



IMPACT OF TESTICULAR CANCER ON SURVIVORS' QUALITY OF LIFE: SYSTEMATIC REVIEW

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Abstract – *This review collects the results of studies on testicular cancer survivors' (TCSs) Quality of Life (QoL). The analyses' results show that there is no significant difference between healthy controls and TCSs health-related QoL. There is a drop of QoL in the phases of diagnosis and treatment, but later it returns on controls level. However, TCSs have to face some chronic illness that affect QoL, like Raynaud-like phenomena, tinnitus, peripheral neuropathy, anxiety, fatigue, sexual, body image and fertility problems. These problems seem not affect QoL measures, but have relevant effects on the life of TCSs.*

Evidence shows that psychosocial, educational, and mind-body interventions are effective for cancer-related fatigue. More specifically, psychosocial interventions are important in support of TCSs, as they have seen their life threatened by cancer.

There is a correlation between the relationship status of the TCSs and the outcomes of the survivorship. Additional research is required on adolescent and young adult patients, only a few studies focus on them, and on preventive and ameliorative therapies for chronic side effects of testicle cancer treatments.

KEYWORDS: *Testicular cancer survivor, QoL, Psychological impact, Sexual impairment.*

INTRODUCTION

Testicular cancer (TC) represents between 1% and 1.5% of male neoplasms and 5% of urological tumors. The vast majority of tumors are diagnosed in young men between 15 and 40 years old.

There are two types of TC: seminoma (SGCT), that affects mainly males between 30 and 35 years old, and nonseminoma, (SSGCT) that affects males between 25 and 29 years and is more aggressive. There is also the spermatocytic seminoma, a rare variant of seminoma (0.61% of all germ cell tumors) that affects men older than 60 years. This neoplasm has some peculiarity, like the inability to metastasize (unless there are sar-

comatous changes), and has a favorable outcome only with orchiectomy¹. Another cancer type, like malignant Leydig tumors, lymphomas of the testis and sarcomas of the paratesticular region, affects elderly patients also: these cancer types are not common, but the testis is the first site of genitourinary involvement for sarcomas in the elderly².

The principal treatment for testicular cancer is surgery. To avoid the high risk of recurrence after orchiectomy, the most used adjuvant treatment is polychemotherapy with the cisplatin-based regimen. The research progress in this setting makes possible to treat a very large percentage of patients, with a consequent long potential life



expectancy, and with the related survivorship issues. So it is important to understand how the experience of diagnosis, treatment, consequences and side effects affects QoL of TCSs. QoL is a subjective experience of complete physical, mental and social health, often called health-related QoL: it is defined by a number of domains that include physical functioning, emotional functioning, role functioning, social functioning, sexual functioning, and existential problems.

In this review, we analyzed the effects of TC on several QoL domains, like mental health, sexual and romantic relationships, body image, and fertility. We used PubMed, MEDLINE, and PsycINFO databases to search published studies that met the inclusion criteria for our literature review.

QoL STUDIES

There are many studies on QoL of TCSs. A 2005 Norwegian study compared 1,409 TCSs treated between 1980-1994 vs. 2,678 men with a similar age distribution in the general population using the Medical Outcome Study 36-item Short Form Survey and the Impact Event Scale of mental symptoms caused traumatic stress³. After an 11-years median follow-up, it has not been reported a clinically significant difference in QoL. A history of treatment for TC only explained 0.3% to 0.7% of the difference in QoL. Survivors showed differences compared with controls, as increased body pain, less vitality, a poorer social function, but the small gap was not considered clinically and statistically significant. The side effects of treatment were strongly associated with a worse quality of life, with relevant side effects, especially gastrointestinal and sexual ones, more common among those who underwent retroperitoneal lymph node dissection (RPLND), radiotherapy or chemotherapy as compared to those treated with orchiectomy only.

A 2002 French study on 71 TCSs and 119 healthy controls with a median follow-up of 11 years reported no differences in health-related QoL or familiar or professional life⁴. However, compared to controls, the cases have reported less pleasure and sexual desire as well as more erectile dysfunction.

In the majority of studies, fatigue was associated with worse QoL scores in functional and symptoms scale as well as a diminished sexual life.

Kim et al⁵ released a case-control study on the members of the U.S. armed forces comparing 246 TCSs and 236 control that pointed out some long-lasting effects on the health and physical

limitations between cases, but reported that global QoL was similar to that of controls. In this study, chemotherapy was associated with lower scores on the physical component, including physical functioning and measures of a physical role, as well as a lower self-reported overall health and social functioning.

A study on 401 Danes survivors of testicular cancer conducted by Rossen et al⁶ reported that QoL among the survivors was the same as that of age-matched men in the general population, but previous chemotherapy treatment was associated with iatrogenic sequelae, such as peripheral neuropathy, ototoxicity, and Raynaud-like phenomena.

These studies indicate that global QoL is similar in testicular cancer survivors and general population with a TCSs subgroup whose quality of life is compromised in ways that appear to be directly related to their illness and treatment.

It is important to underline that many studies are based on small samples with a consequent low statistical power that may explain the lack of reported differences.

Furthermore, many studies could be lost the evaluation of long-term sequelae of treatment on quality of life because of the short time of follow-up.

Fleer et al in 2006⁷ investigated the cancer-related stress symptoms among TCSs to assess whether the objective and subjective aspects of cancer diagnosis and treatment may be associated with the post-cancer phenomena. Thirteen percent of the 354 TCSs of the study experienced cancer-related stress symptoms. Isolated cases, the less educated and the unemployed one, reported higher levels of stress: cancer-related variables did not seem relevant. The information obtained through the interviews suggested that subjective perceptions are more associated with cancer-related stress symptoms compared to the actual medical history; the perceptions do not necessarily coincide with the actual medical history or health status.

A 2013 Australian study reported that, among the 244 testicular cancer survivors who completed a survey, 66% had one or more unmet supportive care needs⁸. The average number was 4.7, and stress and relationship problems were the most relevant. It is an important highlight that there was no control group.

A Swedish study of 974 testicular cancer survivors with an average 11-years follow-up reported that 63% described a crisis linked to their diagnosis of cancer and that more than 60% of these received no counselling about stress and crisis reaction as they wished to have⁹.

MENTAL HEALTH

The cancer diagnosis and treatment is a traumatic psychological experience, and it is especially true for testicular cancer that usually occurs in an era when men do not expect to face a life-threatening illness or aggressive medical care. Studies have^{6,10-13} evaluated whether the survivors of testicular cancer have an increased risk of anxiety or depression.

A 2003 Norwegian study on 791 testicular cancer survivors reported that, compared to the general population, the survivors had a higher rate of chronic fatigue and anxiety and a lower level of depression, defined by the Hospital Anxiety and Depression Scale (HADS)¹².

Several factors have been associated with an increased risk of anxiety disorder, including younger age, economic problems, alcohol problems, sexual problems, fear of relapse, and a history of mental illness. It is possible that anxiety treatments will alleviate some of these problems, and that address some of these problems may relieve the anxiety of survivors¹³.

TCSs may have significant problems that are present also in the general population, such as unemployment, pretreatment economic worries, mental disorders, sexual and relational problems and other physical illnesses. Attributing such problems to treatment strategies and to their side effects, rather than to the general situation of many younger men in society, can be a common mistake. The influence of pretreatment issues on the adaptation after treatment is not well known due to a lack of prospective studies with suitable sample sizes¹¹.

Skaali et al¹⁴ assessed the fear of recurrence in 1,336 testicular cancer survivors at an average of 11 years after diagnosis: 24% and 7% reported "quite a bit" and "very much" fear of recurrence in the week before being surveyed. This fear is positively correlated with stress, fatigue, and neuroticism and negatively with QoL and self-esteem. The TCSs, which see their life threatened by previous testicular cancer experience, should be referred to psychosocial intervention.

An increased incidence of chronic fatigue syndrome in survivors of testicular cancer and other malignancies have documented by some studies. A Norwegian study of 1,431 survivors of testicular cancer and 1,080 age-matched male controls confirmed their previous finding of a higher rate of fatigue in survivors (17.1% vs. 9.7%)¹⁵. In addition, they reported that fatigue was associated with a lower quality of life and multiple psychological and somatic health problems.

On the other side, a French study of 71 testicular cancer survivors found very similar levels of fatigue in survivors and age-matched control

group, although the study was limited by the small sample size and the use of a one-dimensional fatigue measurement⁴.

The etiology of fatigue in cancer survivors of the testis is not well understood, and is not clearly related to treatment modalities. Fatigue in cancer survivors is affected also by some medical conditions, like hypogonadism, substance abuse, cardiac dysfunction, hypothyroidism, anemia, renal failure, relapsed testicular cancer, secondary tumors, depression or other mental illness¹⁶. There is no clear evidence to support the use of pharmacological agents¹⁷.

Randomized controlled trials of psychosocial interventions reported a mild to moderate fatigue reduction in cancer survivors, including cognitive-behavioral therapy, mind-body interventions, educational programs and yoga to manage and reduce fatigue¹⁸⁻²⁴.

BODY IMAGE AND SENTIMENTAL RELATIONSHIPS

Three studies²⁵⁻²⁷ evaluated survivors of testicular cancer engaged in romantic relationships, between 32-35 years old.

There are no study on the effect of relationships issues among adolescents and young testicular cancer survivors. Despite the lack of study focused on young survivors with testicular cancer, key themes are evident. Testicular cancer survivors who were romantically involved at the time of diagnosis describe a better physical and emotional adaptation to the cancer experience. Similarly, men in a relationship during cancer diagnosis and treatment, experience higher levels of social support, self-esteem, and overall mental health than those who did not have a romantic relationship at the time of diagnosis²⁸.

Apart from the positive effects of being involved in a relationship at the time of testicular cancer, evidence suggests that, for a subgroup of survivors, testicular tumor worsens pre-existing relational conflicts, sometimes causing the dissolutions of the relationship^{26,27,29}. Cancer experience can also cause new conflicts that ultimately lead to relationship dissolution. For example, 51.5% of survivors and 55.9% of spouses of survivors indicate, after the diagnosis of testicular cancer and its treatment, emerging problems like financial worries, fear of speaking about cancer, the possibility of relapse, and implications for the future. The relationship problems centered on the misunderstandings, and the inability to express their feelings to wives contributes to the end of the relationship between testicular cancer survivors²⁹.



Change in roles was another frequent conflict of these young couples. The wife can vary from potential sexual partner to a motherly figure or nurse for her husband. TCSs may lose their pride in providing economically to the family and in decision-making, and may regress into an adolescent role or even childish^{29,30}. Obviously is very important for TCSs to carry on their working life after treatment, but only a few studies have addressed this issue.

TCSs without a romantic relationship at the time of diagnosis express concern regarding the fact that testicle cancer history could affect future relationships^{25,27}. The survivors who did not have a relationship at the time of diagnosis report higher levels of cancer-related stress symptoms than the engaged one, suggesting that single survivors have fewer stress-coping resources. Being single at the diagnosis era appears to constitute a vulnerability that remains even when the survivors begin a romantic relationship after completing treatment. TCSs who did not have a relationship since the diagnosis time have worse satisfaction with erections and orgasms and a lower overall sexual satisfaction if compared to survivors who were having an affair since the beginning, despite higher levels of sexual desire³¹.

The body image among the survivors of testicular cancer is a few explored field, as for romantic relationships, and the works in this area focused on adult survivors between 32-35 years old. None of the researches evaluated body image problems among adolescents and young testicular cancer survivors.

A paper by Sheppard et al²⁵ studied 11 older survivors and suggested no difference regardless if patient after an orchiectomy chose to put a prosthesis or not. The participants reported not feeling less masculine, and orchiectomy was perceived acceptable if the loss of a testicle didn't hinder sexual relationships.

More recent researches²⁷ show different results, with a 16 percent of survivors that experience significant concerns of body image. In particular, survivors describe feeling anxious that other people can note the missing testicle, and feeling different from others.

Of course, the choice of a testicular prosthesis is related to body image, and the motifs were focused on fear of manhood loss, concern of self-image, and the desire to appear "normal" and "feeling whole again"^{32,33}. A follow-up evaluation on testicular prosthesis (in a sample that included a significant number of adolescents) shows a significant increase both in the body and the general self-esteem, as well as an important increase in well-being during sexual activity (evaluated only among adults)³⁴.

A research by Hassan et al³⁵ indicated that the testicular cancer survivors with low testosterone serum levels feel less masculine compared with survivors with normal testosterone levels.

These problems may be particularly relevant for male teenagers who are experiencing or have recently experienced the physical changes of puberty, which resulted in a new organization of the sexual sense of self³⁶. Based on data obtained from older men, even if few studies have focused on this topic, it is reasonable to assume that testicular cancer in younger adolescents negatively affects an emergent sexual identity and subsequent relationships.

SEXUAL FUNCTIONING AND FERTILITY

There are two systematic reviews of sexual functioning in TCSs^{36,37}. Treatment strategies for testicular cancer can cause both physiological changes in sexual functioning and the activation of emotional reactions. In general, there seems to be a high correlation between sexual functioning before and after treatment for testicular cancer.

The results should be considered in relation to age and the considerable prevalence of sexual dysfunction in the general population. There are few data available on sexual relationships of the general population of young males, and particularly among the survivors of testicular cancer. Sexual dysfunction among young < 20 years old has not been examined. Considering this, the first study of qualitative interviews with 11 testicular cancer survivors aged between 30 and 35 years old, found that 18% of the survivors have developed mood disorders caused by the changes in orgasm and the lack of the normal ejaculation³⁸.

A following study³⁹ found that the survivors were confident that the ejaculatory process would eventually return, but accepted sexual dysfunction as a necessary sequence of treatment of testicular cancer.

Studies of sexual function pre- and post-treatment among the older survivors found a moderate degree of sexual problems related to sexual satisfaction, sexual frequency and erectile dysfunction⁴⁰⁻⁴². Anxiety regarding sexual performance was more important during treatment than in pre-diagnosis, even if anxiety has decreased after treatment⁴³. Similarly, the problems associated with libido, erection, ejaculation increased significantly during treatment, and functioning did not appear to return to the full level of departure after the end of treatment.

On sexual relationships, survivors report more changes in sexual life compared to controls, mostly

due to the decrease in sexual pleasure and sexual desire^{44,45}, and reported also more ejaculatory dysfunction and erectile dysfunction than controls.

Sexual problems were present in different age groups, with multiple known issues in both the younger (20-39 years) and the middle age (40-59 years) groups, compared to healthy control group⁴⁶. The following characteristics in survivors are associated with sexual problems; increased age, lack of a partner, general anxiety, lower testosterone, have been treated with radiotherapy plus chemotherapy and/or the RPLND^{36,49}. In 2005, in a study of a Norwegian group¹¹ it was found that in TCS, as in the general population, anxiety, depression, financial problems, and not being romantically involved are predictors of sexual dysfunction.

Most of the survivors highlighted a need of information regarding sexuality, in particular, those survivors with evidence of sexual dysfunction⁴⁷.

Few studies considered wives of the TCS. It is interesting to note that 88.2% of TCSs spouses have reported no decrease in partners' attractiveness. A majority of wives reported no change in their sexual satisfaction³⁸. The main concern of wives was having kids, particularly if the couple was childless before the testicular cancer diagnosis.

The main challenge that has to face TCS is the physical impossibility to father a child that have a strong effect on the perception of his manhood, his self-esteem, and his intimate relationships. The inability to father evokes different responses at various points in the life of a man.

Fertility is another topic that has been assessed mainly among testicular cancer survivors of higher ages, as in the case of romantic and sexual relationships and in research on body image. The concern of fertility after the therapy is a relevant problem for more than half of the samples of testicular cancer survivors²⁶. Some survivors deliberately choose to ignore potential post-treatment fertility issues, indicating, as the first reason, the fact that it is not the good moment to start a family. Many participants regret that has not received enough information about fertility preservation treatments available, and that fertility may have been unnecessarily sacrificed. However, a subsequent study on testicular cancer survivors suggested progress in this area; all the participants have received recommendations on sperm bank⁴⁸.

Reduced fertility is related to the diminished quality of life among the testicular cancer survivors. The main causes of reduced fertility are azoospermia, erectile dysfunction caused by psychosocial distress, and permanent dry ejaculation^{49,50}. Although the majority of survivors have

had children, many report more difficulties after the end of treatment than the general population or individuals under surveillance^{33,51,52}. The average time from diagnosis to the birth of the first child after treatment is around 7 years, but varies depending on the treatment, and with the use of assisted reproduction techniques in approximately 5%-22% of couples who try to conceive after treatment^{33,51}.

DISCUSSION

The QoL of TCSs, as a group, is not measurably different from that of the general population.

However, survivors have to manage a variety of chronic side effects affecting the QoL, including fatigue, peripheral neuropathy, Raynaud Phenomena, tinnitus, anxiety, and sexual and fertility problems.

The most appropriate course of action for testicular cancer survivors is to provide standard primary care, with a proper monitor of early and late sign or symptom following diagnosis and treatment of testicular cancer.

It is evident from data that the presence or absence of a partner at the time of diagnosis of cancer of the testis is critically important to determine the results of adaptation to cancer. Among the testicular cancer survivors who were romantically involved at the time of diagnosis, partners play an important role by helping them to change the cancer experience and providing the necessary support, although some evidence suggest that cancer can put a strain in the relationship. Testicular cancer survivors who face the experience of cancer without a partner have specific problems: the main one is the worry of how disclosure of their history of cancer can affect future relationships. Analyzing these differences based on having a partner, it is also important to consider the possibility that it is not having a partner that makes TCSs resistant to the negative effects of cancer and its treatment, but rather the fact that the survivors who have a relationship are systematically different from survivors who do not have a relationship.

On sexual relationships and body image in survivors of testicular cancer, the literature is quite equivocal. Some papers about survivors aged between 30 and 35 suggest the presence of sexual dysfunctions related to orgasm and ejaculation, while other studies have found that sexual function changes after the diagnosis and treatment of testicular cancer are irrelevant. In the same way, some studies have not found significant body image issues, while other researchers



found a significant percentage of testicular cancer survivors actually showing problems with their body. A comparatively bigger work with older testicular cancer survivors reports the presence of significant sexual and body image problems.

Fertility of testicular cancer survivors is the focus of only a small part of the research, even if relatively consistent. Studies suggest that more than half of survivors experience infertility or the fear of infertility. Many survivors have also the fear that fertility may have been sacrificed in vain.

It is important to underline that, when the results were compared between studies, socio-cultural differences in relation to masculinity, sexuality, fertility should be considered.

There are few researches specifically dedicated to the examination of testicular cancer in adolescents and young, as evidenced in 2010 by Carpentier et al⁵³. Most current research does not consider the potential interactions of testicular cancer and its treatments with the developmental tasks of adolescence and youth (for example, exploration of identity and development of intimate relationships). The situations of 15-year-old and 25-year-old men differ greatly, and consequently differ the mechanisms involved in the regulation of each patient, both during and after the treatment of testicular cancer.

CONCLUSIONS

Testis cancer is the most common cancer among males in late adolescence and early adulthood, and the 5-year relative survival rate is 96%, so there are many testis cancer survivors who live along with chronic toxicities, that may impair their quality of life. Gilligan in 2015 noted that there is evidence in support of psychosocial, educational, and mind-body interventions for cancer-related fatigue⁵⁴. TCSs should be referred to psychosocial intervention when they see their life threatened by their experience of testicular cancer. Additional research is required on preventive and ameliorative therapies for chronic side effects of testicle cancer treatment.

During the treatment body image, sexual function and fertility are often compromised, so it is important to focus on them. There is a need of additional qualitative research to explore the effects of testicular cancer on those domains. The collection of such data will allow the identification of survivors' needs, its further development and testing interventions that address those needs.

Only few researches focus on wives. Carpentier et al⁵³ highlighted that monitoring and supporting of survivors should be extended to partners in tandem with the survivors themselves, ensuring

optimal individual and relational function. Moreover, for individuals who were single at diagnosis time, building a relationship after the treatment looks to be not sufficient for a positive adjustment in general mood, social support and quality of life, so we strongly recommended a monitoring of results throughout the life of the survivor.

The influence of pretreatment issues on adaptation after treatment is not well known due to a lack of prospective studies with sufficient sample sizes. Additional searches are justified.

The last point that is important to underline is the lack of specific researches on teens and young cancer survivors. In the crucial years of adolescence and youth, a diagnosis of testicular cancer may have an important influence on timing and/or nature of a successful transition into adult life. It is important to have a careful documentation of the consequences of cancer in this particularly vulnerable population, to design interventions that have to be administered at key moments during the life of these young survivors. For this reason, additional and more specific researches on adolescents and young testicular cancer survivors are requested.

ACKNOWLEDGEMENTS

We acknowledge: Progetto ONCONET2.0 – Linea progettuale 14 per l'implementazione della prevenzione e diagnosi precoce del tumore alla prostata e testicolo – Regione Campania, Italy

CONFLICT OF INTERESTS:

The Authors declare that they have no conflict of interests.

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