


REVIEW ARTICLE

A systematic review of radiation-induced testicular toxicities following radiotherapy for prostate cancer

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Abstract

Background: Prostate cancer is the second most common malignancy in men in the world, and radiotherapy is used as a standard treatment modality for this cancer. Although this treatment modality effectively kills prostate cancerous cells, it unavoidably irradiates the organs/tissues that are away from the treatment site. In this regard, radiation-induced testicular toxicities following prostate radiotherapy can affect sexual function, reproduction, and quality of life in cancer survivors. This review summarizes the available data on testicular exposure to radiation during prostate radiotherapy and the consequences on testicular function.

Methods: To illuminate the radiation-induced testicular toxicities following prostate radiotherapy, a systematic search was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline in PubMed, Web of Science, Scopus, Embase, and clinical trials electronic databases up to September 2018. According to a set of prespecified inclusion and exclusion criteria, 31 eligible articles providing data on testicular function following radiotherapy in patients with prostate cancer were included in the study.

Results: According to the different radiotherapeutic techniques used for prostate cancer treatment, the total tumor dose and scattered testicular dose values were ranging from 36.25 to 78.00 Gy and 0.06 to 6.48 Gy, respectively. Luteinizing hormone and follicle-stimulating hormone levels after prostate radiotherapy were significantly higher in comparison with the pretreatment levels. Around 60% of the studies showed that testosterone levels after prostate radiotherapy were significantly lower than the pretreatment levels. Furthermore, erectile dysfunction (ED), as an adverse side effect resulting from prostate radiotherapy, was reported and this complication is significantly correlated with lower satisfaction with sexual life. Testicular atrophy following prostate radiotherapy has also been observed and its frequency in patients with prior prostate radiotherapy is 2.5 times more than that in the patients without prior radiotherapy.

Conclusion: The data revealed that the scattered dose to testicular tissues during prostate radiotherapy can lead to testicular atrophy, variation of the male sex hormones, and quality of sexual life.

KEYWORDS

prostate cancer, radiotherapy, systematic review, testicular function, testicular radiation dose

1 | INTRODUCTION

Prostate cancer is the second most common malignancy in men in the world and the first most common malignancy in European and American men; as 1.1 million men suffered from this malignancy in the world, about 70% in developing countries (Bray, Lortet-Tieulent, Ferlay, Forman, & Auvinen, 2010; Farhood, Geraily, & Alizadeh, 2018; Ferlay et al., 2015; Sadjadi et al., 2007). Treatment modalities for prostate cancer include radical prostatectomy, radiotherapy, and hormonal therapy (van der Wielen, van Putten, & Incrocci, 2007). External beam radiotherapy (EBRT) has been accepted as a standard treatment modality for prostate cancer, which can be carried out as conventional radiotherapy, three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and ion beam radiotherapy, and so forth (Boehmer, Badakhshi, Kuschke, Bohsung, & Budach, 2005; Yonai, Matsufuji, & Akahane, 2018).

In radiotherapy, the main purpose is covering the treatment volume with sufficient radiation dose whereas minimizing the radiation dose received by the surrounding normal tissues (Farhood, Geraily, & Abtahi, 2018). Nevertheless, this treatment modality unavoidably irradiates the organs/tissues that are away from the treatment site and radiation doses received to these organs/tissues can lead to adverse side effects (Bagheri, Rabie Mahdavi, Shekarchi, Manouchehri, & Farhood, 2018).

Sexual and reproductive complications following prostate radiotherapy are an important consideration owing to the radiosensitive nature of testicular tissues and their close proximity to target radiation volume (Oermann et al., 2011; Yau et al., 2009). These treatment-related toxicities affect sexual function, quality of life, and reproduction of cancer survivors (Nicholas et al., 2017). Testicular tissues have two different compartments that are particularly affected by radiation damage. First, seminiferous tubules, which are responsible for spermatogenesis and considered as radiosensitive tissues; as radiation-induced damage to these tubules may lead to permanent infertility. Second, Leydig cells, which secrete testosterone and are relatively resistant to radiation; as low level of testosterone following radiation may cause decreased libido and sexual function, altered personality, reduced stamina or depression (Ahmadloo et al., 2010; Bruheim et al., 2008; Nicholas et al., 2017). Furthermore, the testicular function is regulated by luteinizing hormone (LH) and follicle-stimulating hormone (FSH) on the Leydig cells and Sertoli cells, respectively. LH through its interaction with Leydig cells (under negative feedback) controls testosterone production; as radiation-induced damage to the Leydig cells will prevent testosterone production and lead to a compensatory increment in LH levels. The Sertoli cells are located inside the seminiferous tubules and are responsible for spermatogenesis; therefore, radiation-induced damage to these cells can impair sperm production and

thereby increment of the pituitary release of FSH (Dueland, Grønlie Guren, Rune Olsen, Poulsen, & Magne Tveit, 2003; Hermann et al., 2005).

To the best of our knowledge, the current study is the first systematic review on the radiation-induced testicular toxicities following prostate radiotherapy. Therefore, the aim of this review is to summarize data regarding the effect of prostate radiotherapy on the testicular function.

2 | METHODS

2.1 | Search strategy

Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines was used to design this systematic review (Moher, Liberati, Tetzlaff, & Altman, 2009). The literature search was performed to evaluate all relevant studies on the electronic databases of Web of Science, PubMed, EMBASE, Scopus, and clinical trials by two study investigators (Bagher Farhood and Hamed Haghi-Aminjan), independently. The search strategy used in the current study was according to the following keywords in the title and abstract: (Radiation OR Radiotherapy) AND (Prostate neoplasms OR Prostate cancer OR Prostate malignancy) AND (Testes OR Testis OR Testicular OR Spermatozoa OR Germ cells OR Leydig cells OR Gonadal hormones OR Seminiferous tubules OR Sex hormones OR Follicle stimulating hormone OR FSH OR Luteinizing hormone OR LH OR Testosterone OR Sperm OR Hypogonadism).

2.2 | Study selection

The current systematic review included all published articles up to September 2018. In this study, original articles with the following inclusion criteria were included: (a) relevant studies with aforementioned keywords; (b) studies with sufficient data; (c) studies with physics contributions; (d) studies with clinical data; (e) unpublished clinical trials with results posted, and (f) studies in English language. Furthermore, exclusion criteria were: (a) articles with unrelated information; (b) articles with insufficient information (d) review articles, (e) editorials, and (f) letter to the editor.

2.3 | Data extraction

Each data of eligible paper was extracted by BF according to a form and checked by HHA. When there was a discrepancy between these two investigators, it was resolved by referring back to the article. Our extraction form includes the following information (a) author name and year of publication; (b) type of study (clinical investigation or physics contribution); (c) therapeutic technique type; (d) total

radiation dose to target volume; (e) radiation dose received to testicular tissues; (f) testicular complication induced by prostate radiotherapy.

3 | RESULTS

3.1 | Literature search

Figure 1 shows the process of study selection.

Our initial search on above-mentioned databases up to September 2018 obtained 8,439 articles. After screening the articles, 8,191 of them were excluded by evaluating their titles and abstracts and 248 articles were qualified for assessment of their full-text. Afterward, studies in consistent with the exclusion criteria or the articles with missing data were excluded. Eventually, 31 remaining studies were contained in this systematic review. Table 1 represents a summary of the obtained data and characteristics of the eligible articles included in this.

3.2 | Radiation-induced testicular toxicities following radiotherapy for prostate cancer

In this section, the relevant studies are presented in two categories: (a) physics contributions and (b) clinical investigations.

3.2.1 | Studies of Physics contributions

Amies, Mameghan, Rose, & Fisher (1995) measured dose values of unshielded-testicular tissues during conventional radiotherapy with 18 MV photon energy in patients with localized prostate cancer by thermoluminescence detector (TLD). The total dose prescribed to the patients ranged from 60 to 66 Gy, and the mean testicular dose values in the patients ranged from 154.3 to 216.8 cGy. Moreover, they stated that distance between the testicular tissues and lower

border of the treatment field is one of the most important factors influencing the dose received by these tissues (Amies et al., 1995).

Budgell, Cowan, & Hounsell (2001) measured scattered dose to the testicular tissues in abdominopelvic radiotherapy. They represented that the dose values received by these tissues during prostate radiotherapy range from 0.2 to 1.3 Gy for 60 Gy prostate treatments (i.e., 0.4–2.2% of prescribed dose; Budgell et al., 2001).

In a study by Boehmer et al. (2005), radiation dose values received by unshielded-testicular tissues of 20 randomly selected patients with prostate cancer during 3D-CRT with 20-MV photon energy were measured by online thermoluminescence dosimetry. For all patients, the total dose delivered to planning target volume was 72 Gy during 40 treatment fractions. Their results demonstrated that the dose values received by testicular tissues during total treatment are ranging from 36 to 557 cGy (with a mean dose of 196 ± 145 cGy). Finally, they concluded that the scattered testicular dose values during EBRT of patients with prostate cancer can lead to an impairment of the reproductive function of testicles (Boehmer et al., 2005).

Deng, Chen, & Nath () evaluated testicular dose resulting from kilovoltage cone beam computed tomography (kVCBCT) on image-guided radiotherapy (IGRT) of prostate cancer by Monte Carlo simulation. Their data showed that kVCBCT can increase the testicular dose to almost 1.2 Gy, up by 330% in comparison with regular IMRT technique without kVCBCT. Furthermore, they revealed that the reduction of the kVCBCT field size from 0.30 to 0.15 m in superior–inferior direction would decrease the dose value received by testes from 4.2 to 0.4 cGy per scan (Deng et al.). In another study, they reported that with increasing photon beam energy of CBCT scan from 60 to 125 kV, and kVCBCT-contributed testicular dose increases exponentially. Finally, they stated that during a regular course of prostate IGRT with 79.2 Gy total dose, the testicular dose contributing from kVCBCT would be about 1.3 Gy (Deng et al., 2012).

King, Maxim, Hsu, & Kapp (2010) assessed and analyzed the contribution of different sources yielding to incidental dose to testicular tissues during image-guided IMRT for patients with localized prostate cancer. Dose prescriptions to prostate and pelvic nodal field were 78 and 50 Gy, respectively. Their findings demonstrated that for 6 and 15 MV photon energies, mean testicular dose receiving from pelvic nodal fields are 172 and 220 cGy and for prostate-only fields are 68 and 93 cGy, respectively. The mean testicular dose resulting from daily portal MV image guidance was 366 cGy. Also, mean neutron dose received by testicular tissues from 15-MV photon energies were 60 and 31 cGy for pelvic and prostate-only fields, respectively. In total, they reported that worst case and best case scenarios can potentially deliver cumulative mean testicular dose values of 630 and 84 cGy, respectively (King et al., 2010).

Banaee, Nedaie, Esmati, Nosrati, & Jamali (2014) investigated dose values absorbed by testicular tissues in prostate radiotherapy with 18-MV photon energies. A total dose of 50 Gy was delivered to the patients and dose values absorbed by the testes were measured

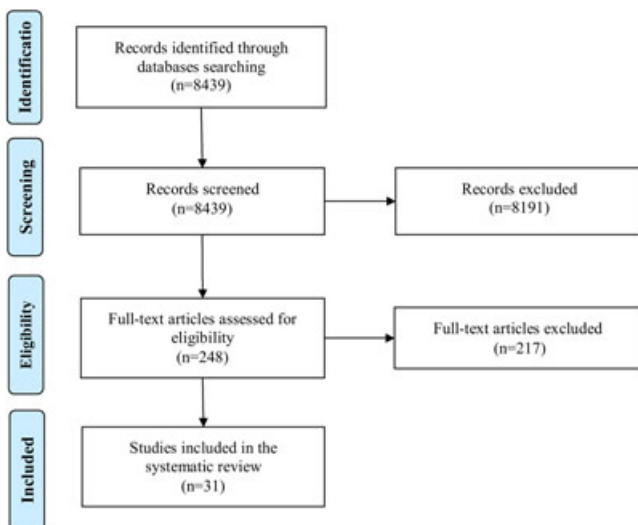


FIGURE 1 Flowchart of the study selection process [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 The details of the included studies

Authors and year	Study type	Patients number	Therapeutic technique type	Total dose to target volume (Gy)	Mean testicular dose (Gy)	Radiation-induced testicular toxicity (clinical output)
Tomic et al. (1983)	Clinical investigation	17	Conventional RT	58.00–71.00	1.00–10.00	↓Testosterone, ↑LH, and ↑FSH
Grigsby and Perez (1986)	Clinical investigation	59	Conventional RT	65.00–70.00	4.50–6.00	Unchanged testosterone, ↓dihydrotestosterone, ↑LH, and ↑FSH
Amies et al. (1995)	Physics contribution	4	Conventional RT	60.00–66.00	1.54–2.17	-
Zagars and Pollack (1997)	Clinical investigation	78	Conventional RT or 3D-CRT	68.00	2.07	↓Testosterone
Daniell and Tam (1998)	Clinical investigation	35	Conventional RT	70.00	-	↑Testicular atrophy
Daniell (1998)	Clinical investigation	35	-	-	-	Radiation-induced testicular atrophy is associated with poor prognosis.
Daniell et al. (2001)	Clinical investigation	33	Conventional RT	70.00	-	↑Hypogonadism
Budgell et al. (2001)	Physics contribution	7	3D-CRT	60.00	0.2–1.3	-
Pickles et al. (2002)	Clinical investigation	666	Conventional RT	52.5–70	2.2 (1.2–5.4)	↓Testosterone
Boehmer et al. (2005)	Physics contribution	20	3D-CRT	72.00	1.96	-
van der Wielen et al. (2007)	Clinical investigation	286	3D-CRT	68.00–78.00	-	↑ED, ↓satisfaction with sexual life
Deng et al. ()	Physics contribution	Monte Carlo simulation	IGRT	-	1.2	-
King et al. (2010)	Physics contribution	10	IMRT	78.00 (prostate) and 50.00 (nodal and seminal vesicle volume)	0.84 (best case)–6.30 (worst case)	-
Kerns et al. (2010)	Clinical investigation	27	3D-CRT or IMRT	72.60	-	Radiation-induced ED is significantly associated with SNP rs2268363.
Oermann et al. (2011)	Clinical investigation	26	SBRT	36.25	2.1	↓Testosterone, unchanged biochemical hypogonadism, unchanged expanded prostate cancer index composite (EPIC) sexual and hormonal scores
Deng et al. (2012)	Physics contribution	3	IGRT	79.20	1.3	-
Nichols et al. (2012)	Clinical investigation	150	Conformal proton therapy	78.00–82.00 GyE	-	Unchanged testosterone
Golfam et al. (2012)	Clinical	20	3D-CRT	76.00	-	Unchanged testosterone

(Continues)

TABLE 1 (Continued)

Authors and year	Study type	Patients number	Therapeutic technique type	Total dose to target volume (Gy)	Mean testicular dose (Gy)	Radiation-induced testicular toxicity (clinical output)
Ishiyama et al. (2012)	Clinical investigation	29	IMRT	76.00	5.3	↓ Testosterone
Kil et al. (2013)	Clinical investigation	217	Proton radiotherapy	70.00–72.50 GyE	–	Unchanged testosterone
Banaee et al. (2014)	Physics contribution	20	Conventional RT	50.00	0.0737 (with shield) and 0.141 (without shield)	–
Markovina et al. (2014)	Clinical investigation	51	IMRT	73.80	0.31–2.43	↓ Testosterone, unchanged biochemical hypogonadism
Kitahara et al. (2014)	Clinical investigation	8	3D-CRT	65.00–70.00	–	Unchanged testosterone, ↑LH, and ↑FSH
Onal et al., (2016)	Physics contribution	Phantom	IMRT or volumetric modulated arc therapy (VMAT)	78.00	0.995 (IMRT) and 0.904 (VMAT)	–
Planas et al. (2016)	Clinical investigation	28	IMRT	75.00	0.47	↓ Testosterone, ↑LH, and ↑FSH
Kowalik et al. (2017)	Physics contribution	Phantom	3D-CRT, IMRT or tomotherapy	76.00	4.37 (3D-CRT), 6.48 (IMRT) and 4.38 (tomotherapy)	–
Lehto et al. (2017)	Clinical investigation	523	–	–	–	↑Sexual dysfunction (such as loss of libido/sexual desire, impotence, or the loss of both potency and desire), ↑permanent sexual difficulties
Pompe et al. (2017)	Clinical investigation	248	3D-CRT or IMRT	70.00	–	↓ Testosterone (75% of patients)
Ataei et al. (2017)	Clinical investigation	30	–	79.00	–	Unchanged production and quality of sperm
Zelefsky (2017) (NCT00142506)	Clinical investigation	77	–	–	↓ International Index of Erectile Function	–
Yonai et al. (2018)	Physics contribution	Monte Carlo simulation	CIRT	57.60 GyE	0.057 (0.116 Sv)	–

Note. ↑: increase; ↓: decrease; CIRT: carbon ion radiotherapy; ED: erectile dysfunction; EPIC: expanded prostate cancer index composite; FSH: follicle-stimulating hormone; IGRT: image-guided radiotherapy; IMRT: intensity-modulated radiation therapy; LH: luteinizing hormone; RT: radiotherapy; SBRT: stereotactic body radiotherapy; SNP: single nucleotide polymorphism; VMAT: volumetric modulated arc therapy; 3D-CRT: three-dimensional conformal radiation therapy.

by TLDs in the absence and presence of testicular shield. Their findings showed that mean testicular dose values in presence and absence of testicular shield are 7.37 ± 0.93 and 14.1 ± 5.09 , respectively. Finally, they concluded that the use of the testicular shield can make a 40–70% reduction in dose absorbed by the testes (Banaee et al., 2014).

Onal, Arslan, Dolek, & Efe (2016) assessed incidental testicular dose values during prostate radiotherapy with IMRT and VMAT techniques at various photon energies. In this study, the total prescribed dose to planning target volume was 78 Gy. In the IMRT plans, the mean scattered testes dose values in the phantom measurements (by metal-oxide-semiconductor field effect transistor detector) were 0.995 ± 0.172 , 1.187 ± 0.164 , and 1.939 ± 0.145 Gy at 6, 10, and 15 MV photon energies, respectively, and corresponding dose values in the VMAT plans were 0.904 ± 0.163 , 1.036 ± 0.164 , and 1.393 ± 0.146 Gy. They concluded that lower photon energy and the IMRT plans lead to lower incidental testes dose values compared with higher photon energy and the VMAT plans (Onal et al., 2016).

Kowalik et al. (2017) measured photon and neutron dose values received by organs at risks during 3D-CRT, IMRT, and tomotherapy in an anthropomorphic phantom by TLDs. For each technique, total dose prescription to planning target volume was 76 Gy. In this study, the photon dose values delivered to testes for 3D-CRT, IMRT, and tomotherapy techniques were 4.38 ± 0.017 , 6.48 ± 0.013 , and 4.39 ± 0.020 Gy, respectively. In addition, mean neutron dose resulting from 20-MV photon beams in IMRT technique was 5.777 ± 0.127 mSv/Gy; as this effective dose did not change significantly over the whole body of the phantom. Finally, they represented that in tomotherapy technique, all organs at risks outside treatment field are well-spared as well as neutron dose resulting from the high-energy photon beam constitutes a considerable contribution (0.5%) of the dose prescription (Kowalik et al., 2017).

Yonai et al. (2018) estimated absorbed dose and dose equivalent to out-of-field organs (by Monte Carlo simulation) during carbon ion radiotherapy for treatment of prostate cancer. Their findings revealed, that the dose value reduces with distance from the target value and absorbed dose and dose equivalent values in the testes (which was located at the distance of 11.3 cm from the center of prostate mass) were 56.7 and 116 mSv, respectively. Furthermore, they reported that the organ dose equivalent in the testes per treatment dose is less than those either in brachytherapy with an Ir-192 source or in 6 MV IMRT (Yonai et al., 2018).

3.2.2 | Studies of clinical investigations

Tomić, Bergman, Bamber, Littbrant, & Löfroth (1983) analyzed male sex hormones of patients with prostate cancer after EBRT. Mean total tumor dose was 63.5 Gy, and absorbed dose values to the testicular tissues were about 1 to more than 10 Gy. Their results showed that the testosterone concentrations after treatment significantly are lower prior treatment. Also, LH and FSH concentrations after treatment significantly were higher prior treatment. The highest testosterone variation was found 1 week after the treatment

in the patients who the testicular tissues had been received more than 10 Gy (Tomić et al., 1983).

Grigsby and Perez determined serum levels of LH, FSH, testosterone, and dihydrotestosterone hormones in patients with prostate cancer treated with EBRT. In this study, a total scattered dose to testicular tissues was ranging from 4.50 to 6.00 Gy. The findings related to before treatment and up to 2 years after completing the treatment we demonstrated that testosterone levels do not change but dihydrotestosterone levels decrease slightly. In addition, LH and FSH levels increased significantly (Grigsby & Perez, 1986).

Zagars and Pollack assessed testosterone levels after prostate radiotherapy. For a total dose of 68 Gy, the mean testicular dose was 2.07 Gy. Mean pre- and 3-month posttreatment testosterone levels were 400 and 356 ng/dl, respectively; as this decrease was significant than the pretreatment value. In conclusion, they stated that the decreased testosterone level after radiotherapy is very small quantitatively and it can be clinically insignificant (Zagars & Pollack, 1997).

Daniell and Tam evaluated the frequency of testicular atrophy in orchiectomy specimens obtained from males with prostate radiotherapy. Their results showed that the patients with prior prostate radiotherapy have testicular atrophy more frequently than males without prior radiotherapy (71% vs. 28%). In addition, they reported that the considerable testicular atrophy happens with similar frequency in specimens from both older and younger males, and it is more common in specimens with 3 years after radiotherapy than those obtained after longer posttreatment (89% vs. 53%; Daniell & Tam, 1998). In another study, Daniell (1998) reported that the testicular atrophy resulting from prostate radiotherapy is associated with poor prognosis. In another work, Daniell et al. (1998) investigated testicular damage resulting from prostate EBRT and confirmed the presence of hypogonadism in males with prior EBRT. Furthermore, they reported that high variations in the degree of hypogonadism among the patients may be because of differences in their age and anatomy.

Pickles et al. investigated testosterone level of patients with prostate cancer after EBRT. For total doses of 52.5–70 Gy, mean testicular dose was 2.2 Gy (1.2–5.4 Gy). Their findings revealed that at a median nadir time of 6 months, testosterone levels decline to an average of 83% of baseline. In conclusion, they stated that temporary testosterone levels decrease following prostate radiotherapy, without impact on subsequent tumor outcomes (26).

van der Wielen et al. (2007) assessed erectile and sexual function of patients during prostate 3D-CRT. Their results demonstrated that after 1, 2, and 3 years of treatment, 27, 36, and 38% of the patients have developed erectile dysfunction (ED). Furthermore, there was a significant correlation between lower satisfaction with sexual life and development of ED (van der Wielen et al., 2007).

Kerns et al. (2010) investigated single nucleotide polymorphisms (SNPs) associated with ED, as an adverse effect resulting from EBRT, among African-American patients with prostate cancer. Their results showed that SNP rs2268363 is significantly associated with ED. This

SNP is located within the follicle-stimulating hormone receptor gene, whose encoded product has a role in the development and function of male gonads (Kerns et al., 2010).

Oermann et al. (2011) evaluated the incidence of hypogonadism following SBRT for patients with prostate cancer. The patients were treated with a 36.25 Gy total dose (in five fractions), and mean scatter dose received to testicular tissues was 2.1 Gy. By comparing pre- and posttreatment total testosterone levels, the results showed that at 1 year after treatment completion, testosterone levels of the patients slowly decrease and these testosterone levels were significantly less than the pretreatment values. Furthermore, they reported that there is no increment in biochemical hypogonadism at 1 year after treatment. The findings related to sexual dysfunction of the patient revealed that average expanded prostate cancer index composite sexual and hormonal scores are not significantly varied by 1 year after treatment (Oermann et al., 2011).

Golfam, Samant, Eapen, & Malone (2012) evaluated testosterone changes in patients with localized prostate cancer treated by 3D-CRT. Their findings revealed that there is no significant decrease in serum testosterone level of the patients during 18 months after radiotherapy.

Ishiyama et al. (2012) investigated the relationship between testosterone level and dose absorbed by testes in prostate cancer patients treated with IMRT. In this study, a mean total dose of 76 Gy was delivered to the prostate and the mean total dose absorbed by the testes was 5.3 Gy. Also, the mean pretreatment testosterone level of the patients was 310 ng/dl; as the mean testosterone levels were significantly reduced at 12, 24, 30, 36 months after IMRT (Ishiyama et al., 2012).

Nichols et al. (2012) evaluated testosterone levels of patients with prostate cancer in pre- and posttreatment with conformal proton radiotherapy. The median pretreatment testosterone level of patients was 357.9 ng/dL and their median posttreatment testosterone values were 375.5, 369.9, 348.7, 353.4, and 340.9 ng/dl at treatment completion, 6, 12, 18, and 24 months after treatment, respectively. In conclusion, they reported that the treatment of prostate cancer with conformal proton therapy does not result in a significant effect on testosterone levels of patients during 2 years after radiotherapy (Nichols et al., 2012).

Kil et al. (2013) assessed testosterone levels of patients with prostate cancer in pre- and posttreatment with proton radiotherapy. The median testosterone level before treatment was 367.7 ng/dl, and the median changes in testosterone levels after treatment completion, 6 and 12 months after treatment were -3.0, -6.0, and +5.0 ng/dl, respectively. Statistically, these changes were not significant. In conclusion, they stated that patients with prostate cancer treated with proton radiotherapy are not confronted with testosterone suppression (Kil et al., 2013).

Markovina et al. (2014) investigated testosterone level and incidence of biochemical hypogonadism in patients with prostate cancer treated with IMRT. A significant decrease in testosterone levels at 6 months after treatment completion was observed, but testosterone levels returned to baseline levels by 1 year after IMRT.

Moreover, none of the increase in biochemical hypogonadism was seen after IMRT (Markovina et al., 2014).

Kitahara, Kobayashi, Yano, Kusuda, & Komatsu (2014) assessed changes in male sex hormone levels following prostate 3D-CRT. The obtained results showed that radiotherapy does not change serum testosterone level, but it significantly increases both LH and FSH in serum level (Kitahara et al., 2014).

Planas et al. (2016) measured pre- and posttreatment serum levels of LH, FSH, estradiol, total testosterone, and free testosterone of patients with prostate cancer treated by IMRT. In this study, the patients were treated with a 75 Gy total dose, and mean scatter dose received to testicular tissues was 0.47 Gy. Their results showed that at 3 months after treatment completion, LH and FSH levels are significantly more than the baseline levels whereas total testosterone and free testosterone levels are significantly lower. At 12 months after treatment completion, FSH levels were significantly more than the baseline levels whereas total testosterone levels remained significantly lower. There were no significant changes related to other hormonal levels at any time after treatment (Planas et al., 2016).

Lehto, Tenhola, Taari, & Aromaa (2017) investigated the adverse effects of prostate EBRT in large population-based samples (523 patients). In this study, 79% of the patients reported sexual dysfunction such as loss of libido/sexual desire, impotence, or the loss of both potency and desire after EBRT. Also, 11% of the patients reported permanent sexual difficulties after EBRT (Lehto et al., 2017).

Pompe et al. (2017) evaluated the effect of prostate EBRT on testosterone kinetics of a large series of patients with cancer. About 75% of the patients revealed a considerable decrease in the testosterone level, and median time to first decrement was 6.4 months after EBRT. More than 60% of the patients with testosterone decrement recovered to at least 90% of baseline levels during 6 months of the nadir. Moreover, their findings showed that there is a lower chance of testosterone recovery for increased body mass index, advanced age, lower nadir level, and higher baseline testosterone level (Pompe et al., 2017).

Ataei, Leventouri, and Pella (2017) investigated the effect of prostate radiotherapy on quality of sperm during and after treatment. Their results demonstrated that there are no variations in the quality of sperm during radiotherapy, but the findings later revealed 1–3% reduce in sperm's life span and 2–3% reduce in the quality of sperm (Ataei et al., 2017).

Zelevsky evaluated male sexual function and ED of patients with prostate cancer treated by radiotherapy (NCT00142506). The International Index of Erectile Function (IIEF) was used for the assessment of male sexual function and diagnostic investigation of ED severity. There are five domains of the IIEF: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. A score of 0–5 was awarded to each question of the IIEF. Total IIEF scores range from 0 to 75. Lower scores indicate severe ED (0 = severe ED), whereas higher scores indicate less ED (75 = no ED). In this report, median IIEF scores in the baseline, 6, 12, and 24 months after radiotherapy were 64

(56.75–69.00), 58 (35.00–64.00), 51 (34.50–63.50), and 54.50 (29.75–64.75), respectively (NCT00142506).

4 | DISCUSSION

In the current study, the data related to clinical studies, which evaluated testicular toxicities resulting from prostate cancer radiotherapy were summarized. Furthermore, the Physics contributions regarding measurement/estimation of dose values received by testicular tissues during prostate radiotherapy were studied. The dosimetric data and clinical outcomes of the above-mentioned eligible studies are represented in Table 1.

Referring to Table 1, it is found that according to the various radiotherapeutic techniques, the total dose to planning target volume ranges from 36.25 to 78.00 Gy. Furthermore, testicular dose values resulting from prostate EBRT ranged from 0.06 to 6.48 Gy. There are several factors, which can affect scattered dose values to testes during prostate radiotherapy and their subsequent adverse side effects including beam and energy type used for prostate radiotherapy, different treatment techniques used, distance between the testicular tissues and lower border of treatment field, energy beam and field size of KVBCBT, and absence/presence of testicular shield.

The findings of the current study revealed that the prostate radiotherapy can lead to changes in testicular function following which will be explained in detail in each case.

4.1 | Effects of prostate radiotherapy on spermatogenesis

Spermatogenesis starts in the testicular tissues during early puberty. It includes the whole development course, from spermatogonia to sperm. This course happens in the seminiferous tubules and comprises the various stages of differentiation of Sertoli cells and germ cells (Harel, Ferme, & Poirot, 2011). The seminiferous tubules are radiosensitive and dose values as low as 0.1 Gy may result in the temporary arrest of spermatogenesis (Pryzant, Meistrich, Wilson, Brown, & McLaughlin, 1993).

It was reported that there are no significant changes in sperm production and its quality 2–3 years after prostate radiotherapy (Ataei et al., 2017). According to a study in a population of healthy prisoners, it was shown that dose values of 4–6 Gy led to a significant decrease in the numbers of spermatozoa (Rowley, Leach, Warner, & Heller, 1974). In another study, in patients irradiated for Hodgkin's disease, it was revealed that a testicular dose between 0.2–0.7 Gy leads to a decrease in sperm concentration (Kinsella et al., 1989). In general, a radiation-induced permanent azo-ospermia may happen with a total testicular dose of about 1.2–1.4 Gy during a fractionated radiotherapy (Buchli, Martling, Arver, & Holm, 2011). Radiation-induced azo-ospermia has been observed at dose values of 0.65 and 4–6 Gy during 9–18 months and 5 years to permanently, respectively (Patel & Rossi, 2014). Furthermore, a high risk of permanent azo-ospermia has been reported for fractionated-testicular dose values

>1.5 Gy (Piroth, Hensley, Wannemacher, & Zierhut, 2003). Radiation may also lead to DNA fragmentation in sperm and subsequently a negative effect on future fertility (González-Marín, Gosálvez, & Roy, 2012).

4.2 | Effects of prostate radiotherapy on male sex hormones

LH and FSH are pituitary hormones that regulate testicular function. Moreover, testosterone is produced mainly in Leydig cells and the number of these cells is in turn controlled by LH and FSH. The amount of testosterone generated is controlled by the hypothalamic–pituitary–testicular axis; as when its amount decreases, the hypothalamus releases gonadotropin-releasing hormone and this hormone stimulates the pituitary gland to release LH and FSH. It is noteworthy, that the two hormones of LH and FSH stimulate the testicular tissue to generate testosterone (Planas et al., 2016). The Leydig cells have a lower radiosensitivity compared with the seminiferous epitheliums, and hence cancer treatments by radiation rarely cause clinical hypogonadism (Sklar, 1999).

The findings of the current study demonstrated that the male sex hormone levels of LH and FSH following prostate radiotherapy significantly increase in serum level (Grigsby & Perez, 1986; Kitahara et al., 2014; Planas et al., 2016; Tomic et al., 1983). Furthermore, it was reported that the dose values less than 20 cGy have no effect on FSH secretion, whereas higher dose values lead to a temporary FSH increase (Sedlmayer et al., 1999). In addition, it was shown that LH levels increase after 75 cGy (Rowley et al., 1974). However, there were sparse data on testosterone levels following prostate radiotherapy, which may be due to different scattered dose value to testes. Ishiyama et al. (2012) reported that there is a relatively weak correlation between dose absorbed by the testes and ratio of posttreatment to pretreatment testosterone level. The results presented in Table 1 demonstrates that 60% of studies reveal that prostate radiotherapy can lead to a significant decrease in testosterone levels.

4.3 | Effects of prostate radiotherapy on quality of sex life

Although survival of patients with prostate cancer is good, their quality of life outcome is impaired by the adverse side effects of treatment modalities, and these negative effects vary by treatment modalities (Lehto et al., 2017). In a study by Lehto et al. (2017), which was performed on a large population with 523 patients, the negative effect resulting from prostate EBRT on quality of sex life was explained in details. In another study, Oermann et al. (2011) reported that the sex life of patient following the prostate radiotherapy does not significantly vary by 1 year after treatment. In the other hand, ED as an adverse effect resulting from prostate EBRT has been reported by several studies (Kerns et al., 2010; van der Wielen et al., 2007). Significantly, there is a correlation between this negative effect induced by radiation and lower satisfaction with sexual life (van der Wielen et al., 2007).

4.4 | Effects of prostate radiotherapy on testicular size

Testicular atrophy following prostate radiotherapy has been reported by Daniell (1998) and Daniell & Tam (1998). Among the characteristic of testicular atrophy are loss of seminiferous tubular epithelium, thickening of the tubular basement membrane, reduction of spermatogenesis, relative numbers of Sertoli cells located in the seminiferous tubular epithelium, and amount of tubular and peritubular fibrosis (Andres, Bierman, & Hazzard, 1985; Robbins, Cotran, & Kumar, 1984).

According to studies performed by Daniell' and group, the frequency of testicular atrophy in patients with prior prostate radiotherapy was 2.5 times higher than that in the patients without prior radiotherapy. Moreover, testicular atrophy, as an adverse side effect of prostate radiotherapy, can be associated with poor prognosis (Daniell, 1998; Daniell & Tam, 1998).

5 | CONCLUSION

Although radiotherapy is a standard treatment modality for patients with prostate cancer, the scattered testicular dose values can lead to testicular atrophy, variation of the male sex hormones (LH, FSH, and testosterone) and quality of sex life. These scattered dose values and their associated toxicities can vary by several factors such as treatment technique used, the distance between the testicular tissues and lower border of treatment field, and absence/presence of testicular shield.

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