REVIEW

Talking about sex: erectile dysfunction in the oncology patient

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Abstract

Cancer-related diagnosis and treatments can profoundly affect every aspect of an individual's life. The negative impact on the sexual sphere can manifest with onset or worsening of the most frequent male form of sexual dysfunction, that is the erectile dysfunction (ED), with an estimated incidence ranging from 40 to 100% in patients living with cancer. Cancer and ED are strictly related for many reasons. First, the psychological distress, the so-called 'Damocles syndrome', afflicting cancer patients contributes to ED onset. Second, all cancer therapies can variably lead to sexual dysfunction, even more than the disease itself, having both direct or indirect effects on sexual life. Indeed, alongside pelvic surgery and treatments directly impairing the hypothalamus–pituitary–gonadal axis, the altered personal-body-image frequently experienced by people living with cancer may represent a source of distress contributing to sexual dysfunction. It is undeniable that sexual issues are currently neglected or at least under-considered in the oncological setting, mainly due to the subjective lack of preparation experienced by healthcare professionals and to scant information provided to oncological patients on this topic. To overcome these management problems, a new multidisciplinary medical branch called 'oncosexology' was set up. The aim of this review is to comprehensively evaluate ED as an oncology-related morbidity, giving new light to sexual dysfunction management in the oncological setting.

Key Words
- erectile dysfunction
- oncology
- cancer
- sexual dysfunction

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Introduction

The fight against cancer has largely influenced the scientific research in recent decades, leading to important achievements in both diagnostic and treatment paths and significant increase in patients' survival. Cancer diagnosis and treatments impact on every aspect of patients' life, including the sexual sphere (Albers *et al.* 2020). Albeit historically underestimated, an increasing literature is available on erectile dysfunction (ED), representing the most frequent sexual disorder in men (Corona *et al.* 2006, Fisher *et al.* 2009, Salonia *et al.* 2012*b*). According to the DSM-5, ED is defined as a 'marked difficulty in obtaining or maintaining a penile erection until completion of sexual activity or a marked decrease in erectile rigidity on almost or all (75–100%) occasions of sexual activity'

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(Vahia 2013). Considering ED etiology, ED is classically classified in organic, psychogenic or mixed forms, while recently the terms 'primary organic' and 'primary psychogenic' ED have been suggested (Salonia *et al.* 2021). Many epidemiological studies tried to evaluate ED incidence/prevalence in different oncological clinical setting, but a homogeneous reliable result has not been obtained so far. Indeed, these studies are highly heterogeneous, differing in (i) ED definition, (ii) tools used to evaluate sexual dysfunction (interviews, self-administered questionnaires, structured interviews, single questions and surveys) and (iii) population characteristics (Eardley 2013, McCabe *et al.* 2016). Thus, not surprisingly, the overall ED incidence in patients living with cancer widely fluctuates from 40% to 100% (Salter & Mulhall 2021). However, it is undeniable that ED represents an epidemiologically clinically relevant comorbidity in oncology. In this setting, the ED pathogenesis is multifactorial, depending on (i) the cancer histotype, (ii) the type and duration of cancer-related treatments, (iii) the patient age at the time of treatment and (iv) the presence of other comorbidities (Sadovsky *et al.* 2010, National Cancer Institute 2022, Almont *et al.* 2019). Indeed, oncological patients recognize an ED organic component, due to the adverse effect of cancer-related treatments, together with a psychological factor, due to the psychosexual burden of the oncological condition (Rosendal *et al.* 2008) (Fig. 1).

Historically, sexual dysfunction is scantily investigated and discussed in oncological setting, as a result of conversational difficulties by both clinicians and patients themselves (Flynn *et al.* 2012, Carter *et al.* 2018). While clinicians generally claimed lack of time, lack of training, insufficient skills, feelings of embarrassment or discomfort (Carter *et al.* 2018, Albers *et al.* 2020, Santi *et al.* 2022*a*), oncological patients experienced difficulties in the doctor–patient communication, particularly when the topic is perceived as uncomfortable and/or embarrassing (Carter *et al.* 2018, Santi *et al.* 2022*a*). On the other hand, some

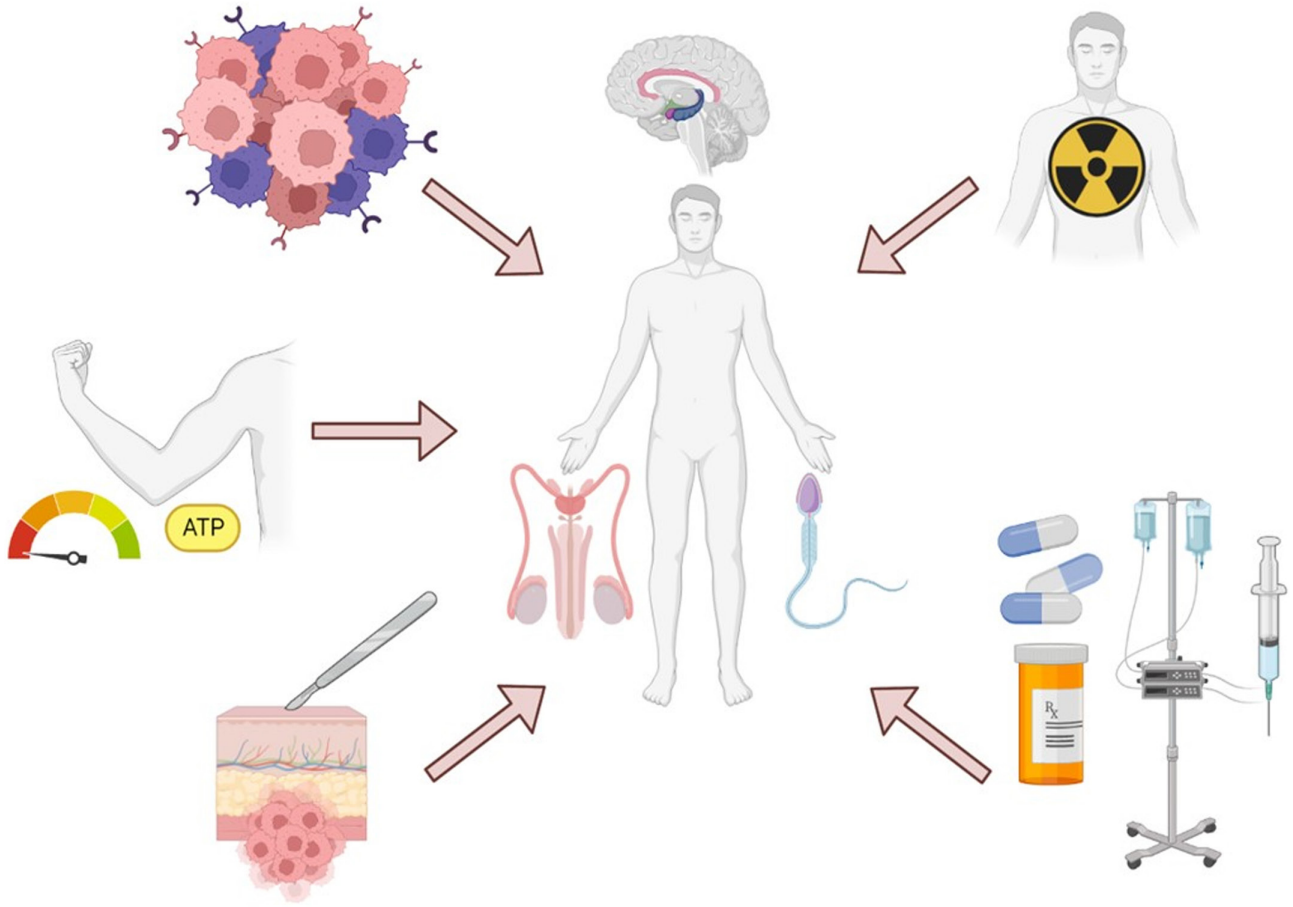

Figure 1
Schematic representation of the main factors affecting male sexuality in oncological setting. ATP, adenosine triphosphate. A full color version of this figure is available at https://doi.org/10.1530/ERC-22-0401.

oncological patients consider sexual dysfunctions foreign to the oncological field; therefore, they avoid discussing these issues with the oncologist (Carter *et al.* 2018). In this complex 'unsaid scenario' to which both physician and patient contribute, sexual health is often simply underestimated (Dizon *et al.* 2014, Carter *et al.* 2018).

Considering the high prevalence of ED in oncological patients, the heterogeneity of ED etiology/management and the sexual issue-related communication problems, there is the need to comprehensively evaluate this potential cancer-related comorbidity, collecting the most relevant findings. With this in mind, the main purpose of this review is to elucidate how and to what extent cancer can negatively impact the male sexual sphere. This overview does not claim to transform the oncologist into an andrologist but has the hope to make clinicians more sensitive to sexual health issues in such complex patients, giving them instruments to at least recognize sexual dysfunctions and possibly activate proper multidisciplinary management.

Cancer diagnosis and erectile function

Overall, cancer incidence and mortality are rapidly growing worldwide. These trends reflect both aging and growth of the population as well as changes in the distribution of risk factors associated with socioeconomic development, including, diet, lifestyle, obesity and environmental exposures (Sung *et al.* 2021). Interestingly, also the incidence of early-onset cancers (defined as cancers diagnosed in adults <50 years of age) in the breast, colorectum, endometrium, esophagus, extrahepatic bile duct, gallbladder, head and neck, kidney, liver, bone marrow, pancreas, prostate, stomach and thyroid has increased in multiple countries since the 1990s (Ugai *et al.* 2022). According to the GLOBOCAN estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer (Sung *et al.* 2021), the incidence rate for all cancers combined was 19% higher in men (222.0 per 100,000) than in women (186 per 100,000) in 2020. Particularly, in men, prostate cancer is the most frequently diagnosed cancer in 112 countries, followed by lung cancer in 36 countries and colorectal cancer and liver cancer each in 11 countries (Sung *et al.* 2021).

Cancer diagnosis has a huge and dramatic impact on patients' quality of life (QoL), obviously representing a psychological distress source (Alabdaljabar *et al.* 2021). This cancer-related distress is so evident and strictly connected with the underlying disease that it has been given a specific name, i.e. the so called 'Damocles syndrome' (Alabdaljabar *et al.* 2021). Indeed, Damocles lived with a sword hanging over his head, which could at any time drop and kill him. Similarly, individuals affected by cancer live with a constant state of threat that could be compared to that sword (Tan *et al.* 2021). Accordingly, previous studies investigated the prevalence of depression in cancer patients, reporting a high incidence, ranging up to 38% for major depression and up to 58% for depression spectrum syndromes. Although the definition of depression remains heterogeneous, any patient living with cancer has to deal with a higher rate of depression compared to the general population (Massie 2004). Alongside depressive symptoms, emotional distress embraces a large spectrum of nuances among the anxiety depressive disorder, ranging from loneliness to anger (Rice *et al.* 2021). Thus, it should be more appropriate to refer to 'psychosocial distress' in oncological patients (1999), which could be detected already at early stages of the diagnosis, due to the climate of uncertainty and fear for the future (Tan *et al.* 2021).

Psychological distress negatively impacts on QoL as a whole and therefore also on sexual habits (Sadovsky *et al.* 2010, Almont *et al.* 2019). Bandini *et al.* evaluated more than 2000 cancer male patients consulting for sexual dysfunction using the structured interview on erectile dysfunction (SIEDY) and the Middlesex Hospital Questionnaire (MHQ). The depressive symptoms domain at MHQ was positively related to ED onset and to SIEDY item 3, evaluating the psychogenic ED component (Bandini *et al.* 2010). Accordingly, a meta-analysis confirmed the strict correlation between depression and ED, highlighting an increase in ED risk by 39% in patients with depression and an ED incidence 1.39-fold higher in patients with depression rather than those without depression (Liu *et al.* 2018). However, the ED–depression connection is 'circular', since ED, in turn, increases the risk of depression, with a depression incidence 2.92-fold higher in patients with ED than in those without (Liu *et al.* 2018). Two mechanisms have been proposed to clarify the underlying link between these two conditions. First, patients with depression tend to think negative and to be less confident, turning into an anxious status which further affects erectile function (Makhlouf *et al.* 2007, Liu *et al.* 2018). Second, depression could promote an excess of catecholamine production that counteract the penile cavernosal muscle relaxation, which, in turn, could represent the first step in ED onset (Liu *et al.* 2018, Goldstein 2000). Moreover, the cancer diagnosis itself seems to have a detrimental effect on sexual function,

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as reported in a Danish nationwide register study including men diagnosed with prostate cancer, compared to age-matched subjects without cancer (Duun-Henriksen *et al.* 2022). Comprehensively, prostate cancer patients showed a higher rate of new prescription of ED drugs in the 3 years after diagnosis compared to control group (Duun-Henriksen *et al.* 2022). This result could simply be explained by prostate surgery complications and/or anti-androgen drugs used in prostate cancer management. Unexpectedly, this difference reaches a seven-fold higher amplitude immediately after diagnosis, giving relevance to the 'psychological heart quake' occurring after cancer diagnosis more than to the cancer-management sequelae (Duun-Henriksen *et al.* 2022).

Moreover, cancer patients could experience body uneasiness, emotional and physical distress and concerns for the treatment side effects, which contribute to the deterioration of relationship and intimacy with the partner (Sadovsky *et al.* 2010, Schover *et al.* 2014, Almont *et al.* 2019), leading to sexual dysfunction onset and/or persistence. The intimate relationship can be affected also when the oncological patient is the female partner. In particular, in female patients, painful intercourse is the most frequently reported sexual issue (Jensen *et al.* 2004). Other sexual problems include loss of sexual desire, vaginal lubrication dysfunction and limited ability to reach sexual arousal and orgasm (Wenzel *et al.* 2002, Aerts *et al.* 2009).

Noteworthy, this burden can affect the male subject even when he is not the patient but the caregiver. Indeed, since cancer involves all the family members (Woźniak & Iżycki 2014), male partners of oncological patients may experience emotional distress leading to sexual issues (Iżycki *et al.* 2016). In this context, the male partner could experience feelings of unattractiveness, fear to start sexual activity and loss of libido, up to the occurrence of ED (Andersen *et al.* 1997, Iżycki *et al.* 2016).

However, independent of its severity and of its etiology, sexual dysfunction can be felt either as a little trouble or as a significant problem affecting the QoL (Stanford *et al.* 2000). Thus, sexual life should be investigated starting from the moment of the diagnostic work-up of the malignancy, to fully support patients through the delicate and generally long oncological path.

Cancer treatment and erectile function

Cancer-related treatments could negatively impact sexual life, even more than the disease itself. Sexual functions could be differently impaired by cancer therapy, depending on the organ(s) affected and on the type of treatment(s) applied (Katz & Dizon 2016). In a survey conducted to explore the prevalence of reproductive health problems in cancer patients, 49% of male respondents complained about ED onset after cancer treatment, while 30% of men had problems in reaching orgasm (Huyghe *et al.* 2009). Accordingly, although 80% of men at cancer diagnosis were sexually active, this percentage decreased to 60% after treatment start (Huyghe *et al.* 2009). Interestingly, a sample of 74 testicular cancer survivors felt that surviving the treatments was both a triumph and a trade-off, with about half of the cohort complaining permanent sexual dysfunction (Rieker *et al.* 1985).

Most treatment-related sexual health problems are connected to both surgical approaches in pelvic area and to those treatments impairing the hormonal system which controls sexual function (Schover 2006). However, not only genitourinary surgery could induce sexual dysfunction, since also surgeries not directly involving sexual organs could damage sexual health in an indirect way. Indeed, every kind of surgery may leave an indelible mark on patient's confidence and/or psychological frailty, since even scars can be a constant reminder of the illness (Ofman 2004). Cancer treatments could indeed affect sexual function throughout an alteration in the masculine self-image, having detrimental psychological effects, potentially impacting on sexuality (Cecil *et al.* 2010). Indeed, altered personal-body-image can lead to feelings of shame and even avoidance of self-looking in the mirror, as it was shown in men carrying enteral ostomies for colorectal cancer (Manderson 2005). Moreover, alterations in weight (gain or loss), inability to powerfully work out, decreased body hair, gynecomastia and genital shrinkage are described in oncological patients, leading to a feeling of unattractiveness (O'Shaughnessy & Laws 2009, Katz & Dizon 2016). In this delicate context, where men experience their 'diminished' body as a source of distress (Hedestig *et al.* 2005), the ED onset or worsening could not be a surprise.

Surgery for cancer and erectile function

Although surgery is, when possible, the first-line approach to treat cancer, its side effects must be considered. Considering sexuality, the disruption of neurovascular pathways involved in sexual function during pelvic surgery can lead to devastating consequence on sexual life (Ofman 2004). Indeed, penile erection is both a central psychoneuroendocrine and a peripheral neuro-vasculo-

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tissutal event, starting with a sexual/erotic stimulus, which leads to blood supply to the sinusoidal spaces of the corpora cavernosa and the corpus spongiosum (Giuliano 2011). The capacity to obtain and maintain an erection depends on many mechanisms, such as penile innervation, the vascular tree and the biochemical signaling in the corpora cavernosa. Nerve injury can lead to the inability to reach penile erection, while vascular damage can negatively impact the ability to maintain it (Voznesensky *et al.* 2016).

The innervation of the penis is both autonomic and somatic. The former consists of sympathetic and parasympathetic systems, linked into the cavernous nerves that enter the corpora cavernosa and the corpus spongiosum, regulating penile erection, orgasm and tumescence (Voznesensky *et al.* 2016). In humans, cavernous nerves and several arteriovenous branches form the neurovascular bundle (NVB), which runs along the posterolateral border of the prostate gland and extends laterally to the lateral pelvic fascia and pararectal fascia and posteriorly to the dorsal layer of Denonvilliers' fascia, that in turn separates the prostatic capsule from the rectum (Costello *et al.* 2004). The NVB somatic component derives from the pudendal nerve and is responsible for both penile sensitivity and contraction of bulbocavernosus and ischiocavernosus muscles (Dean & Lue 2005).

Pelvic surgery could damage penile innervation throughout direct and indirect actions, leading to acute or chronic nerve injury. Acutely, surgery could lead to nerve damage due to intraoperative pulling, clamping, dissection, freezing, electrocautery, excision and irradiation (Jiang *et al.* 2021). Peripheral nerve injury can be classified into three types with different degrees of nerve disruption and different abilities to regenerate (Seddon 1943). Nerve injury is the final result of neurapraxia, axonotmesis and neurotmesis (Seddon 1943, Sunderland 1978). Neurapraxia means that the nerve is intact but cannot transmit impulses due to segmental demyelination (Campbell 2008). In axonotmesis, the axon is damaged or destroyed, but most of the connective tissue frameworks is still present (Campbell 2008). Finally, in neurotmesis, the nerve trunk is completely disrupted, as well as the connective tissue framework that is at least distorted (Campbell 2008).

Nerve injury causing sexual dysfunction can be caused by different pelvic surgical approaches of many disease involving the pelvis, affecting the prostate gland, bladder, colon and rectum (Zippe *et al.* 2006), penis and testes (Voznesensky *et al.* 2016).

Prostate surgery deserves an in-depth analysis talking about ED, both for epidemiological and for anatomical reasons. Indeed, prostate cancer is the second most frequent malignancy diagnosed in men (Rawla 2019). The gold standard for clinically localized disease is radical prostatectomy (RP), consisting in removing the entire prostate gland with its capsule intact and seminal vesicles (Ju *et al.* 2021). Many surgical approaches have been developed since the first open RP technique, passing from perineal and retropubic open approaches to laparoscopic and robotic assisted techniques (Millin 1947, Reiner & Walsh 1979, Young 2002). Despite the large discrepancy in describing ED prevalence rate after RP, many studies concluded that nearly 85% of the RP-treated patients developed ED (Schover *et al.* 2002, Nelson *et al.* 2013, Resnick *et al.* 2013). The refinement of surgical techniques has allowed to develop a nerve-sparing RP, aimed at maximally preserving NVB without compromising cancer control (Walsh *et al.* 1983, Lepor 2005). However, when the disease extent allows this procedure, negative sequelae on sexual function are not set to zero, since ED could develop as a consequence of stretching, heat or direct trauma to the nerve (Lima *et al.* 2021). Although the identification and the preservation of pelvic autonomic nerves are important to avoid further morbidity, it still remains challenging for surgeons. A first meta-analysis based on 31 records on different RP techniques showed that, in nerve-sparing RP, ED was observed in 10–46% of patients after 12 months and in 6–37% after 24 months from surgery (Ficarra *et al.* 2012). However, robot-assisted RP was associated to a reduction of 23.6% in ED onset compared to retropubic RP (Ficarra *et al.* 2012). Accordingly, a recent systematic review compared 6135 patients who underwent robot-assisted RP to 7617 men treated with laparoscopic RP, showing that erectile function recovery rate at 12 months was higher for robot-assisted RP group (OR: 2.16; 95% CI 1.23–3.78; $P = 0.007$) (Carbonara *et al.* 2021). After surgery, the penile erection recovery occurs in about 50% of cases within the first 3 months (Montorsi *et al.* 2008). Then, the recovery would be expected until 24 months after surgery (Sivarajan *et al.* 2014). Accordingly, in a large long-term longitudinal trial, a 36.5% of penile function recovery was detected in the second year after surgery, while a negligible recovery rate was recorded in the third year (Mandel *et al.* 2017). With this in mind, post-prostate surgery ED could be virtually considered irreversible after 24 months (Mandel *et al.* 2017).

Typically, erectile function recovery does not occur spontaneously, but penile rehabilitation should be started as soon as possible after surgery (Liu *et al.* 2017, Lima *et al.* 2021). Many studies confirmed the relevance of precocious rehabilitation in improving the overall erectile

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function, although an agreement on the best treatment strategy has not been achieved (Sari Motlagh *et al.* 2021). Mulhall and colleagues evaluated two approaches of penile rehabilitation (rehabilitation starting <6 months vs rehabilitation starting >6 months after RP). A significant 2 year improvement in erectile function as per the International Index of Erectile Function (IIEF) was detected in the early group compared to the delayed group (Mulhall *et al.* 2010). Similarly, Jo *et al.* treated patients subjected to prostate surgery with sildenafil 100 mg twice weekly, comparing early (treatment started immediately after urethral catheter removal) and delayed (3 months after nerve-sparing RP) approaches. At 12 months of follow-up, the proportion of patients recovering erectile function was significantly higher in the early group than in the delayed group, suggesting that early rehabilitation is more efficient (Jo *et al.* 2018). A very recent meta-analysis on 22 randomized clinical trials concluded that among 16 different penile rehabilitation approaches, an early initiation of 100 mg sildenafil once daily after nerve-sparing RP was associated with a significant higher erectile function recovery (Sari Motlagh *et al.* 2021). This result suggests that a chronic assumption of high-dose phosphodiesterase type 5 inhibitor (PDE5-i) could be efficient in improving erectile function, while the PDE5-i on-demand administration failed to achieve this target (Sari Motlagh *et al.* 2021). In this setting, statistically significant efficacy was demonstrated also for pelvic floor muscle training, which might be considered either in combination therapy with 100 mg sildenafil regular dose or alone when PDE5-i is contraindicated (Sari Motlagh *et al.* 2021). Vacuum device is another potential non-pharmacological, non-invasive approach during penile rehabilitation. This approach creates a negative pressure within the penis, leading to a passive repletion of the corpora cavernosa, regardless of nerve disturbance (Lehrfeld & Lee 2009, Lima *et al.* 2021). The use of vacuum device in penile rehabilitation after neuropraxia has been proven to be efficient in animal models, improving ICP/MAP ratio, decreasing hypoxia-inducible factor-1 α and tumor growth factor-ß1 levels, collagen deposition and smooth muscle cell apoptosis and increasing the level of endothelial nitric oxide synthase and α-smooth muscle actin (Yuan *et al.* 2009, 2010, Qian *et al.* 2016). However, in humans, vacuum device was efficient only in combination with PDE5-i and not as a single treatment (Raina *et al.* 2006, Basal *et al.* 2013).

Penile rehabilitation relying on PDE5-i is one of the most used, since it is easy to use and efficient. Of note, in order for PDE5-i to exert its therapeutic effect, the integrity and the proper function of tissue effectors, i.e. nerves, blood vessels and cavernous tissues, is mandatory (Cai *et al.* 2020). In this context, nerve injury or vascular damage caused by RP, or radiation of the pelvis leading to the death or fibrosis of cavernosal smooth muscle cells, nerve cells and vascular smooth muscle cells, results in a lack of efficacy of PDE5-i (Barazani *et al.* 2015, Chiang & Yang 2019). Indeed, if the damage is great, patients suffering from ED will be classified as non-responders to PDE5-i (Cai *et al.* 2020).

Low-intensity extracorporeal shockwave therapy is one of the most recent therapeutic non-invasive approaches of penile rehabilitation, developed with the aim to restore the physiological mechanism of penile erection (Vardi *et al.* 2012). A pilot study in Sprague–Dawley rats undergoing early shockwave therapy after bilateral cavernous nerve injury reported angiogenesis, tissue restoration and nerve regeneration, with a direct effect of Schwann cell proliferation (Li *et al.* 2016). Also, 1 year later, in the same animal models, the activation of local progenitor cells after shockwave therapy was detected (Li *et al.* 2016). A recent study in men used the expanded prostate cancer index composite to evaluate patient sexual function after robot-assisted RP, evaluating early and delayed intervention with shockwave therapy (Inoue *et al.* 2020). A significant amelioration in sexual function in patients treated with shockwave therapy was detected at 6, 9 and 12 months after surgery, whereas there was no difference between early or delayed approach (Inoue *et al.* 2020). However, the intensive application of shockwave therapy as a penile rehabilitation method is still not supported by strong evidence.

When neuropraxia remains after 2 years from surgery, the most efficient clinical approach remains the intracorporeal injection (ICI) of vasoactive drugs, such as prostaglandin E1 (PGE-1) (Santi *et al.* 2022*b*). The injection of a vasoactive agent within the penis corpus cavernosum leads to trabecular smooth muscle relaxation, arterial dilation, blood filling and finally penile erection (Kim *et al.* 1991, Rajfer *et al.* 1992, Hew & Gerriets 2022, Santi *et al.* 2022*b*). ICI should be performed just before the sexual intercourse, and its effects last for about 2 hours after the injection, usually having tolerable side effects (Zorgniotti & Lefleur 1985, Lima *et al.* 2021, Santi *et al.* 2022*b*). Recently, new routes of administration were developed, and PGE-1 could be used also intraurethrally (Lima *et al.* 2021). However, this approach has been poorly evaluated in patients with neuropraxia-induced ED (Raina *et al.* 2007, McCullough *et al.* 2010, Lima *et al.* 2021).

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In this setting, the future in terms of novel therapeutic options is represented by stem cell therapy (SCT) (Wani *et al.* 2022). SCT shows immunoregulatory, immunosuppressive and regenerative properties, and several evidences in animal penile tissues highlighted their ability to differentiate into endothelial, neuronal or smooth muscle cells, repairing structural damages (Yiou 2017, Wani *et al.* 2022). Some authors investigated the SCT efficacy on ED due to bilateral cavernous nerve injury, both in animals (29 studies) and in humans (3 studies) (Wani *et al.* 2022). In animal models, SCT was efficient at improving intracavernosal pressure (ICP) and ICP/mean arterial pressure (MAP) ratio, leading to relevant histological and molecular changes in penile tissues (Wani *et al.* 2022). In humans, SCT improved erectile function evaluated through IIEF and erection hardness score, as long as urinary continence was not compromised (Koehler *et al.* 2012).

Finally, irreversible post-RP ED could be treated with penile prosthesis (Baas *et al.* 2020). The surgical implantation of penile prosthesis could be suggested to those patients who are not suitable or who are non-responders to other treatments or who prefer a definitive solution (Antonini *et al.* 2016). In the oncological field, the surgical approach could be preferred since the penile prosthesis implant could be performed together with the surgical treatment of stress urinary incontinence, addressing both problems at the same time. Penile prosthesis implantation carries a high grade of satisfaction among patients (Bettocchi *et al.* 2010, Salonia *et al.* 2012*a*, 2021, Chierigo *et al.* 2019). Nevertheless, also for penile implant surgery, there is a non-negligible psychological component, and so structured psychosexual counseling may help both patients and their partners (Pisano *et al.* 2015, Salonia *et al.* 2021). Thus, it is important to advise the patient, suggesting all possible options and choosing together the most suitable treatment for the patient himself.

Radiotherapy and erectile function

Cancer irradiation remains a relevant therapeutic option for many types of cancer, with both neoadjuvant and/or adjuvant purposes. The advent of brachytherapy (BT) and the use of radiotherapy (RT) techniques like intensity-modulated RT, image-guided RT and proton therapy limited toxicity and improved post-radiation outcomes (Challapalli *et al.* 2012, Incrocci 2015, Madan *et al.* 2020). However, RT is not free of adverse events also for sexual life (Morris & Haboubi 2015), including ED, with an estimated incidence from 24% (BT) to 45% (external-beam RT) (Robinson *et al.* 2002, Madan *et al.* 2020). However, a recent meta-analysis evaluating over 26,000 men RT treated for prostate cancer demonstrated that ED occurs independently of the RT type applied (BT vs external-beam RT) with increasing incidence during each year of follow-up (Gaither *et al.* 2017). Moreover, the sexual damage induced by RT seems even more relevant than the surgical damage, as suggested by a recently randomized controlled trial on 1643 patients with clinically localized prostate cancer (Donovan *et al.* 2016). Indeed, while both RT and RP groups showed a decrease of erectile function 6 months after treatment beginning, the worst scores on erectile function were recorded in the RT group (Donovan *et al.* 2016). Moreover, the RP group showed the highest recovery rate of erectile function after 6–12 months of follow-up (Donovan *et al.* 2016).

The mechanism by which RT can alter sexual function seems to be mainly related to arterial damage, although an RT-related nerve damage should be considered (Akbal *et al.* 2008). In particular, pelvic RT could affect the prostatic neurovascular plexus, both directly or indirectly throughout the release of pro-inflammatory cytokines, which is directly related to the extension of the irradiated tissue. This inflammatory cascade could lead to a severe acute neurovascular toxicity (Ramirez-Fort *et al.* 2020) and accelerated atherosclerosis of the small cavernosal vessels (Levine *et al.* 1990). Preclinical models demonstrated decreased conduction times of the pudendal and cavernosal nerves after radiation (Nolan *et al.* 2015, Mahmood *et al.* 2017). Even if the evolution of techniques reduced the overall RT toxicity, there are still no conclusive data on the most appropriate RT procedure to preserve sexual functions, and its specific influence on ED remains unclear (Akbal *et al.* 2008). Comprehensively, it can be said that both RT and BT increase the risk of developing ED in men with cancer.

Hormonal treatment and erectile function

Testosterone is involved, directly or indirectly, in several mechanisms mediating penile erection and detumescence, and it has a role both in organic and in intrapsychic dimensions of sexual dysfunction. Moreover, testosterone controls male sexual behavior and male attitudes and is involved in mood regulation (Corona & Maggi 2010). Thus, not surprisingly, a decrease in testosterone levels, both medically and surgically induced, is demonstrated to negatively impact QoL as a whole and be detrimental to sexual health (Sadovsky *et al.* 2010). In an oncology

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setting, several treatments, especially pharmacological, could interfere with the hypothalamic–pituitary–gonadal axis functionality. Among these, androgen deprivation therapy (ADT) is largely proposed in patients with prostate cancer with the aim to inhibit the pro-proliferative stimulus exerted by androgens on the prostate gland (White *et al.* 2015). Indeed, the reduction of testosterone levels is necessary in prostate cancer, since testosterone has a role in the growth of cancer cells (van Poppel & Nilsson 2008). However, it should be noted that the interplay between testosterone and testosterone-sensitive tissues in terms of oncological risk is not so linear (Michaud *et al.* 2015, Morgentaler & Rhoden 2006, Shin *et al.* 2010, Sansone *et al.* 2017). Accordingly, some studies highlighted a paradoxical increase of prostate cancer risk in patients with low endogenous testosterone levels (Morgentaler & Rhoden 2006, Shin *et al.* 2010, Michaud *et al.* 2015). As proposed by Morgentaler and Traish in their 'Saturation Model' (Morgentaler & Traish 2009), the prostate gland is highly sensitive to androgen concentrations at lower limits, with little or no effect for higher testosterone concentrations, explaining the high prevalence of prostate cancer in elderly people (Morgentaler & Traish 2009). However, these observations do not justify the indiscriminate use of testosterone replacement therapy in prostate cancer (Sansone *et al.* 2017), which is not recommended in patients with active prostate cancer but could be considered in selected cases of low-risk cured prostate cancer (Isidori *et al.* 2022).

The androgen action inhibition could be achieved through different ways (White *et al.* 2015), i.e. suppressing the secretion of testicular androgens or combining it with the androgen receptor blockade (Pagliarulo *et al.* 2012), or through bilateral orchiectomy (Desmond *et al.* 1988). Bilateral orchiectomy is the quickest and most effective approach to rapidly low circulating testosterone levels (Desmond *et al.* 1988). However, it is an invasive and irreversible approach, mainly considered for patients who need an immediate androgen deprivation or for those who cannot tolerate side effects of hormonal treatments (Desmond *et al.* 1988, van Poppel & Nilsson 2008). The effect of orchiectomy on sexual function has been extensively evaluated, showing a variable degree of ED after surgical testis removal, together with a reduced libido, arousal and orgasm (Jonker-Pool *et al.* 1997).

Among hormonal strategies, the most used drugs are long-acting luteinizing hormone-releasing hormone (LHRH) agonists (Hogenhout *et al.* 2022), such as triptorelin, goserelin and leuprolide . Acting as agonists, the first injection provokes a transient increase in luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to a 'testosterone surge', which in turn produces a transient increase in tumor growth with a worsening in the clinical status, known as the 'clinical flare' (van Poppel & Nilsson 2008). This status is characterized by bone pain, ureteral and bladder obstruction, spinal cord compression and cardiovascular death due to hypercoagulation status. For these reasons, concomitant therapy with anti-androgens for at least 2 weeks decreases the incidence of these complications (Bubley 2001). After the transient increase in testosterone levels, a biochemical castration is reached within 2–4 weeks, reaching testosterone levels below 50 ng/dL (1.7 nmol/L) (Klotz *et al.* 2008, Hogenhout *et al.* 2022). To counteract the flare status, LHRH antagonists (such as degarelix) have been developed, since they immediately lead to a decrease in LH, FSH and testosterone serum levels and causing an iatrogenic hypogonadotropic hypogonadism (Klotz *et al.* 2008). Although LHRH antagonists avoid flare status and its consequences, they are not free of adverse effects, including decreased libido, ED and hot flushes, albeit to a lesser extent than LHRH agonists (Abufaraj *et al.* 2021). LHRH agonists and antagonists can stop androgen secretion by testicles, but cells in other parts of the body, including adrenal glands and prostate cancer cells themselves, can still release male hormones, which can promote cancer growth. In this setting, non-steroidal anti-androgens do not suppress testosterone secretion but its action, and they can be used both in monotherapy and in combination with drugs active at central level to achieve a combined androgen blockade (Iversen *et al.* 2000). The first-generation antiandrogens (bicalutamide, nilutamide and flutamide) exclusively target androgen receptor translocation to the nucleus and prevent downstream signaling, while second-generation antiandrogens (enzalutamide, apalutamide and darolutamide) improve upon this mechanism, whereas abiraterone acetate prevents androgen biosynthesis (Rice *et al.* 2019). The main advantage of non-steroidal anti-androgen monotherapy is the bone protection and apparently a better preservation of libido and overall physical performance (Smith *et al.* 2004, Wadhwa *et al.* 2009).

Irrespective of the drugs used, continuous ADT leads to loss of libido and subsequently to ED. Potters *et al.* showed that erectile function in patients treated for localized prostate cancer was worse when ADT was added to RT (Potters *et al.* 2001). In particular, regression analysis demonstrated that neoadjuvant ADT was a strong predictor of ED ($P = 0.0001$) (Potters *et al.* 2001). A recent single-center, cross-sectional, questionnaire-based study

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on 76 patients who received ADT for more than 6 months showed that only one patient had erections sufficient for penetrative intercourses. Noteworthy, 29 patients were still interested in sexual activity after ADT, meaning that other factors, such as psychological and emotional factors, may play a relevant role (Fode *et al.* 2020).

In general, erectile function is affected when testosterone levels are about 10% below of the normal range with a dose-dependent impairment (Mazzola & Mulhall 2012). Some authors suggested that free testosterone, rather than total testosterone is mainly associated with erectile function (Ahn *et al.* 2002, Martinez-Jabaloyas *et al.* 2006). However, testosterone may not be the only androgen involved in erectile function, and the potential role of 5α-dihydrotestosterone and adrenal androgens has been suggested (Mazzola & Mulhall 2012).

Despite the high incidence of the ADT-related ED, this sexual dysfunction responds well to most pharmacological treatments for ED (Sadovsky *et al.* 2010). Moreover, the recovery of erectile function, even if delayed or incomplete, is possible after discontinuation of short-term ADT (Wilke *et al.* 2006, Li *et al.* 2015).

Chemotherapy and innovative anti-neoplastic drugs

Despite poorly investigated, chemotherapy seems to play a role in sexual dysfunctions development. Indeed, chemotherapeutic agents such as cisplatin, vincristine and vinblastine can cause both vascular toxicity and neurotoxicity, leading to altered ejaculation and/or infertility (van Basten *et al.* 1997). Alkylating agents can lead to primary hypogonadism that in turn causes loss of libido, ED and decreased semen volume. Finally, the graft vs host disease can provoke penile curvature and ED (Sadovsky *et al.* 2010).

A relatively recent new cancer treatment is represented by molecular targeted therapies (MTTs), which interfere with specific proteins involved in tumorigenesis (Baudino 2015). Within this class, many drugs were developed with an anti-angiogenetic aim against solid tumors, changing the management of previously poor-prognosis tumors (Bessede *et al.* 2011). As well as for other drugs, MTTs also show target-related adverse effects. However, their impact on sexual life has been poorly studied (Bessede *et al.* 2011). A study on 35 male patients on MMT for advanced renal cell carcinoma (51% on sunitinib, 31% on sorafenib and 17% on mTOR inhibitors) showed an IIEF score at 30–60% of the maximum for each domain, with the majority of patients falling into the 'severe ED' group. Accordingly, the ED severity was higher in MMT cohort compared to age-matched controls (Bessede *et al.* 2011). The negative effects of antiangiogenic therapy (mostly sunitinib, pazopanib, everolimus and tivozanib) on erectile function were confirmed in a prospective, longitudinal study on 37 patients with locally advanced or metastatic renal carcinoma, with a significant IIEF-5 decrease after 12 weeks of therapy start (Marcon *et al.* 2021).

Recently, a new class of anticancer drugs was developed, shifting the therapeutic target from cancer cells to host immune cells, in order to enhance the body's immune system to fight cancer (Ruggeri *et al.* 2019). These drugs, called immune checkpoint inhibitors, represented a milestone in modern cancer treatment (Stelmachowska-Banas & Czajka-Oraniec 2020). However, the same mechanism by which immune checkpoint inhibitors exert their incontrovertible efficacy is the same mechanism responsible for the onset of immune side effects that can affect various biological structures, including endocrine organs and systems (Castinetti *et al.* 2019). Sexual life of patients undergoing immune checkpoint inhibitor therapy can be affected by the onset of hypophysitis, which can be the consequence of the use of cytotoxic T-lymphocyte antigen 4 inhibitors (such as ipilimumab), especially if in combination with programmed cell death protein 1 inhibitors (such as nivolumab) (Caturegli *et al.* 2016, Stelmachowska-Banas & Czajka-Oraniec 2020). Indeed, together with no specific symptoms, hypophysitis can result in multiple hormone deficiencies affecting also the pituitary–gonadal axis, leading to hypogonadotropic hypogonadism that can in turn manifest with ED (Hattersley *et al.* 2021). Although many phase III clinical trials with immune checkpoint inhibitors evaluated the QoL as a secondary endpoint, sexuality remains a neglected topic (Garutti *et al.* 2021). A pilot cross-sectional study (Salzmann *et al.* 2021) involving 25 males currently or previously treated with immune checkpoint inhibitors did not report any impairment of sexual function or sexual activity. Interestingly, only one patient reported a light restriction of erectile function. These data seem to suggest a limited toxicity of immune checkpoint inhibitors on sexuality, but larger and prospective studies are awaited to draw any conclusion.

To conclude, considering the overall improved survival of cancer patients due to new and better cancer treatments, it is important not to overlook the possible side effects that can affect sexuality and QoL.

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Oncosexology

The improvement of survival rate in cancer patients increased the need to evaluate QoL (Hughes 2000, Enzlin & Clippeleir 2011). In this context, sexual life is an important factor pertaining to the overall well-being of an individual. Thus, the development of new strategies of care in the oncological setting is required.

Oncosexology refers to a new multidisciplinary approach, aiming to address sexual issues in cancer patients (Enzlin & Clippeleir 2011, Salter & Mulhall 2021). Many healthcare providers, such as physicians, nurses and psychologists, must be involved in oncosexology (Salter & Mulhall 2021). It is important that healthcare professionals initiate an open dialogue after cancer diagnosis, accompanying patients into the diagnostic therapeutic work-up. Indeed, talking about sexuality in the early stages of treatment improves sexual outcomes (Enzlin & Clippeleir 2011, Incrocci 2011).

In order to educate both healthcare professionals and population for the improvement of communication about sexuality (Incrocci 2007), the American Cancer Society published guidelines for cancer patients for the management of sexual dysfunction, assessing that talking about sex with partners and cancer-care team must be the first step. Actually, surveys in the field showed that patients and their partners claim for information about sexual effects of the disease and its treatments, but they complained for a lack of information, support and suggestions provided by healthcare professionals (Enzlin & Clippeleir 2011). The healthcare professionals, in turn, do not feel skilled or confident enough to talk about sexual issues and are worried to ask too intimate questions. (Gamel *et al.* 2000, Wilmoth 2006).

A recent cross-sectional, questionnaire-based study performed on a cohort of 165 volunteer healthcare professionals showed that only the 32% of the cohort was specialized in sexology. However, it is worth noting that more than two-thirds of responders (75.8%) wish additional training in oncosexuality, meaning that there is a real need and will for physicians to acquire new skills (Almont *et al.* 2019).

Bearing this in mind, it is of utmost importance to train both healthcare professionals and patients to talk about sexual problems from the beginning of the therapeutic alliance, helping the feeling that every aspect of their life is salient and deserves some time. Last but not least, this multidisciplinary management requires the consideration of known, modifiable risk factors for sexual dysfunction, such as smoking, alcohol abuse and lack of physical exercise (Sansone *et al.* 2022). The efficacy of lifestyle intervention in reaching a good general, reproductive and sexual health is worldwide accepted (Sun *et al.* 2017, Sansone *et al.* 2018), and the oncological patient is no exception.

Conclusion

In conclusion, cancer diagnosis and its treatments can profoundly affect the bio-psycho-social basis of sexuality. Among sexual dysfunction, ED can be the results or multiple different mechanisms that can act independently or not and are not necessarily related to genitourinary malignancies (Salter & Mulhall 2021). In this context, it is important for the patient to be adequately informed, supported and encouraged from skilled and trained healthcare professionals. For this reason, it is mandatory that oncosexology, which means a multidisciplinary, full integration of sexual rehabilitation, becomes the routine in the oncological supportive care (Enzlin & Clippeleir 2011).

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