Mini-Review

Side effects of prostate cancer therapies and potential management

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Abstract

Prostate cancer (PCa) remains a significant health challenge, necessitating diverse therapeutic interventions to manage the disease effectively. While these treatments offer promising outcomes, they are often accompanied by a range of side effects that can impact patient quality of life and treatment compliance. This review provides an overview of the common side effects associated with various PCa therapies, including prostatectomy, radiation therapy, thermal therapy, hormone therapy, chemotherapy, and targeted drug therapy, among others. We summarized and discussed the reported side effects encompassing ureteral problems, sexual issues, gastrointestinal symptoms, fatigue, anemia, thrombocytopenia, hematologic abnormalities, nausea, vomiting, and liver enzyme elevation. Specific managements, such as personalized treatment plans, proactive symptom monitoring, supportive care interventions, and hematological assessments, are crucial in mitigating these side effects and optimizing treatment outcomes. By prioritizing patient-centered care and tailored interventions, health-care providers can enhance treatment efficacy and improve the overall well-being of individuals undergoing PCa therapies.

Keywords: Prostate cancer, Cancer therapies, Side effects

1. INTRODUCTION

Prostate cancer (PCa) is a notorious malignancy afflicting males. The incidence of PCa has been on the rise in recent years. Early prophylaxis, early diagnosis, and early treatment are the "golden rules" for the prevention and management of PCa. For clinical assessment of the specific progression of the cancer, the "TNM staging system" is used for the classification of PCa [1]. T represents the size of the primary tumor, N indicates the lymph node status, and M refers to distant metastasis, including metastases to bone, distant lymph nodes, or other distant organs. Clinical localization means the tumor is confined to the prostate, and is classified as T1/T2 stage; "local invasive" lesions represent the tumor that extends beyond the prostate and is classified as T3 stage; the condition falls into T4 stage when PCa metastasizes beyond the prostate and spread to other sites such as the bladder and rectum. N1-N3 indicate varying degrees of lymph node metastasis, and M1 is indicative of the presence of distant metastasis. Apart from "TNM staging," other risk factors, such as prostate-specific antigen (PSA) levels and Gleason scores, are also integrated into the clinical evaluation of PCa, and different treatment approaches are adopted based on such risk factors and stages. To improve early detection rates, it is recommended that men over 50 should be subjected to PSA screening regularly. If the PSA screening result indicates "abnormal," prostate magnetic resonance imaging should also be performed. Patients with nodules or abnormal lesions should undergo a prostate biopsy to determine whether it is PCa or not.

Numerous approaches have been developed for tackling PCa, and the choice of therapies for PCa treatment depends on the type and stage of the cancer as well as the specific condition of each patient (Figure 1). The major PCa therapies include prostatectomy, radiation therapy, thermal therapy, hormone therapy, chemotherapy, and targeted drug therapy. Table 1 shows the advantages, application scenarios, and side effects of these different therapies.

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Received: 20 June 2024; Revision received: 25 July 2024; Accepted: 31 July 2024; Published: 22 August 2024

How to cite this article: Xiao J, Zhang M, Wu D. Side effects of prostate cancer therapies and potential management. *J Biol Methods.* 2024;11(3):e99010018. DOI: 10.14440/jbm.2024.0019

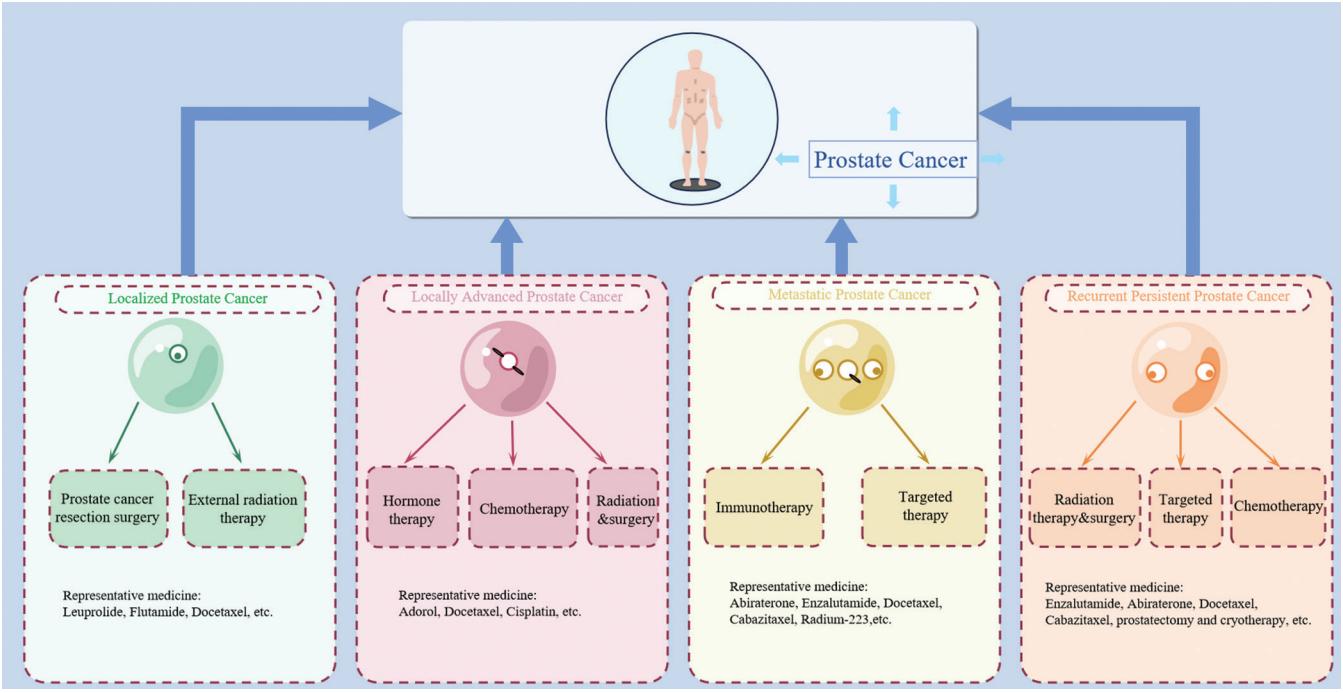

Figure 1. Current therapies for prostate cancer at different stages. Specific treatment and representative medicine for each treatment are listed underneath each stage of prostate cancer. Adopted from [1].

2. PROSTATECTOMY

Surgery is the most common treatment option for PCa, particularly when the cancer is confined to the prostate gland. Surgical removal of the prostate is also known as radical prostatectomy (RP). The procedure involves excision of the prostate gland, surrounding tissues, and possibly some lymph nodes. Different surgical techniques, such as robot-assisted laparoscopic prostatectomy or retropubic surgery, are used, depending on the size and location of the cancer.

2.1. Common post-operative complications

Two major concerns of patients after prostate surgery are urinary issues and erectile dysfunction (ED). The assessment of these problems can be challenging because so far incontinence or impotence is not well defined, and data collection methods used vary with different centers, including surveys, phone interviews, or assessments by surgeons. Results for treating continence and potency are more favorable when patients are carefully selected, especially younger and healthier individuals. Urinary incontinence can be a significant problem after surgery, but the rates reported varied widely. Most high-volume centers registered a continence rate between 80% and 95%. Factors that can improve post-operative continence include younger age, nerve preservation, no avoiding strictures, sufficient urethral length, and right bladder neck position. Pelvic floor exercises and biofeedback can help ease incontinence, and improvement may take up to 2 years [2]. If incontinence persists, further tests can help determine the cause and guide decision-making about treatments [3]. Before the surgical techniques were refined, most patients suffered from ED after surgery. Understanding the nerve network responsible for erections led to improved surgical methods and better outcomes. Factors such as age, cancer stage, and nerve preservation influence the recovery of sexual function. Some patients may regain erectile function gradually over time, and medications such as sildenafil can help [4]. Studies exhibited that recovery of sexual function increases with younger age and are more common in men with earlier-stage tumors [5].

Another common complication after prostate surgery is a urine leak from the connection between the bladder and urethra, known as anastomosis [6]. This leak can occur shortly after surgery or later on. It is more frequent with laparoscopic procedures compared to their traditional counterparts [7]. To prevent leaks, the surgeon should ensure the catheter is correctly placed in the bladder and check the connection during surgery. If a leak is found after surgery, it is important to keep the drain in place and maintain bladder drainage until the leak stops. Another complication is bladder neck contracture, which usually develops later [6]. It occurs in a small portion of patients receiving laparoscopic and traditional surgeries [8]. Factors such as previous prostate surgery, significant blood loss during surgery, and urine leakage at the connection site may increase the risk. Treatment usually involves minor surgical procedures to improve urine flow.

2.2. Potential complications during surgery

Nerve injuries can happen intraoperatively, such as direct nerve damage or stretching from improper patient positioning.

Table 1. The advantages, scenarios, and side effects of different treatments

Treatment	Advantages	Scenarios	Side effects		
			Common side effects	**Less common side effects**	**Long-term side effects**
Prostatectomy (Surgery)	Removal of the cancerous tissue, potentially curing the cancer	Early-stage localized cancer, high-risk localized cancer, cancer recurrence after radiation therapy	• Urinary incontinence (leakage of urine) • Erectile dysfunction (difficulty achieving or maintaining an erection) • Pain at the incision site • Infection • Bleeding	• Scrotal swelling (from fluid buildup) • Urinary tract infection • Rectal injury (rare) • Blood clots	• Urinary incontinence may improve over time with pelvic floor exercises and other treatments. • Erectile dysfunction may be treated with medication, devices, or surgery. • Some patients may experience chronic pain.
Thermal Therapies (e.g., HIFU and Cryotherapy)	Minimally invasive, targeted treatment, preserves surrounding tissues.	Early-stage localized cancer, localized cancer in patients unsuitable for surgery or radiation therapy	• Erectile dysfunction (more common with cryotherapy) • Urinary problems (such as frequent urination, burning sensation, or blood in urine) • Pain • Bruising • Swelling	• Rectal injury (rare) • Bowel problems (such as diarrhea or constipation) • Blood in urine • Blood in semen	• Erectile dysfunction may persist and require treatment. • Urinary problems may persist and require further treatment.
Radiation Therapy	The therapy is non-invasive and can be used alone or with surgery.	Early-stage localized cancer, localized cancer in patients unsuitable for surgery, cancer recurrence after surgery	• Urinary problems (such as frequent urination, burning sensation, or blood in urine) • Erectile dysfunction • Bowel problems (such as diarrhea, constipation, or blood in stool) • Fatigue • Skin irritation	• Bladder or bowel obstruction (rare) • Rectal injury (rare) • Radiation proctitis (inflammation of the rectum)	• Erectile dysfunction may persist and require treatment. • Urinary problems may persist and require further treatment. • Bowel problems may persist and require further treatment.
Hormone Therapy	It slows cancer growth by lowering testosterone levels.	Advanced cancer that has spread to other parts of the body, cancer that has stopped responding to radiation therapy or surgery	• Hot flashes • Weight gain • Fatigue • Decreased libido • Loss of muscle mass • Osteoporosis	• Depression • Insomnia • Anxiety • Memory problems • High blood sugar • High cholesterol	• Loss of bone density and increased risk of fractures • Increased risk of heart disease and diabetes • Cognitive impairment
Chemotherapy	It kills cancer cells throughout the body.	Advanced cancer that has spread to other parts of the body, cancer that has stopped responding to hormone therapy	• Nausea and vomiting • Fatigue • Hair loss • Mouth sores • Nerve damage • Increased risk of infection	• Prone to bruising or bleeding • Changes in skin color • Swelling • Kidney damage • Liver damage	• Heart damage (in some cases) • Permanent nerve damage • Increased risk of developing other cancers
Immunotherapy	It induces the immune system to kill cancer cells.	Advanced cancer that has stopped responding to other treatments	• Fatigue • Skin reactions (such as rash, itching, or swelling) • Joint pain • Flu-like symptoms (such as fever, chills, and muscle aches)	• Hypothyroidism • Colitis • Pneumonitis • Liver inflammation • Kidney inflammation	Some side effects may persist or become chronic.
Targeted Drug Therapy	It targets specific cancer cells while sparing healthy cells.	Advanced cancer that has specific genetic mutations	Varies with specific drugs, but may include • Rash Diarrhea • Nausea • Fatigue • High blood pressure • Liver damage	Varies with specific drugs, but may include • Heart problems • Blood clots • Bleeding • Allergic reactions	Varies with specific drugs, but may include • Long-term damage to organs such as the liver or kidneys • Increased risk of developing other cancers

One specific nerve, the obturator nerve, can be affected during pelvic lymphadenectomy in RP and laparoscopic RP, leading to leg movement issues. Surgeons should visually identify the obturator nerve before cutting it to avoid complications. If the nerve is accidentally tied without being cut, the release of the clip typically resolves the issue, although patients may still experience symptoms [9]. In cases where the obturator nerve is cut during RP, it can often be restored by suturing

the nerve sheath [10]. Rectal injuries represent a particular category of bowel trauma that may happen during prostate surgical procedures. These injuries can happen during the placement of instruments, tissue dissection, or the use of electrocautery devices. The risk is higher with laparoscopic surgery due to the proximity of the bowel to the surgical area. Prompt identification of bowel injuries during surgery is crucial to the prevention of serious complications. Delayed recognition of these injuries can lead to severe health issues [11]. If bowel injury is suspected after surgery, imaging tests such as abdominal pelvic computed tomography scans or diagnostic laparoscopy can help confirm the diagnosis with high accuracy [12].

Injuries to the rectum are a special type of bowel injury that can occur during prostate surgery. These injuries are more common during laparoscopic procedures, particularly when dissecting the back of the prostate [13]. Rectal injuries can also be caused by heat or electricity during surgery [14]. It is crucial to identify and address rectal injuries immediately during the operation to reduce complications. Once diagnosed, the injury should be carefully closed in two layers [15]. In some cases, a temporary colostomy may be needed, especially if there is significant fecal leakage or other risk factors. Failure to recognize or properly repair rectal injuries can lead to serious health issues [16]. Some bleeding is normal during surgery, but when it is beyond what is expected or requires extra intervention, it becomes a complication. In laparoscopic prostate surgery, vessel injuries can happen during certain steps of the procedure, although they are rare. Minimally invasive surgery is thought to reduce bleeding compared to traditional surgery. Blood transfusion rates can indicate the severity of bleeding issues [17]. Bleeding during prostate surgery mainly comes from specific areas such as the dorsal venous plexus and prostatic pedicles [18]. Properly managing bleeding at these sites can prevent serious hemorrhage. If bleeding is not controlled, it can lead to complications such as pelvic hematomas, which may need drainage [19]. Lymphoceles, a common complication of lymphadenectomy, can also cause issues and may require drainage if infected [20].

Ureteral complications are rare during prostate surgery, occurring in <1% of cases [21,22]. These injuries can happen due to heat, electricity, or sutures placed near the ureter. It is important to identify and treat ureteral injuries promptly. Repair techniques include stent placement or ureteroneocystostomy. If a ureteral injury goes unnoticed, it may require further procedures or temporary tube placement. Symptoms of ureteral injury can vary and may include nausea, fever, or abdominal pain [23]. Complications resulting from untreated ureteral injuries can lead to kidney obstruction, abdominal pain, and other serious issues. A suspected urine leak can be verified by testing the drain fluid for creatinine concentrations to aid in diagnosis. Bladder injuries are rare with traditional prostate surgeries but can occur during laparoscopic procedures. These injuries usually happen during specific parts of the surgery and are typically identified and repaired during the operation. Patients who have had previous hernia surgery with a prosthetic mesh may be at higher risk for bladder injury [24]. Deep vein thrombosis and pulmonary embolism are serious but uncommon complications of prostate surgery. Preventative measures such as using blood thinners and compression stockings, along with early movement after surgery, can minimize the occurrence of these complications. Previous studies reported higher rates of thromboembolic events compared to current laparoscopic surgery data [25]. In cases where these events occur, patients are often bedridden for extended periods due to other complications [26,27].

3. THERMAL THERAPIES

Ablative therapies use cold or heat to destroy prostate tissue. This can involve freezing (cryoablation) or heating the tissue (HIFU). These treatments are used for small PCa's when surgery is not an option or for advanced cancers when other treatments have not worked. Researchers are investigating focal therapy, where only the part of the prostate containing the most aggressive cancer cells is targeted. This approach aims to reduce side effects, but it is uncertain if it provides the same survival benefits as the treatment of the entire prostate.

3.1. Complicates for cryotherapy

The potential of whole-gland cryotherapy has been limited by a relatively high incidence of side effects. A 2007 Cochrane review by Shelley *et al.* reported impotence (47 – 100%), incontinence (1.3 – 19%), urethral sloughing (3.9 – 85%), fistula (0 – 2%), bladder-neck obstruction (2 – 55%), stricture (2.2 – 17%), and pain (0.4 – 3.1%) [28]. In contrast, primary focal cryotherapy studies have shown lower rates of side effects, with the incontinence rate ranging from 0 to 3.6% and ED from 0 to 42%. Other side effects such as hematuria, strictures, and rectal fistulae were rare. Primary focal cryotherapy is attractive as it reduces morbidity while maintaining good cancer control. However, evidence on salvage focal cryotherapy is limited, with only two studies reporting outcomes. Salvage prostatectomy for radio-recurrent disease is a common treatment option, but it is technically challenging due to radiation-induced fibrosis and tissue plane obliteration. Complications such as blood loss, ED, incontinence, anastomotic stricture, and rectal injury are frequently observed. Although long-term oncological data on focal salvage cryotherapy is still lacking, initial results showed a biochemical disease-free survival rate of 50 – 68% with low side effects such as incontinence (0 – 5%), ED (60 – 71%), and no cases of recto-urethral fistula development [29].

3.2. Complicates for thermal therapy

Acute urinary retention was found to occur in 3.9 – 28.3% of patients undergoing HIFU treatment, and, as a complication, is not consistently recognized by all authors. The main complication associated with the procedure was recto-urethral fistula, with rates varying from 3.6% to 30.2%. Some authors reported no cases of this complication, while others did not provide data on it. Management of recto-urethral fistula involves either conservative treatment (prolonged catheterization) or open reconstructive surgery. Urethral stenosis was reported in up to 30.2% of overall cases but the studies reviewed failed to detail its severity, and its relationship with acute urinary retention was not explored. Urinary tract infections were postoperatively seen in 0.8 – 24.3% of cases, with data available in 12 out of 16 studies. Post-operative pain was mentioned in five out of 16 studies, but no information was provided regarding the pain assessment scale used [30].

4. RADIATION THERAPY

Radiation therapy is a treatment for PCa that uses strong energy to destroy cancer cells. There are two main types of radiation therapy for PCa. External beam radiation therapy (EBRT) uses a machine to direct high-energy beams, such as X-rays or protons, at the PCa from outside the body. Treatments are typically administered 5 days a week for several weeks. Some centers offer a shorter, more intense course of radiation over fewer days. This treatment is used for localized PCa or after surgery to kill any remaining cancer cells. Brachytherapy involves placing tiny radioactive seeds into the prostate tissue. These seeds give off low doses of radiation over time. Brachytherapy is used for cancer that has not spread outside the prostate.

4.1. Acute urinary complications

Acute urinary problems caused by EBRT are usually due to inflammation and tissue damage in the bladder neck, prostate, and prostatic urethra. Symptoms typically start a few weeks after entry into the treatment and can last until the damaged tissue heals. Urinary irritation and obstructive symptoms are common, particularly in males with enlarged prostates [31]. Medications such as alpha-blockers and anticholinergics can help tackle these symptoms, but caution should be exercised needed when anticholinergics are given to men with enlarged prostates since the agents carry the risk of urinary retention [32,33]. Late side effects of EBRT can develop months or years after treatment. These symptoms arise from alterations in the blood vessels within the treated areas, resulting in long-term oxygen deficiency, tissue atrophy, and abnormal vascular proliferation. Patients might have painless hematuria, akin to that of chronic interstitial cystitis, or bladder disturbances, including increased urinary frequency, discomfort during voiding, and bladder spasms [34]. Incidence of urethral stricture is minimal but is more prevalent in individuals who have previously undergone transurethral resection [35]. For brachytherapy, a study found that within 60 days of the procedure, 37% of patients had mild urinary problems, 41% suffered from moderate issues, and 2.2% developed severe complications. These symptoms typically peak around 1 month after the procedure and usually resolve within a year [36]. Most cases can be managed with medication. Larger prostate glands have a higher risk of urinary retention, which can be mitigated with corticosteroids. Some patients may experience rare complications such as urethral necrosis, leading to incontinence. Less common side effects include rectal irritation, bleeding, and loose stools [37]. Diarrhea can be managed with medication, while other symptoms may improve with dietary changes or the use of suppositories [38]. The risk of rectal toxicity is correlated with the radiation dose administered, and the use of hyaluronic acid as a barrier between the prostate and the rectal wall can potentially decrease the incidence of side effects [39]. Rectal fistulas, though rare, can occur in some patients, especially those with certain medical conditions or who have had post-implantation biopsies.

4.2. Gastrointestinal complications

Gastrointestinal side effects from radiation therapy for PCa are mainly result from the irradiation of the front wall of the rectum. Men may suffer from increased rectal urgency and the sensation of incomplete evacuation, known as tenesmus, during the course of treatment. In the years following treatment, similar to bladder issues, the rectum may develop bleeding or, in rare cases, ulcers. Men who receive radiation to the pelvic lymph nodes may have more bowel-related side effects, such as cramps, diarrhea, and adhesions in the small bowel [40]. In a review of 192 patients undergoing prostate radiation therapy, two-thirds reported no or only mild gastrointestinal disturbances, while the other third dealt with more significant symptoms, ranging from moderate to severe, including rectal bleeding, urgency, or the necessity for medical procedures [41]. The lesser–severe symptoms are often manageable through alterations in eating habits, increased fiber consumption, or the use of hydrocortisone suppositories [42]. For persistent bleeding, abnormal blood vessels can be electrosurgically treated. Late rectal problems are most severe in the first 3 years after treatment and may improve gradually over time.

4.3. Sexual function-related complications

Radiation therapy can lead to decreased sexual function in men due to radiation effects on the nerves, blood vessels, and

penile tissue. This can result in ED [43]. Men with pre-existing potency issues, diabetes, or those who receive hormone therapy are at higher risk for impotence after treatment [44]. Studies have shown that phosphodiesterase inhibitors can help improve erectile function in many men who experience dysfunction after radiation therapy [45,46]. Brachytherapy, similar to EBRT, can lead to sexual dysfunction [47]. Studies indicated that bout half of potent men with normal erectile function who underwent seed implantation maintained their sexual potency over a 3-year period, with the average duration before potency loss being 5.4 months [48]. Factors such as radiation dose and pre-treatment potency levels can predict treatment-induced impotence [49]. The potency rate was higher for those who received seeds alone compared to those who also underwent EBRT or androgen deprivation therapy (ADT) [50]. In cases of impotence, the use of sildenafil helped many men achieve erections suitable for intercourse, especially when ADT was not part of the treatment [51].

4.4. Potential rare complications

Radiation therapy can rarely lead to the development of second cancers in normal tissues. Studies have shown a 1% increased risk of developing cancers such as bladder and rectal cancer 10 or more years after radiation treatment for PCa [52]. Although modern techniques may lower this risk, it is still important to consider this possibility when treating younger men [53]. Recent research on patient outcomes has shifted toward a more comprehensive assessment of quality of life, known as health-related quality of life (HRQOL) [54]. This approach considers how side effects of treatment impact a patient's overall well-being, including their expectations, relationships, satisfaction, and happiness [55]. Standardized questionnaires are used to directly gather information from patients, with specific tools available for PCa patients to assess the impact on aspects such as bowel, bladder, and sexual function. Researchers have employed these questionnaires to assess HRQOL across various treatment modalities [56]. Findings from various studies have shown changes in HRQOL over time after treatments such as radiotherapy, EBRT, and brachytherapy [57]. These changes included differences in urinary, bowel, and sexual function compared to controls, with some improvements noted in certain aspects over time [58]. Overall, HRQOL outcomes vary, depending on the treatment received, with some areas showing improvement while others presenting deteriorating results.

5. HORMONE THERAPY

Hormone therapy is a treatment that aims to halt the production of the male hormone testosterone, which PCa cells rely on for growth. By cutting off the testosterone supply, cancer cells may either die or grow more slowly. Treatment options for hormone therapy include medications that prevent the body from producing testosterone, such as LHRH or GnRH agonists and antagonists, as well as anti-androgens that block testosterone from reaching cancer cells. Hormone therapy is commonly used to manage advanced PCa by shrinking the tumor and slowing its progression. It is also utilized before radiation therapy for localized PCa to reduce the tumor size and enhance the effectiveness of radiation treatment.

5.1. General metabolic complications

ADT prompts swift and substantial alterations in physical makeup. Research on individuals receiving GnRH-agonist treatment has observed an upsurge in adipose tissue, ranging from 9.4% to 11% over the course of a year, alongside a reduction in muscle mass by 2.7 – 3.8% [59]. The bulk of the added fat is accumulated in the subcutaneous layer as opposed to the abdominal cavity [60]. Further studies in individuals with non-spreading PCa revealed that average adipose tissue could increase by 8.5% or 4.3% within the first 3 months of ADT, suggesting that these impacts can be pronounced even during brief treatment periods [61]. Considering the correlation between weight gain, adiposity, and insulin resistance, ongoing inquiries are examining the relationship between ADT and the development of insulin resistance [62]. Treatment-related changes in body composition led to negative metabolic effects. GnRH agonists have been shown to elevate levels of serum total cholesterol, low-density lipoprotein cholesterol, and triglycerides [60]. For instance, in a 12-month study, GnRH agonists increased these levels by 9.0%, 7.3%, and 26.5%, respectively [63]. These agonists also raise fasting plasma insulin levels, indicating insulin resistance [64]. Studies on men with PCa have demonstrated that initiating GnRH-agonist therapy could lead to a 26% increase in fasting plasma insulin levels and an 11% decrease in whole-body insulin sensitivity [65]. The term "metabolic syndrome" refers to a cluster of cardiovascular risk factors linked to insulin resistance. Studies have shown a higher prevalence of metabolic syndrome in men receiving GnRH agonists compared to untreated men with or without PCa [66]. While men on GnRH-agonist therapy may exhibit increased abdominal girth, elevated triglycerides, and elevated fasting plasma glucose, they also show unique metabolic changes, such as preferential increase in subcutaneous fat, higher levels of high-density lipoprotein cholesterol, and elevated serum adiponectin levels [67]. These distinct metabolic alterations suggest that GnRH agonists induce a different pattern of metabolic changes compared to the traditional metabolic syndrome. The adverse effects on weight, physique, lipid levels, and insulin responsiveness associated with treatment heighten worries about a potential elevation in the risk for these issues with ADT. A pivotal research effort led by Keating and associates examined 73,196 individuals with localized or

regionally advanced PCa from 1992 to 1999, with surveillance continuing through 2001. One-third of these men received ADT during the study period. The analysis, which considered patient and tumor characteristics, revealed that ADT with a GnRH agonist was linked to a higher risk of developing diabetes, coronary heart disease, and admission for myocardial infarction. Another study using the same database confirmed the association between ADT and the onset of cardiovascular disease [68].

5.2. Physiological complications

Men undergoing hormone therapy may commonly experience hot flashes, which are abrupt feelings of severe heat in the upper body and face, commonly paired with sweating. While some individuals may turn to natural remedies like acupuncture or soy products to manage these symptoms, the scientific evidence supporting their effectiveness is limited. Medications such as estrogen or megestrol acetate have been shown to alleviate hot flashes, but they may also come with potential side effects such as breast swelling or weight gain [69]. In addition, selective serotonin uptake inhibitors such as venlafaxine or paroxetine have shown promise in providing relief from hot flashes in men, although more research is needed to fully understand their efficacy in this specific population [70].

Fatigue is a prevalent and significant side effect of ADT. Around two-thirds of men experience heightened fatigue following treatment with a GnRH agonist. The alterations in body composition, including a reduction in lean body mass, could potentially play a role in the development of fatigue associated with treatment. In addition, anemia may also be a contributing factor to the fatigue experienced during treatment [71].

Gynecomastia is the non-cancerous growth of glandular tissue beneath the areola, while mastodynia refers to tenderness in the breast or nipple area. The occurrence of gynecomastia and/or mastodynia can vary, depending on the type and duration of ADT used. Between 10% and 15% of males might develop gynecomastia subsequent to bilateral orchidectomy or therapy with a GnRH agonist. Conversely, gynecomastia is a common occurrence in those receiving monotherapy involving an antiandrogen [72]. Preventive breast irradiation is viewed as the premier strategy for forestalling or mitigating the development of gynecomastia, whereas interventions commenced post-development may alleviate discomfort without necessarily reversing the breast enlargement [73]. Tamoxifen stands out as the top medical option for addressing gynecomastia, mastodynia, or both. In rare cases where severe breast symptoms persist despite medical intervention, breast reduction surgery could be beneficial [74].

5.3. Complicates affecting circulatory system

Androgens stimulate the production of erythropoietin and directly activate erythrocyte progenitors, promoting erythropoiesis. In men with PCa, GnRH agonists have been found to significantly reduce hemoglobin levels [75]. This decrease is typically around 1 g/dL, which can lead to anemia in most individuals [76]. However, the anemia associated with treatment is generally mild and does not present with noticeable symptoms. It is typically normochromic and normocytic in nature. While erythropoietin can help increase hemoglobin levels in men receiving GnRH agonists for PCa, the need for specific treatment for anemia in this context is uncommon [77].

5.4. Complications affecting bone health

ADT leads to a notable and lasting reduction in bone mineral density (BMD) in men with PCa, with studies showing a continual decrease at a rate of 2 – 3% per year during treatment [78]. This ongoing decline in BMD heightens the risk of fractures and the development of osteoporosis, which rises steadily with the duration of therapy. The mechanism underlying this decline is linked to increased bone turnover due to ADT, as indicated by markers in blood and urine reflecting heightened activity of both bone-forming cells (osteoblasts) and bone-resorbing cells (osteoclasts). In addition, changes in bone sensitivity to parathyroid hormone may contribute to the activation of osteoclasts and the decrease in BMD [79]. Osteoporosis is a prevalent condition in men, affecting over 2 million men in the US, with hypogonadism being a common cause, along with factors such as alcohol abuse and prolonged glucocorticoid therapy. The reduced BMD and elevated risk of osteoporosis associated with ADT in men with PCa are closely linked to an increased risk of fractures. For instance, one analysis showed that men with PCa receiving GnRH agonists were 1.4 times more likely to experience fractures compared to those not receiving this treatment [80]. The National Institute of Health recommends a daily intake of 1200 to 1500 mg of calcium and 400 IU of Vitamin D for adults [81]. While calcium and Vitamin D supplements can help reduce fractures in older men and women, they are not enough to prevent bone loss in men on ADT treatment for PCa [82]. To address the increased risks of osteoporosis and fractures in these men, studies have explored the use of bisphosphonates such as pamidronate and zoledronic acid (ZA). Research demonstrated that ZA could help prevent ADT-related BMD loss, with a significant increase in BMD observed in the hip and spine [77]. Ongoing trials are investigating the impact of denosumab, toremifene, and ZA on fracture prevention in men on ADT [83,84]. It is recommended to routinely supplement calcium and Vitamin D for all men on ADT to assess fracture risk and consider drug therapy for those at higher risk of fractures.

6. CHEMOTHERAPY

Chemotherapy employs medications to eliminate fast-growing cells, such as cancer cells. It can be delivered through a vein in the arm, in the form of pills, or a combination of both. Chemotherapy is considered a treatment choice for PCa that has metastasized to other parts of the body. It can also be a viable option for cancers that do not positively respond to hormone therapy. It is crucial to consider the toxicity of individual drugs as well as the impact of each drug when used together. The combined toxicity of multiple drugs may be additive, although this is not consistently observed. For instance, the combination of vinblastine with estramustine is found to be less harmful to bone marrow compared to vinblastine used alone.

6.1. Common physiological complications

Nausea and vomiting during chemotherapy can be triggered by the direct impact of the drugs as well as by neurotransmitters released after treatment that affect the chemoreceptor trigger zone (CTZ) in the brain. The CTZ, located at the caudal end of the fourth ventricle in the area postrema, sends signals through the subnucleus gelatinosus [85]. Within the nucleus tractus solitarius, a convergence of afferent neurons from the vagal and vestibular pathways and efferent neurons from the area postrema occurs. Substance P (SP), a neurokinin-1 (NK-1) receptor agonist, serves as the primary chemical messenger for communication among these neurons. SP signals activate the emetic center in the brain, leading to vomiting. Alongside SP, various neurotransmitter systems, including dopaminergic, histaminic, serotonergic, and cholinergic (muscarinic) systems, are believed to contribute to the emetic response. Blocking all five of these receptor systems has been instrumental in the development of modern antiemetic medications. Most PCa treatment regimens have a low or moderate likelihood of causing nausea and vomiting, and advancements in preventing and managing these symptoms have significantly alleviated this issue [86]. Advancements in preventing and managing nausea and vomiting have been driven by improved insights into the mechanisms underlying chemotherapy-induced nausea and vomiting [85]. Various comprehensive guidelines, which are generally similar, are now accessible [87]. Factors related to both the treatment regimen and the individual patient that heighten the risk of nausea and vomiting are better understood. Enhanced knowledge of the effective utilization of serotonin antagonists, expanded use of corticosteroids, and the introduction of the first NK-1 antagonist represents significant progress in this field [88].

Techniques such as acupressure, acupuncture, and acustimulation may help with chemotherapy-induced nausea and vomiting. Clinical trials have shown varying results, with some studies suggesting modest benefits, especially for men [89]. Glutamine is being studied for managing paclitaxel-related muscle pain and nerve issues, with mixed results so far [90]. A small study found that topical honey reduced radiation-induced mouth sores compared to no treatment, but more research is needed to make solid recommendations on complementary approaches in cancer care. Non-infectious diarrhea can be managed with kaolin–pectin compounds, loperamide (Imodium), or prescription antidiarrheal medications. Diuretics are used to control fluid retention. Certain chemotherapy drugs such as paclitaxel and docetaxel may require specific premedication to reduce allergic reactions and fluid buildup. Patients should be well-informed about potential complications to actively participate in their prevention and treatment. Special attention should be given to education about neutropenic fever [91].

Mucositis, or breakdown of the lining inside the mouth, is a common side effect of many cancer treatments. Regular dental check-ups can help prevent oral infections when white blood cell counts are low. It is important to maintain good oral hygiene and rinse with saline solutions regularly. Other methods such as cryotherapy, chlorhexidine rinses, and various products may help prevent mucositis, but their effectiveness varies [92]. Keratinocyte growth factor may be safe and beneficial for patients on certain types of chemotherapy, but more research is needed to confirm its effectiveness, especially for PCa patients [93]. Oral ulcers can be managed with numbing agents, soothing treatments, and pain relievers as needed. Antibiotics, antifungals, or antivirals may be used if an infection is suspected.

6.2. Common metabolic complications

Bone marrow suppression (myelosuppression), hair loss, and mucositis are common side effects of antiproliferative agents that target tissues reliant on cell proliferation for their maintenance [94]. The likelihood of myelosuppression varies significantly, depending on the drug, dosage, and treatment schedule. Factors such as existing bone marrow involvement with cancer or prior marrow-damaging treatments can also influence this risk. The risk of mucositis similarly varies and can be influenced by previous therapies and oral hygiene practices [95]. The occurrence and severity of alopecia can vary between different chemotherapy drugs. In most cases, hair typically regrows after chemotherapy, although the texture of the new hair may be different. Growth factors help maintain chemotherapy doses and prevent fevers in patients getting curative treatment. In advanced PCa, low-dose medication treatment is preferred after fever attacks, as these attacks often lead to a decrease in white blood cell count [96]. Sometimes, medications such as sargramostim, filgrastim, or pegfilgrastim are used in very sick patients or those with low

white blood cell counts from PCa. For PCa patients, red blood cell growth factors such as epoetin alfa or darbepoetin alfa are commonly used. They help ease anemia and fatigue caused by cancer treatments [97]. These growth factors boost red blood cell levels, reduce the need for blood transfusions, and lessen fatigue in many cancer patients. Epoetin alfa is usually given weekly, while darbepoetin alfa is administered every 2 or 3 weeks [98]. Before using growth factors for anemia, other causes such as iron or vitamin deficiencies should be checked.

7. IMMUNOTHERAPY

Immunotherapy harnesses the power of the immune system to combat cancer. Cancer cells can evade detection by the immune system due to the proteins they produce, but immunotherapy disrupts this process. In the case of PCa, immunotherapy options include engineering of the patient's immune cells in a laboratory to target cancer cells (such as with Sipuleucel-T) or the use of drugs to help immune cells recognize and attack cancer cells. These treatments are especially beneficial for advanced PCa that is resistant to hormone therapy.

Sipuleucel-T was developed by Valeant Pharmaceuticals and was the first FDA-approved oncology vaccine for the treatment of desmoplasia-resistant PCa. This is an autologous dendritic cell vaccine that works by binding to a fusion protein that binds prostatic acid phosphatase to granulocyte-macrophage colony-stimulating factor. Sipuleucel-T was shown to improve overall survival for patients with asymptomatic or minimally symptomatic metastatic desmoplasia-resistant PCa (mCRPC) in the phase III IMPACT trial and was approved by the US FDA in 2010 [99]. Pembrolizumab is an anti-PD-1 immune checkpoint inhibitor that has shown some potential in some cases, although it has had limited success as a monotherapy for PCa in some clinical trials [100]. Nivolumab is another anti-PD-1 immune checkpoint inhibitor, similar to pembrolizumab, and is still being studied for its effectiveness in PCa treatment [101]. Ipilimumab is an anti-CTLA-4 immune checkpoint inhibitor that has been tested in a number of clinical trials for the treatment of PCa with limited success [102]. Cabozantinib was primarily used as a multi-targeted tyrosine kinase inhibitor and it has also been linked to immunomodulation and has been approved for the treatment of certain types of PCa. Common side effects include nausea, diarrhea, and joint pain as well as immune function side effects. In severe cases, it can cause varying degrees of damage to heart, liver, and kidney functions [103].

8. TARGETED DRUG THERAPY

Targeted drug therapies are designed to pinpoint and inhibit specific abnormalities found within cancer cells. By targeting these specific abnormalities, these drugs have the potential to induce the death of cancer cells. In the cases of advanced or recurrent PCa, where standard hormone therapy is ineffective, targeted therapy drugs may be recommended as an alternative approach. Certain targeted therapies are effective only in individuals whose cancer cells harbor specific genetic mutations. To determine if a patient may benefit from these targeted therapies, cancer cells can be tested in a laboratory setting to assess the presence of these mutations and the potential efficacy of the drugs for the specific case.

Pluvicto (lutetium Lu 177 vipivotide tetraxetan) was developed by Novartis and approved by the FDA in 2022 for the targeted treatment of PSMA-positive metastatic desmoplasia-resistant PCa (mCRPC) in adults. Pluvicto may cause severe and life-threatening bone marrow suppression, including anemia, nephrotoxicity, thrombocytopenia, leukopenia, and granulocytopenia [104]. Olaparib (Lynparza) and Rucaparib (Rubraca), both PARP inhibitors for the treatment of mCRPC with BRCA mutations, were approved by the FDA in 2020. Side effects of these medicines may include less severe symptoms such as anemia, fatigue, nausea, and vomiting. Detailed side effect information needs to be determined on a patient-specific basis and according to the response to treatment [105,106].

9. CONCLUSIONS

As the incidence of PCa rises, understanding its etiology and implementing preventive measures become increasingly crucial. The continuous evolution of treatment modalities, including precision medicine, novel drug therapies, advanced radiation techniques, immunotherapy, and innovative approaches to address bone-related complications, provides a wide spectrum of promising options for patients. Looking ahead, ongoing research efforts hold the potential for significant advancements in PCa management. Emphasizing the management of side effects associated with these therapies will not only improve treatment outcomes but also enhance the overall quality of care for individuals battling PCa. By prioritizing research into minimizing treatment-related side effects, we can further optimize the effectiveness of therapies and ultimately improve the quality of life of those affected by this disease.

ACKNOWLEDGMENT

None.

FUNDING

This work was supported, in part, by the National Key Research and Development Plan of China (2022YFE021600), the National Key Research and Development Program of

China (2022YFA1105403), Guangdong Province Grant for Belt and Road Joint Laboratory (2022A0505090006) and Science and Technology Planning Project of Guangdong Province, China (2023B1212060050 and 2023B12120009).

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of this review.

AUTHOR CONTRIBUTIONS

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA

Not applicable.

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