulty to express such feelings to wives, and the misunderstandings, contribute to the end of romantic relationships between TCSs<sup>45</sup>. In these cases, TCSs change their mindset on life, avoiding in the future relational conflicts and, more in general, conflicting relationships.

TCSs without sentimental relationship during the diagnosis were concerned that testicle cancer history could have an impact on future relationships<sup>50,52</sup>. Studies indicated higher levels of cancer-related stress symptoms in the TCSs who did not have a partner at the moment of diagnosis, compared to the engaged survivors, underlying that single survivors have less stress-coping resources<sup>19</sup>. People that were single at the moment of the diagnosis had some problems that persisted also if they started a relationship after the end of the treatment<sup>54</sup>. Compared to TCSs who had a partner since the beginning, these TCSs single at the moment of the diagnosis had higher level of sexual desire, but lower levels of sexual satisfaction, both on erection and orgasm<sup>55,56</sup>.

In 2011, Carpentier et al<sup>57</sup> had finally focused on the impact of TC on romantic relationships among adolescents and young adults. Based on a sample of 21 AYA from 18 to 34 years, it confirmed the effects of relationship status to the TCSs outcomes, and the special intervention needs of unpartnered survivors. This subgroup reported more difficulties than partnered in the cancer disclosure: they felt as they were defective goods, and they believed that their illness experience could have a negative impact in their romantic relationships.

### ***Studies on Changes in Body Image***

'Because of the symbolism associated with testes, castration has the potential to cause intense concerns about masculinity and body image. The traumatic effect of (hemi) castration may be caused by fantasies, beliefs, myths and cultural values on the testes; being aware of these, it is important to understand and to anticipate the psychological consequences of (hemi) castration' (Van Basten et al)<sup>58</sup>.

As few studies focused on romantic relationships, there was the same lack of studies on the body image of TCSs. The few studies available were mainly on survivors of average age between 32-35 years.

A study<sup>50</sup> on 11 older TCSs reported they were not worried of orchiectomy, regardless if the prosthesis had been chosen or not. They did not feel less masculine, and orchiectomy was indicated as acceptable if the loss of a testicle not hindered sexual relationships.

More recent investigations have had different results, with a 16% of survivors worried of their body image after orchiectomy<sup>52</sup>. The biggest concern is that they will perceive themselves differ-

ent after the operation, and they were also worried that someone can note the missing testicle.

Rudberg et al<sup>59</sup> released that 15% of Swedes TCSs considered themselves less attractive, as well the 33% of the Japanese TCSs<sup>60</sup>. No negative impact of orchiectomy was reported, respectively, in Scottish and Italian TCSs samples<sup>61,62</sup>.

Other researches of testicular cancer survivors in the same age group (32-35 years) reported the same effects on body image. It is interesting to note that even if the 52% of the survivors expressed the feeling that their bodies changed after cancer and treatment<sup>63</sup>, the 88.2% of TCSs spouses have indicated no changes in partners' attractiveness<sup>64</sup>.

The worries on the loss of manhood and the perception of the body image are the reason of the choice of a testicular prosthesis: patients want to appear "normal", and want to "feel whole again"<sup>65,66</sup>. One year after the adoption of a testicular prosthesis, there is an increase in body and in general self-esteem, and in well-being during sexual activity, as described in a follow-up study on prosthesis that has included also adolescents<sup>67</sup>.

The testosterone level has an impact in the masculine perception of TCSs: low testosterone levels were associated with lower masculine image perception<sup>68</sup>.

These problems may be relevant for teenagers and adolescents who are living the physical changes of puberty, which bring to a new sexual sense of self, but few studies have focused on this point<sup>69</sup>.

Gynecomastia is a quite common situation in male puberty, with a prevalence of 11% among TC patients, while a 4% of males assessed for gynecomastia have an associated testicular cancer<sup>70</sup>.

In the study of Carpentier et al<sup>57</sup> on the body image problems in AYA TCSs, the reported feeling of being defective goods is probably related with the orchiectomy, which causes the feeling of having lost part of their male characteristics.

### ***Studies on Sexual Functioning***

Two systematic reviews were available on sexual functioning in TCSs<sup>71,72</sup>. Therapies for testicular cancer may bring physiological changes in sexual functioning, as well as the activation of different emotional reactions. Fatigue and general discomfort can have a relevant effect on the libido, as well as hair loss and changes in the body weight. Sexual functioning before the treatment for testicular cancer is strongly correlated with the functioning after the treatment, even if

this should be analyzed considering age and the standard prevalence of sexual problems in the population.

There were few data on sexual relationships of young males in the general population, particularly among the TCSs. In a first qualitative study, 11 TCSs aged between 30 and 35 years have been interviewed, and the 18% of them were irritated or saddened by the changes in orgasm and for the lack of the normal ejaculation<sup>48</sup>.

A later study<sup>51</sup> indicate that survivors accepted sexual dysfunction as an inevitable consequence of treatment of testicular cancer, but they were confident that after some time the ejaculation would be returned.

A different study brings to opposite conclusion, revealing few sexual problems and few or no changes in sexual activity and satisfaction in TCSs<sup>52</sup>.

Studies on changes in the sexual function after the treatment in the older survivors showed few sexual problems related to erectile dysfunction, sexual frequency, and sexual satisfaction<sup>60</sup>. Anxiety levels about the effects on sexual performance were higher during treatment than in pre-diagnosis and decreased after treatment<sup>54</sup>.

Studies on the comparison of the sexual relationships of testicular cancer survivors with a healthy control group indicated that survivors have more changes in sexual life, and the main origin was the less sexual pleasure and sexual desire<sup>59,63,65</sup>. Survivors reported also 40% erectile problems more than controls, two or more years after treatment<sup>15</sup>. Sexual problems seem to be present both in the younger (between 20 and 39 years) and in the middle age groups (between 40 and 59)<sup>73</sup>. Survivors with sexual problems are associated with the following characteristics: lower testosterone, increased age, anxiety, lack of a partner, treated with radiotherapy and chemotherapy, and/or the RPLND<sup>45,47,59,65,68,73</sup>. In 2005, a Norwegian group<sup>21</sup> reported that in TCS depression, anxiety, not being engaged in a relation and financial problems are predictors of sexual dysfunction, as in the general population.

The majority of the survivors reported the need of information on sexuality, in particular survivors with sexual dysfunction<sup>74</sup>.

Sexual dysfunction among teens under the age of 20 has not been examined.

The Carpentier study<sup>57</sup> on AYA indicated that partnered TCSs tend to delay the moment where they restart to have sex with their partner, even if they reported the feeling that their partner were supportive.

In 2012, a more recent study on 401 TCSs of Rossen et al<sup>75</sup> reported that sexual problems of TCSs (problems with sexual desire, erectile dysfunction, ejaculatory difficulties), may be connected with physical, emotional and body image issues of orchiectomy, as the retrograde ejaculation is caused by pelvic lymph node dissection. TCSs have a higher rate of erectile dysfunctions than the general male population, and at a high rate of erectile dysfunction was related negative effects in body image.

### **Studies on Fertility Problems**

The impossibility to have a child have an impact to self-esteem and the perception of manhood, and can create problems in his relationships. Some articles indicate infertility, and related psychological effects, could be an important factor of stress in the relationships, but has not been found significant relationship between infertility related to testicular cancer and marital separation<sup>40,47</sup>.

As we have analyzed in studies on romantic and sexual relationships, and in researches on body image, fertility issues have been mainly analyzed among TCSs of higher ages. More than 50% of TCSs reported as an important problem their worries about fertility after the therapy<sup>48</sup>. Some survivors deliberately decide to not think about potential fertility problems of the treatments, motivating this behavior with the fact that it is not the right moment to have children. Other survivors noted that they have not received information on the available techniques to preserve fertility, and remained with the doubt that was not really necessary to lose fertility. A later study on TCSs indicated that recently there are better results on this point, as all the subjects of the study have received information on sperm bank<sup>51</sup>.

Reduced fertility is linked to a reduction of QoL in TCSs<sup>45</sup>. The main problems that cause a reduced fertility are erectile dysfunction caused by psychosocial distress, azoospermia, and dry ejaculation<sup>76</sup>. Most of TCSs have had children after the treatment, but they have had more problems compared to the controls or the surveillance groups<sup>60,68,77,78</sup>. Survivors have the first children post-treatment after an average time of 7 years, with some variations depending from the treatment received. About 5%-22% of couples resorted to assisted reproduction techniques after treatment<sup>68,77</sup>. The quality of the semen in patients after the orchiectomy is variable, according to

the type of tumor cell: the men that had a non-seminomatous tumor had a lower average sperm count than men with seminomatous tumors<sup>79</sup>. The treatment with chemotherapy and secondary retroperitoneal tumor resection bring more often to an unsatisfied desire to have children, compared with survivors treated with chemotherapy only, surveillance, or primary RPLND<sup>75, 80-83</sup>. Cryopreservation of sperm before treatment was chosen only by the 24% of TCSs. It is interesting to underline that men who choose cryopreservation are, on average, 10 years younger and with less desire to have children at diagnosis than men who refuse cryopreservation<sup>84</sup>. Just less than 10% of the survivors uses the sperm preserved.

Kim et al<sup>85</sup> reported on 246 TCSs that these patients face greater fertility distress, have higher likelihood of fertility testing, and have more difficulties to father children, but the data suggested that they have the same possibility to father children than the other men. This research focused on nonseminoma cases, TC treated with surgery only or with surgery plus chemotherapy. This work suggested that these treatments do not permanently affect fertility, but there is also the possibility that survivors are more resolute in their attempt to have children, or that they try at a younger average age than the normal population.

## Discussion

Testicular cancer survivors have an overall quality of life that is not different from the level of the general population. Even if QoL deteriorates at the time of diagnosis and throughout treatment, afterward returns to normal levels. But survivors have to live with some chronic side effects that have an influence on the QoL, like Raynaud Phenomena, peripheral neuropathy, fatigue, anxiety, sexual and fertility problems.

The evaluation of the available cancer therapies has to consider both effectiveness and the cost. The three classical analysis approach are: cost/utility, cost/benefit, and cost/effectiveness<sup>86</sup>. Considering the latest one, should not be recommended survivorship care plans, as they take hours to be done and have no evidence of effectiveness. The most effective protocol for testicular cancer survivors seems to adopt a standard primary care, with a monitoring of early and late symptom after diagnosis and treatment of testicular cancer, including fatigue, neuropathy, Raynaud's phenomenon, anxiety, and depression<sup>87</sup>.

## Clinical Implications

An important study<sup>24</sup> indicated that the subjective perceptions of the TCSs on the impact of the disease on the current and future life were strongly related to the stress symptoms of cancer, more than the real medical situation.

The data pointed out that the result of the adaptation to cancer is strongly related to the partnered or unpartnered status at the moment of diagnosis, supporting the patient have an impact on the outcomes. Partners have an important role for TCSs who had a relation at the moment of diagnosis: they help them to change the cancer experience and support during the path, even if, according to some studies, there is the risk that cancer can create problems in the relationship. TCSs without a partner during the experience of cancer were worried of how this experience could have an influence on future relationships. There is also the possibility, analyzing all these difference among partnered and unpartnered, that the real difference is not the partner, but the fact that engaged survivors have some differences with unpartnered ones.

Researches about survivors aged between 30 and 35 have found that changes in the sexual function after the treatment of TC were not relevant, while other works reported the presence of sexual problems related to ejaculation and orgasm.

The same effect is present in the studies on the perception of the body image: some researches have failed to find relevant problems, while other works have found a relevant percentage of TCSs with problems with their bodies.

A bigger work with TCSs of higher average age highlighted the presence of relevant body image, fear of loss of virility and sexual problems, in particular a decrease in libido and sexual satisfaction, as well as an increase in erectile and ejaculatory dysfunction. More sexual dysfunctions are related to RPLND or secondary resection after chemotherapy, which are more invasive treatments. More than 50% of TCSs reported infertility or the fear of infertility.

Kim et al<sup>85</sup> suggested that TCSs (nonseminoma cases) have the same possibility to father children than the other men: the treatments do not permanently affect fertility, but there is also the possibility that survivors are more resolute in their attempt to have children, or that they try at a younger average age than the normal population.

Some results reported that changes in body image after orchiectomy could explain the variation in sexual dysfunctions both in short-term and in long-term.

Socio-cultural differences in relation to masculinity, sexuality, fertility, should be considered when the results are compared between studies.

### **Study Limitations**

Methodological aspects has not been considered as selection criteria. This could have an effect on this review, reducing the power of the findings. On the other side, researches with methodological shortcomings considered some specific issues not covered by methodologically stronger studies, and this can address future researches.

Same aspects of QoL have been evaluated with different instruments in the various researches, and this created some difficulties in comparing results. Therefore, some differences among findings could be generated by different instruments used by authors, even if they were validated measures.

### **Conclusions**

Testicular cancer have a survival rate of 96% at 5 years: for this reason, many TCSs live many years after the end of the therapy with chronic side effects that can have an impact on their quality of life.

The effects on adaptation after the therapy of the preexisting problem are not well known, as prospective studies on this topic have too small sample sizes. Additional searches on this area are justified.

There are data that support the positive effects of psychosocial, educational, and mind-body interventions for fatigue related to cancer<sup>29-33</sup>. TCSs that still see their life threatened by their experience of testicular cancer should be referred to psychosocial intervention<sup>24</sup>. The treatment of the psychological and social effects of cancer has a positive effect on the cancer therapies too, as these factors have a great influence on the immune system of the patients<sup>88</sup>. Other researches should be conducted both on preventive therapies and on ameliorative treatments for chronic side effects that persist after the therapy.

In few studies on the cognitive functioning in TCSs, it has been observed a decrease in cognitive function in the 20% of TCSs, but it

seemed to be a temporary effect. Cognitive issues have been correlated to emotional distress. Prospective studies are also recommended, for a better evaluation of cognitive functions changes in TCSs.

Continuation of the scheduled education and working life after treatment is very important for TCSs, and the employment is important for their QoL, but few studies have addressed this issue.

Sexual function and body image are often compromised during treatment. Few researches focus on fertility of testicular cancer survivors.

Other qualitative researches should consider the consequence of testicular cancer in those areas, and collecting more data on this issue will be possible to define the survivor's needs and consequent interventions. Some results<sup>75</sup> suggest further researches on the effects of counseling about body image changes after orchiectomy, as this support could produce a lower risk of permanent sexual problems in TCSs.

Investigations with methodological shortcomings gave some indications for future researches. The main one is the effects of testicular cancer on adolescents and young adults, with the consequent implications on body image and relationships. Few studies were available in this field, and most of them suffered of methodological issues, mainly of small sample sizes. One of the most relevant studies on this subgroup<sup>57</sup> underlined that additional researches on young adults and adolescents TCSs is highly recommended, recognizing the limits of the available researches, to have a proper comprehension of the effects of testicular cancer on this vulnerable subgroup.

Studies did not consider the crossing effects between the treatments of testicular cancer and the typical problems of the adolescence on youth. We have to point out that testis is the core of the masculinity, and the effects of cancer on sexual function and relationships can overlap with the aspects of adolescent developmental stage. The foundation of a sexual identity starts when the physical changes of puberty bring questions like "How much am I becoming a normal male?" or "How am I being sexually attractive?". There are many differences between a 15-year-old and a 25-year-old, and these differences affect the regulation of each patient. For this reason, it is important to adopt a developmental structure of the questions to ask adolescents and young adults TCS, and the way we assess them.

The selection of adolescents and young adults testicular cancer survivors at all stages of the

continuum of development (from puberty to adolescence up to young adults) and the follow-up of survivors during all the steps of sexual development is essential to have a full comprehension of the effects of testicular cancer in adolescents and young adults. This is essential also in the design of interventions appropriate at the moment of the life of the adolescent survivors, to achieve the best results for this population that have specific needs. This is the reason to focus more specific researches on the peculiarity of adolescents and young adults TCSs.

It is also expected that the experiences of testicular cancer will be useful for developing approaches to survival in other common cancers in adolescents and young adults, and in other testis diseases.

As few studies were available on wives, it is important to underline that partners should be included in monitoring and supporting program for survivors, to include the relational function in the intervention areas<sup>89</sup>. TCSs who were single at the moment of the diagnosis seems to not have a positive adjustment in quality of life when they start to have a partner after the treatment: a periodical review of findings along the life of the TCSs is suggested.

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#### Conflict of Interest

The Authors declare that they have no conflict of interests.

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