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Erectile dysfunction and cancer: current perspective

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Erectile dysfunction (ED) is one of the major but underreported concerns in cancer patients and survivors. It can lead to depression, lack of intimacy between the couple, and impaired quality of life. The causes of erectile dysfunction are psychological distress and endocrinal dysfunction caused by cancer itself or side effect of anticancer treatment like surgery, radiotherapy, chemotherapy and hormonal therapy. The degree of ED depends on age, pre-cancer or pre-treatment potency level, comorbidities, type of cancer and its treatment. Treatment options available for ED are various pharmacotherapies, mechanical devices, penile implants, or reconstructive surgeries. A complete evaluation of sexual functioning should be done before starting anticancer therapy. Management should be individualized and couple counseling should be an integral part of the anticancer treatment.

Keywords: Erectile dysfunction, Neoplasm, Surgery, Radiotherapy

Introduction

Cancer diagnosis and its management lead to physical and emotional distress in patients. Sexual dysfunction is one of the common problems encountered in these patients which can occur due to direct or indirect pathways. Sexual dysfunction can be in the form of erectile dysfunction (ED) and ejaculatory dysfunction such as decreased or absent semen. Chemotherapy, radiation, hormonal therapy and surgery all can lead to erectile dysfunction. ED has been widely described after prostate cancer treatment. Incidence of post-treatment ED in prostate cancer can vary from 24% (brachytherapy alone), 40% (brachytherapy plus external beam radiotherapy [EBRT]), 45% (EBRT alone), 66% (nerve-sparing radical prostatectomy [RP]), 75% (non-nerve sparing RP), and 87% for cryosurgery [1]. Recently in a population based study patient reported sexual outcome after different types of prostate cancer treatment were reported [2]. Sexual dysfunction after treatment was related to pre-treatment potency, age and type of treatment. No difference in sexual function score was noted in EBRT and brachytherapy at 2 years. Compared with EBRT alone, EBRT with androgen deprivation therapy (ADT) and RP (with or without nerve sparing) was associated with higher incidence of sexual dysfunction. Incidence of ED in cancer patients has been shown in Table 1.

Besides disease control, restoration of quality of life (QoL) is also very important due to increase number of cancer survivors. Evaluating ED using valid questionnaires and management of ED is one of the important aspects of QoL which is particularly important in developing countries where people are not comfortable discussing about their sexual issues. Age and degree of ED before the diagnosis and mode of treatment play an important role in predicting the post-treatment ED. For this review, we searched PubMed data using words "cancer related erectile dysfunction", "erectile dysfunction in cancer", "sexual dysfunction in genitourinary malignancies," and "psychosocial outcome of cancer survivors". All studies reporting erectile dysfunction in cancer patients and survivors were reviewed. Around 60 studies were screened and data from 54 studies that reported sexual dysfunction or erectile dysfunction in cancer was included in the review.

Table 1. Erectile dysfunction in cancer (original)

S. No.	Study	Year	No. of patients	Age (yr)	Primary tumor	Treatment modality (% of patients)	RT dose (Gy)	Probability of sexual function preservation	Incidence of ED	Remarks
1	Mullins et al. [2]	2019	835	63.7 (mean)	Prostate	EBRT (23%) Brachytherapy (15%) EBRT + ADT (12%) RP + NS (41%) RP + non-NS (10%)	-	EBRT (14%–70%) Brachytherapy (14%–70%) EBRT + ADT (8%–52%) RP + NS (4.7%–45.3%) RP + non-NS (5%–34%)	-	RT alone results in the best preservation of sexual function
2	Resnick et al. [8]	2013	1655	55–94	Prostate	Prostatectomy (70.3%) EBRT (29.6%)	-	-	Prostatectomy (46.7%) EBRT (39.7%)	Patients underwent prostatectomy were more likely to have erectile dysfunction at 2 years and 5 years
3	Hekal et al. [12]	2011	45	31–64	Urinary bladder	RC + NS (46.6%) RC + non-NS (53.4%)	-	RC + NS (spontaneous erection, 57.8%) RC + non-NS (no spontaneous erection)	RC + NS (42.2%) RC + non-NS (100%)	Gradual progressive improvement was observed in vasogenic competence in NS cases
4	Zippe et al. [13]	2004	49	57.8 (mean)	Urinary bladder	RC + NS (33%) RC + non-NS (67%)	-	RC + NS (spontaneous erection, 50%) RC + non-NS (spontaneous erection, 3%)	RC + NS (50%) RC + non-NS (97%)	-
5	Loh-Doyle et al. [14]	2020	151	66.1 (median)	Urinary bladder	RC (100%)	-	-	Loss of penile length, ≥2.54 cm (55.1%)	RC can result in significant sexual dysfunction, as the significant loss in penile length
6	Tal et al. [20]	2014	76	29 (mean)	Testicular cancer	Orchiectomy (100%) EBRT (26.3%) Chemotherapy (47.3%) RPLND (19.7%)	-	-	Loss of ability to maintain erection (84%)	ED after treatment appear to have normal erectile haemodynamics on penile duplex Doppler and all responded to treatment
7	Capogrosso et al. [21]	2016	143	42 (median)	Testicular cancer	Orchiectomy (100%) EBRT (32.9%) Chemotherapy (81.8%) RPLND (42.8%)	20–24	-	24.5%	Adjuvant therapy was not associated with impaired recovery of normal sexuality
8	Duran et al. [22]	2015	56	27–79	Rectum	APR (19.6%) LAR (80.4%) RT (80.4%)	-	-	21.8%	Lower 1/3 of tumor location, age younger than 60 years, RT, and stoma were risk factors for ED
9	Pokharel et al. [25]	2019	26	26–75	Colorectal	NACRT (100%) APR (7.6%) LAR (92.3%)	-	Sexual desire (57.7%)	ED (42.3%) Not able to attain erection (38.4%) Unable to ejaculate (34.6%)	-
10	van der Wielen et al. [27]	2007	268	68 (median)	Prostate	EBRT; standard vs. dose escalation 3DCRT in both arms	68 vs. 78	Sexual desire (41%)	38%	In sexual function, no significant differences were found between the two dose-arms

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Table 1. Continued

S. No.	Study	Year	No. of patients	Age (yr)	Primary tumor	Treatment modality (% of patients)	RT dose (Gy)	Probability of sexual function preservation	Incidence of ED	Remarks
11	Pinkawa et al. [31]	2011	156	55–83	Prostate	EBRT (3DCRT vs. IMRT)	70 vs. 76	Patients with erections firm enough for sexual intercourse; 32% vs. 65%	86% vs. 70%	Dose escalation with IMRT is not associated with increased sexual morbidity
12	Mangar et al. [33]	2006	51	47–78	Prostate	EBRT; standard vs. dose escalation Conformal RT	64 vs. 74	Remained potent (23.5%) Reduced potency (43.1%) Impotent (33.3%)	78%	Penile bulb dose; D_{90} > 50 Gy significant risk of erectile dysfunction
13	Fisch et al. [34]	2001	21	72 (mean)	Prostate	EBRT; 3DCRT	67.3–87.3	Remained potent (38%) Reduced potency (38%) Impotent (24%)	62%	70 Gy to more than 70% volume of penile bulb, high risk of ED
14	Bruner et al. [36]	2015	1006	50–88	Prostate	EBRT (3DCRT vs. IMRT)	79.2 vs. 79.2	No statistically significance differences were observed between two groups in erectile function scores	-	Penile bulb dose does not correlate with ED
15	Thor et al. [38]	2015	501	-	Prostate	EBRT; 3DCRT (60.2%) RP + 3DCRT (39.8)	70	Suggested that presence of naturally occurring erections were crucial for erectile and orgasmic function	41%	Strong association found between ED and doses to total penile structure than penile bulb
16	Zelefsky et al. [53]	2006	561	≥60	Prostate	EBRT; ADT + IMRT vs. IMRT	81	Sexual desire (51%)	ADT +IMRT (57%) IMRT alone (43%)	Addition of short-term ADT significantly increased the risk of ED in these patients
17	Pinkawa et al. [54]	2009	123	53–84	Prostate	EBRT ± PDE-5i	70.2–72	Ability to have an erection (70%) Erections firm enough for sexual intercourse (53%)	30%	Age and diabetes are risk factors for post EBRT ED

RT, radiotherapy; ED, erectile dysfunction; EBRT, external beam radiotherapy; ADT, androgen deprivation therapy; RP, radical prostatectomy; NS, nerve sparing; RC, radical cystectomy; RPLND, retroperitoneal lymph node dissection; APR, abdominoperineal resection; LAR, low anterior resection; NACRT, neoadjuvant chemoradiotherapy; 3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; PDE-5i, phosphodiesterase 5 inhibitors.

1. Psychological and emotional impact of ED

The loss of erectile ability leads to depressive symptoms, lack of sexual satisfaction and general happiness in life. Men who fail to achieve erection tend to lose confidence [3]. Depression and sexual avoidance in turn can affect the intimacy level and relationship of the couple. Studies have reported that ED after curative treatment is one of the common causes of depression in prostate cancer patients.

2. Mechanism of penile erection

Blood supply to the penis occurs via branches of external and internal pudendal arteries. Penile innervations are derived from pudendal and cavernous nerves. Pudendal nerve is responsible for somatic motor and sensory nerve supply. Cavernous nerve is a part of autonomic nervous systems and includes sympathetic and parasympathetic fibres. It runs in crus and corpora of the penis and regulates the blood flow during erection and flaccid state [4].

An erection begins with sensory and mental stimulation. Sexual arousal leads to relaxation of smooth muscles of the penile arteries which increases the blood flow to penis. This leads to rigidity and thus erection of the penis. While returning to flaccid state, penile muscles contract and increase the venous outflow and decrease the length and girth of the penis. The ability to attain and sustain erection depends on integrity of vascular supply and nerve supply.

Causes of ED in Cancer

Causes of ED in cancer patient are follows: (1) emotional, physical and financial stress; (2) pain, anxiety and disturbed body image; (3) damage to penile nerve and vessels during surgery, radiotherapy (RT) and chemotherapy; (4) ADT; (5) penectomy for cancer penis; Nitric oxide (NO) pathway plays an important role in achieving erection. NO is the principle agent responsible for relaxation of penile smooth muscles and thus erection. Radiation leads to damage and inflammation of cavernous nerves, leading to decreased production of nitric oxide synthase and NO which subsequently leads to ED [5]; Fibrotic changes in blood vessels and atrophy of corpora cavernosa due to surgery and RT lead to reduced blood flow in erectile chamber, making it less expansile for blood accumulation during erection.

1. ED in surgery

Prostate cancer is one of the most common cancers in males worldwide. Due to widespread use of prostate-specific antigen (PSA), increased numbers of young and healthy men are diagnosed with prostate cancer as compared to past. RP leads to excellent survival and is one of the established treatments for early stage prostate cancer. With excellent disease control, potential side effects of surgery are a growing concern out of which ED is one of the important focuses [6]. Wide range of ED (14%–90%) has been reported after RP due to methodological differences in various studies [7]. Resnick et al. [8] published data from the Prostate Cancer Outcomes Study (PCOS) comprising of 1,164 patients who underwent prostatectomy and 491 patients who received RT. These patients were followed up for 15 years. Incidence of ED at 2 years (78.8% vs. 60.8%) and 5 years (75.7% vs. 71.9%) was higher in surgery as compared to RT. However, the difference was not significant at 15 years. It has been thought that new surgery techniques, i.e., robotic surgery may reduce other side effects, its role in reducing ED is not clear. Nerve sparing surgery in prostate cancer may reduce the incidence of ED. Despite the sparing of cavernous nerve in most of the prostate surgery, it tends to get some sort of bruising and trauma during the surgery which can take up to 2 years to heal. During this time period, men may have difficulty in achieving natural erection which can lead to degeneration of penile tissue and structural alterations [9]. Thus only 9%–40% patients resume their sexual function after surgery [10,11]. Hekal et al. [12] noted veno-occlusive dysfunction after nerve sparing and non-nerve sparing surgery, which was significantly improved 1 year after nerve-sparing group and spontaneous erections returned after 12 months.

ED can be commonly seen after surgery for bladder cancer. Zippe et al. [13] followed 49 preoperatively sexually active men for 47 months who underwent radical cystectomy (RC) for bladder cancer. At least some degree of ED was found in 86% of the patients after surgery.

Perception of reduced penile length has been seen after RP and RC. Loh-Doyle et al. [14] analysed sexual function in 151 patients who underwent RC for bladder cancer and observed that 55% patients perceived loss in penile length and out of the 55% patients, approximately half of them reported a shortening of 1 inch or more. Erectile dysfunction has also been seen after transurethral resection of bladder tumor (TURBT) and after urinary diversion procedure due to presence of a stoma and sense of disturbed body image [15]. Surgery for penile cancer can also significantly jeopardise sexual function. Scarberry et al. [16] found that after partial penectomy half of the patients can still have normal erection. Gulino et al. [17] reported that after 6 months of conservative surgery (glansectomy) for localized penile cancer, 73% had spontaneous rigid erections.

Testicular cancer is commonly seen in young patients and thus determining sexual function is even more important. After treatment of testicular cancer, 12%–40% of patients can have ED due to hormonal imbalance including low testosterone, orchidectomy

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or retroperitoneal lymph node dissection [18,19]. Tal et al. [20] reported that 84% patients had loss of sustained erection after treatment although 24% patients had transient ED even before the diagnosis. In one study it was found that out of every four patients, one patient develops ED, out of which 10% will have severe ED [21].

Colorectal cancer (CRC) is another common malignancy in males. Surgery for these cancers may also impair sexual function due to hypogastric and autonomic nerve injury [22]. After CRC surgery, sexual dysfunction can range from 10% to 50%, depending on the assessments used [23,24]. In one study, 18% patients had decreased ejaculation and erection after abdomino-pelvic resection (APR) or low anterior resection (LAR) [22]. A recent study observed that 11 out of 20 patients (42.3%) had sexual dysfunction after APR/LAR for colorectal cancer [25].

2. Radiotherapy-induced ED

Radiotherapy-induced erectile dysfunction (RIED) occurs due to higher dose to penile bulb, crura and neurovascular bundle especially in bladder and prostate cancer. Incidence of RIED has been mentioned above. RIED generally take over 1 year to develop, gradually increases and becomes constant after 3 years [26]. It depends on pre-treatment potency level, RT dose to the penile bulb and use of other concomitant treatment modalities. In a dose escalation study of prostate cancer, incidence of newly diagnosed ED was reported as 36% and 38% at 2 and 3 years post-RT [27]. Recent studies have shown that approximately 30%–40% patients develop ED after RT [26] as compared to 60%–70% in earlier studies [28]. In one study, ejaculatory disturbance (decreased or absent semen, pain during ejaculation and hemospermia) have been reported in 2%–56% after RT while dissatisfaction with sex life can vary from 25% to 60% and lack of sexual desire can vary from 12% to 58% of the patients with prostate cancer patients after RT [28]. Decreased intensity of orgasm has also been reported. In one study of 262 prostate cancer patients of age ≤60 years, 73% patients reported either no or only minimal decline in ED after 2 years of RT as compared to baseline [29]. Over the past few years, there has been decrease in the incidence of adverse effects of RT including ED due to increased use of brachytherapy as compared to the past [30] and newer and sophisticated RT techniques like intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), and proton therapy although data is insufficient pertinent to ED. In one study, it was reported that sexual function was more retained at 1 year in IMRT arm (30%) as compared to three-dimensional conformal radiotherapy (3DCRT) arm (14%) [31]. Siglin et al. [26] showed that decline in sexual function occur maximum after 2 years of RT and then starts stabilising and occasionally can return to baseline.

3. Radiotherapy dose

Till date, there is no definite data to suggest the co-relation of RT dose and ED. Relating ED to RT alone is difficult as multiple other factors also contribute to ED like smoking, diabetes mellitus, hypertension, concomitant treatment, etc. Earlier in a study by RTOG group, Roach et al. [32] observed that median penile bulb dose of >52.5 Gy is responsible for high risk of ED. In a dose escalation study for prostate cancer, Mangar et al. [33] reported that risk of impotency was significant higher in those whom penile bulb received 50 Gy or more dose of RT.

Few studies have observed that ED and penile bulb dose show a dose volume relationship. Fisch et al. [34] reported ED in 0%, 80%, and 100% of patients when dose received by 70% of penile bulb volume (D_{70}) was 0–40 Gy, 40–70 Gy, and >70 Gy, respectively. Similarly, Mangar et al. [33] observed that if the dose received by 90% of penile bulb volume (D_{90}) is 50 Gy or more, it significantly increases the risk of ED. Wernicke et al. [35] reported that dose received by 30%, 45%, 60%, and 75% volume of penile bulb (D_{30}, D_{45}, D_{60}, and D_{75}, respectively) are also important parameters to define the risk of ED.

QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) has defined that penile bulb may not be a critical structure for ED but may act as surrogate for yet to identified critical structures for ED and suggested a mean dose of not more than 50 Gy to 95% volume of penile bulb. In a recently published preliminary patient reported outcomes in RTOG 0126 trial, at 2 years, no significant difference in sexual function was reported in 3DCRT (high penile bulb dose) or IMRT (lower penile bulb dose) arm [36]. However It is recommended that mean RT dose to penile bulb should be kept <50 Gy and it is important to limit the D_{70} to 70 Gy and D_{90} to 50 Gy [37].

Based on the patient reported outcomes, Thor et al. [38] identified three domains of sexual dysfunction in males after radiotherapy for prostate cancer, namely ED, orgasmic dysfunction, and pain. He studied the involvement of various penile structures by radiotherapy in ED and observed that other than penile bulb, RT dose to corpora cavernosa (CC) and total penile structure is also important to maintain intact erectile function.

4. Chemotherapy and hormonal therapy

Chemotherapy and hormone therapy also play a role in ED. Several chemotherapeutic agents are known to cause ED by causing neural and vasculature damage. These are mainly cisplatin, vincristin and vinblastin. Wiechno et al. [19] found that out of 269 men with testicular cancer, 40%, developed ED after platinum based chemotherapy. Similarly 20.8% (out of 202 men) patients with testicular cancer developed ED after platinum based chemotherapy [39]. ED

has been also observed after high-dose chemotherapy with melphalan, cyclophosphamide or etoposide along with total body radiotherapy in haematological malignancies [40].

ADT is commonly used in the treatment of prostate cancer which is known to cause lack of sexual interest. Loss of libido usually develops within the first several months, and ED follows. In one study sexual inactivity started 6 months after starting ADT [41]. Couples should be counselled before ADT is started. Recovery of erectile function is possible after discontinuation of short-term ADT. However, recovery may be delayed or incomplete [42]. One study has reported that prostate cancer patients who received ADT, are 23% more likely to develop depression due to ED [43].

Management of ED

Age of patient and his sexual partner is one of the most important factors while deciding the treatment plan.

1. Oral and injectable pharmacotherapy

Phosphodiesterase-5 inhibitors (PDE-5i)/sildenafil citrate (Viagra) is highly an effective and most commonly used oral agent as a first line therapy used in clinical practice [44]. Injury during surgery may lead to hypoxia in penile tissue. PDE-5i increase the release of NO resulting in smooth muscle relaxation and increased blood flow in corpus cavernosum. Sildenafil has an onset of action time, approximately 30 minutes to 1 hour. Cavernous nerve initiates the required erectile pathway so that PDE-5i can be effective. Thus, the effectiveness of these drugs is limited by severity of cavernous nerve injury. Although PDE-5i is the first line treatment for ED, 30%–40% patients do exhibit little or no response to it [45]. Prophylactic role of sildenafil citrate in prostate cancer patients was shown by Zelefsky et al. [46]. Patients were randomized to receive either sildenafil daily 50 mg or placebo during and 6 months after RT. In sildenafil arm, significant improvement in ED was noted at 6, 12, and 24 months [46]. Common side effects of sildenafil are headache, facial flushing, stuffy nose and gastrointestinal upset. PDE-5i use is contraindicated in patients taking nitrates for chest pain. It should be used carefully in those who are on alpha-blockers.

Alprostadil (synthetic form of prostaglandin E1 [PGE1]), phentolamine (vasodilator) or papaverine (smooth muscle dilator) can be used for intracavernosal injection [47]. Combination of the drugs is used if one drug fails. As it is a relatively invasive procedure for the patients, it is generally used as a second line therapy in well counselled and motivated patients once treatment becomes refractory to oral agents. Side effects are related to injection site pain and fibrosis.

2. Intraurethral PGE1

Alprostadil (MUSE) suppository is inserted in urethra via a small applicator. It creates a vaso-dilatory effect on penile blood vessels and thus helps in penile erection [48].

3. Vacuum erection device

It is a battery powered device and can be used in conjunction with a PDE-5i to help maintain and sustain an erection. It consists of cylinder with a pump and constriction ring. Cylinder and pump create vacuum that helps in penile erection while constriction ring helps in maintain erection. Although it is an inexpensive approach, mechanical failure is a problem. Other problems with this device are infection and penile discomfort.

4. Penile prosthesis implants

Inflatable or non-inflatable penile implants is an effective safe and durable treatment option for ED and are generally used once patient becomes refractory to other treatment options. In one study it was reported that only $<5\%$ men underwent penile implantation after RP [49]. Wilson et al. [50] found that 10- and 15-year revision-free survival was 68.9% and 59.7%, respectively after first time implant.

5. Vascular reconstruction

Vascular reconstruction in the form of arterial vascularisation, venous arterialization or venous stripping improves blood flow to corpora cavernosa and thus helps in achieving and maintaining erection [51]. This procedure is generally reserved for those who do not respond to oral or injectable pharmacological therapy.

6. Low-intensity extracorporeal shock wave therapy

It is a non-invasive newer technology for the treatment of ED. It acts by inducing localized angiogenesis, and pushing blood to the penis [52]. It is safe and can be used in men with failed medical therapy.

Conclusion

Cancer diagnosis and its treatment can lead to variable degree of sexual dysfunction in patients ranging from loss of libido to complete loss of erection. As sexual issue is a generally less discussed topic, ED is one of the underreported issues in cancer patients. ED can lead to depression and impaired quality of life. Thus, it is very important to evaluate ED before and after treatment. For men who have ED or in those when ED is predictable, couple counselling should be an essential component of the cancer management. Method of sexual rehabilitation should be individualised for each patient.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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