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REVIEW

Mechanisms underlying prostate cancer sensitivity to reactive oxygen species: overcoming radiotherapy resistance and recent clinical advances

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ABSTRACT Prostate cancer (PCa) is a leading cause of cancer-related mortality among men. Radiotherapy is the cornerstone of PCa treatment. However, a major limitation of radiotherapy is the development of resistance, which compromises treatment efficacy. Reactive oxygen species (ROS), which are generated by radiation, have a dual role in PCa by inducing DNA damage and apoptosis, while also promoting tumor progression and radioresistance. Elevated ROS levels enhance metabolic reprogramming, activate oncogenic pathways, and influence the tumor microenvironment by modulating immune responses and promoting the epithelial-mesenchymal transition (EMT). Key molecular mechanisms, including the Nrf2/Keap1 signaling axis, Bcl-2 mutations, and Speckle-type POZ protein alterations, contribute to radioresistance by enhancing antioxidant defenses and DNA repair capacity. Additionally, the interplay between hypoxia, androgen receptor variants (AR-Vs), and ferroptosis regulators further influence radiotherapy outcomes. Understanding these resistance mechanisms is crucial for developing targeted strategies to enhance radiosensitivity and improve therapeutic outcomes in PCa patients.

KEYWORDS Prostate cancer (PCa); radiation therapy (RT); reactive oxygen species (ROS); radiotherapy resistance; antioxidants

Introduction

Prostate cancer (PCa) detection and management have improved since the introduction of prostate-specific antigen (PSA) testing in the early 1990s. Nevertheless, PCa remains the second leading cause of cancer-related mortality in men in the United States with an estimated 299,010 new cases and 35,250 deaths projected in 2024[1]. Racial disparities persist because Black patients have nearly twice the lifetime risk of PCa-related deaths compared to non-Hispanic White patients, in part due to differences in access to care and disease biology[2].

Androgen deprivation therapy (ADT) is the cornerstone of PCa treatment, particularly in combination with radiotherapy for intermediate- and high-risk localized PCa[3,4]. However, challenges remain, including uncertainty regarding the optimal use and duration of ADT following radical prostatectomy[5]. In addition, combination therapies increase toxicity and raise concerns about the development of drug resistance with prolonged use, underscoring the need for continued monitoring and novel strategies to mitigate resistance[6].

Radiation therapy is a critical component of cancer treatment and is used in greater than one-half of all cancer patients as the first-line approach. Radiation therapy induces reactive oxygen species (ROS) and DNA damage, which leads to tumor cell apoptosis and cell death, and ultimately increases patient survival[3,7-9]. Advances in radiation therapies, including

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external beam radiation therapy (EBRT), which remains the most widely used method for targeting early-stage prostate tumors, have improved patient survival[10]. Emerging techniques [e.g., proton beam therapy, stereotactic body radiation therapy (SBRT), and intensity-modulated radiation therapy (IMRT)] offer improved precision, while minimizing exposure to adjacent structures[11-13]. SBRT uses advanced image-guidance for precise radiation delivery, which makes SBRT particularly beneficial for isolated bone metastases, while IMRT modulates beam modulation to reduce exposure to nearby healthy tissues, reducing treat-associated side effects[14-17].

Brachytherapy, an internal radiation technique, involves implanting radioactive sources directly into tumors. Brachytherapy has demonstrated high efficacy in PCa with > 80% achieving a 10-year overall survival and < 10% incidence of distant metastases for patients receiving low- or high-dose brachytherapy (LDBT or HDBT, respectively)[18]. However, radiation resistance remains a challenge, resulting in disease relapse several months after treatment[19,20]. PCa develops mechanisms to resist radiation-induced apoptosis and promote tumor proliferation. One key strategy for tumor survival is developing antioxidant defenses following radiation exposure, which enables escape from radiation-induced cell death[9,17]. Understanding resistance mechanisms and developing targeted strategies to overcome resistance mechanisms will be crucial in further optimizing radiotherapy for PCa[3,15]. In this review the mechanisms underlying the radioresistance mechanism is explored with a focus on antioxidant material development, pathway mutations, and immune environment regulation that contribute to radioresistance after radiation. Moreover, the clinical trials targeting these mutation or pathways are summarized, highlighting the potential to overcome radioresistance. This review provides insights into future drug development targets and emphasizes the importance of addressing these mechanisms to enhance therapeutic efficacy in PCa.

Dual role of ROS in tumor biology and mechanisms underlying tumor resistance to oxidative stress

Radiation exposure induces rapid production of ROS in < 1 s, including superoxide anion (O^{2-}), hydrogen peroxide (H_2O_2), hydroxyl radical (OH), and singlet oxygen (O_2). These ROS contribute to DNA damage, such as frequent double-strand break (DSB) damage and single-strand breaks (SSBs), leading to intracellular damage at tumor sites. However, ROS have dual effects in tumorigenesis and antitumor effects[21].

PCa cells exploit ROS production to support tumor progression and survival. Elevated intracellular ROS levels have been reported in PCa cell lines (DU145, PC3, and LNCaP) compared to normal prostate epithelial cells, which contribute to malignant transformation[22]. ROS accumulation induces chromosomal abnormalities, including rearrangements, amplifications of tumor promoter genes, and deletions of key tumor suppressor genes, such as PTEN, TP53, and RB1, which promote tumor progression[23]. The tumor suppressor protein, p53, has a pivotal role in regulating apoptosis. Upon activation, p53 induces the expression of pro-apoptotic proteins, including B-cell lymphoma-2 (Bcl-2) associated X protein (BAX) and p53 upregulated modulator of apoptosis (PUMA). BAX facilitates apoptosis by permeabilizing the mitochondrial outer membrane, leading to the release of cytochrome c and the subsequent activation of caspases that execute cell death. However, moderately elevated ROS levels can inhibit p53, thereby suppressing apoptosis[21,24]. Additionally, ROS dysregulation disrupts mitochondrial function, leading to metabolic reprogramming. Dysfunctional mitochondria shift cancer cells towards glycolysis, supporting tumor survival. Inhibiting ROS production reduces matrix metalloproteinase 9 (MMP-9) activity, mitochondrial dysfunction, and PCa cell invasion, thereby enhancing cell death. Moreover, NAD(P)H oxidase (Nox) inhibitors, such as diphenyliodonium, impair tumor proliferation by modulating key survival pathways, including ERK1/2, p38 mitogen-activated protein kinase (MAPK), and AKT, and induce G_2/M cell cycle arrest[24,25] (**Figure 1**).

ROS also influence the tumor microenvironment (TME) by activating the immune cells and stimulating pro-inflammatory cytokine release, such as TNF-α and IL-6, to create a tumor-supportive environment in tumorgenesis[4,8] (**Figure 1**). In addition, ROS stimulate angiogenesis and activate oncogenic pathways, including MAPK and nuclear factor (NF)-κB, further driving signaling pathways[26]. MEKK3 and MEKK6 are upstream MAP3Ks that regulate MAPK signaling (JNK and p38). ROS upregulation induce TNF-α expression, which subsequently activates RIP and MEKK3/6 signaling. This pathway has a critical role in cancer progression, therapy resistance, and immune responses[27]. Conversely, ROS-mediated DNA damage has a key role in radiation therapy-induced tumor cell death. Tumor cells utilize adaptive mechanisms to counteract ROS-induced damage, primarily through non-homologous end joining (NHEJ) and homologous recombination (HR)

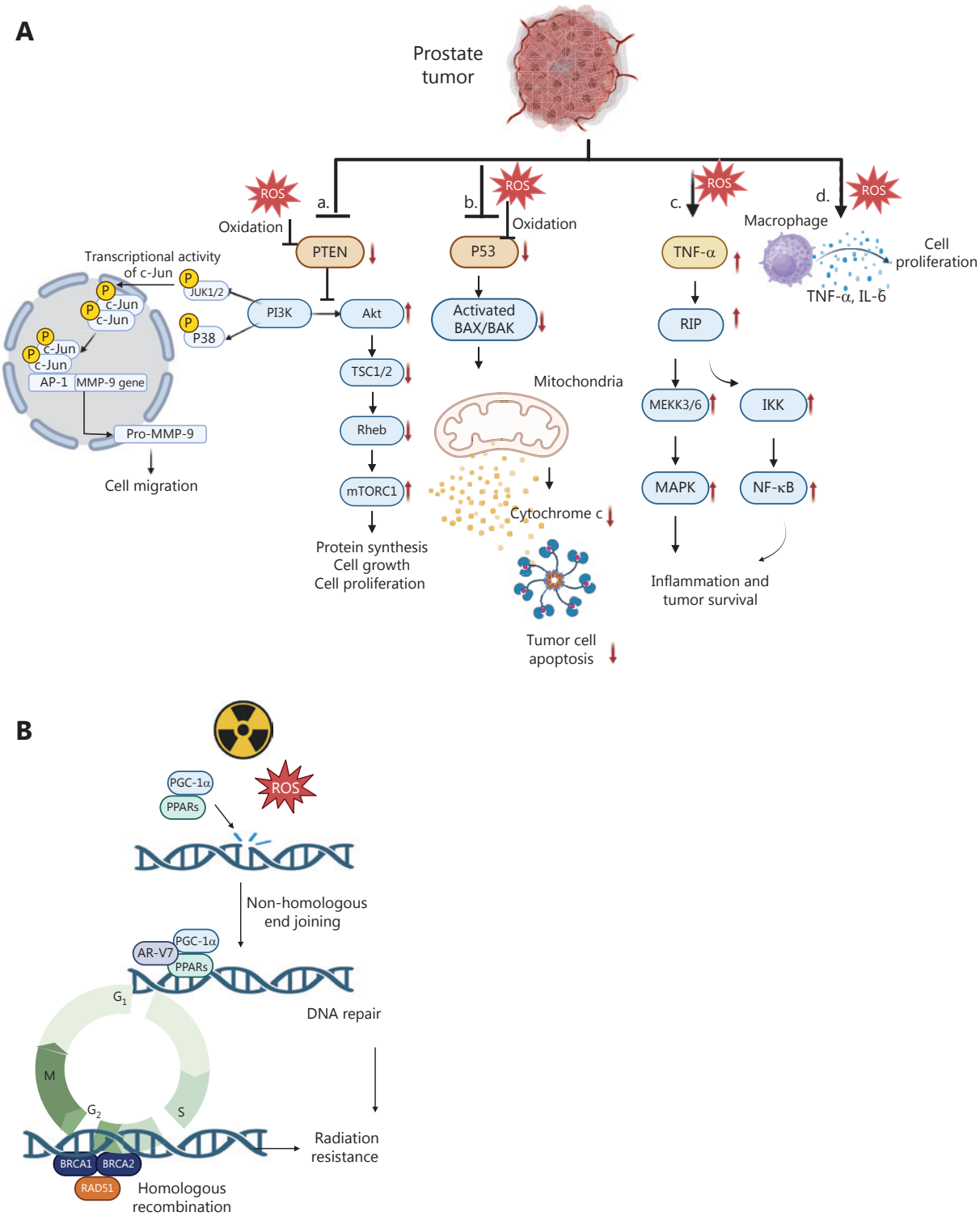


Figure 1 ROS production induces tumor progression and proliferation in prostate cancer. (A) ROS have a critical role in prostate cancer progression by inhibiting key tumor suppressor pathways, including p53 and PTEN, thereby promoting tumor development. (a) ROS-induced PTEN oxidation leads to PTEN inhibition, resulting in activation of the PI3K pathway signaling, which contributes to cancer progression through multiple downstream pathways. One pathway involves activation of JNK1/2 and p38 phosphorylation, which subsequently upregulates pro-MMP-9 expression, facilitates extracellular matrix degradation, and enhances tumor cell migration. Another pathway involves PI3K-mediated

activation of downstream effectors, such as Akt and mTORC1, leading to increased protein synthesis, cell growth, and proliferation; (b) ROS induce p53 inhibition through oxidation and enhances suppression of cytochrome c release; (c, d) ROS promote pro-tumor signaling and reshape the tumor immune microenvironment by inducing the expression of inflammatory cytokines, such as TNF-α and IL-6, which further contributes to tumor progression and immune evasion in chronic inflammatory environment. This multifaceted role of ROS highlights the importance in prostate cancer development and therapy resistance, making ROS a potential target for therapeutic intervention. (B) Radiation-induced ROS causes DNA damage, leading to distinct repair mechanisms depending on the cell cycle phase. DNA repair occurs primarily through NHEJ in the G1 phase and is facilitated by AR-V7, while tumor cells activate HR for error-free repair in the S and G2 phases. Both pathways contribute to radiation resistance by enabling tumor cell survival and genomic stability. PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; JNK1/2, c-Jun N-terminal kinase 1 and 2; AKT, protein kinase B; mTOR, mammalian target of rapamycin; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; HR, homologous recombination; NHEJ, non-homologous end joining; Pro-MMP-9, pro-matrix metalloproteinase 9; AR-V7, androgen receptor splice variant 7.

repair pathways, allowing tumor cells to acquire mutations that enhance survival. NHEJ, the dominant repair mechanism in G1-phase tumor cells, contributes to mutational burden, conferring resistance to radiotherapy[28].

Androgen receptor splice variants, particularly AR-V7, contribute to radiotherapy resistance by enhancing the DNA damage response (DDR) and promoting HR and NHEJ repair mechanisms. AR-V7 upregulation post-radiation reduces the synthetic lethality response to PARP-1 inhibitors and interacts with DNA-PKcs to enhance DNA repair efficiency, fostering resistance in PCa cells[29]. Mutations in tumor suppressor genes, such as TP53 and PTEN, further disrupt ROS regulation. PTEN loss alters intracellular signaling, while TP53 mutations impair antioxidant responses, facilitating redox homeostasis and treatment resistance[30] (**Figure 1**).

Notably, high glucose levels induce p53 phosphorylation at Thr55 *via* TAF1 kinase, enhancing ROS generation and radiation resistance. Inhibiting TAF1 or p53 Thr55 phosphorylation suppresses ROS generation and restores radiosensitivity[21,31-33].

In summary, the intricate interplay between ROS, DNA repair mechanisms, and metabolic reprogramming has a crucial role in PCa progression and treatment resistance. Targeting ROS regulatory pathways and metabolic adaptations presents a promising strategy to overcome radiotherapy resistance and improve therapeutic outcomes in PCa.

Role of ROS and ROS involvement during radiotherapy in PCa patients

ROS have a dual role in PCa progression and treatment. Without radiation, ROS accumulation promotes tumorigenesis by activating oncogenic pathways, shifting the TME into a pro-inflammatory state, releasing tumor promoting cytokines, and altering mitochondrial respiration[15,34]. ROS accumulation within tumor cells enhances treatment efficacy by inducing direct oxidative damage and ROS-mediated cell death[35].

Water radiolysis rapidly generates free radicals within fractions of a second upon radiation exposure, leading to substantial DNA damage. This initial genomic injury triggers a cascade of biological responses that sustains ROS production for several hours and ultimately promoting tumor cell degradation[35,36].

Radiation induces ROS production through direct effects or ROS-mediated cells death. For direct ROS effects, radiation energy interacts with DNA, proteins, and lipids, causing immediate damage. Additionally, radiation induces mitochondrial DNA (mtDNA) damage and upregulates NADPH oxidase (NOX) enzymes, leading to elevated intracellular ROS levels and oxidative stress, ultimately resulting in cell death[37]. For ROS-mediated cell death, increased ROS levels directly damage DNA strands, triggering cell cycle arrest and apoptosis, particularly during the G2/M phase[38].

Genetic mutations significantly influence how PCa cells respond to ROS-induced DNA damage and radiation therapy. BRCA1 and BRCA2, critical genes for HR repair, have a key role in repairing ROS-induced DNA damage during the S and G2 phases. Between 1% and 2% of PCa patients harbor BRCA1/2 mutations, leading to defective DNA repair, increased radiosensitivity, and heightened susceptibility to ROS-induced cell death[39,40].

Notably, studies have shown that combining ADT with radiotherapy significantly improves 5-y survival rates in BRCA2-mutant PCa patients, demonstrating the synergistic effect of hormone therapy and radiotherapy[39]. Several factors influence the ROS-mediated radiation response in PCa, with ADT having a key role in enhancing the sensitivity of AR-positive cells

to oxidative stress[29]. Research has indicated that ADT induces a radiation response by modulating ROS levels. Specifically, testosterone increases basal ROS levels in a dose-dependent manner, leading to the activation of phospho-p38 and pAKT, as well as upregulation of clustering, catalase, and manganese superoxide dismutase[17,21].

ROS accumulation by radiation attacks lipid membranes, generating lipid peroxides, which can induce ferroptosis, an iron-dependent form of cell death. PCa cells, characterized by high iron levels, are particularly vulnerable to ferroptosis induction. Acyl-CoA synthetase long-chain family member 4 (ACSL4) has a crucial role in regulating arachidonic acid and eicosatetraenoic acid metabolism, leading to ferroptosis[41].

Recent evidence suggested that ionizing radiation enhances ACSL4 expression, thereby increasing radiosensitivity[42]. Furthermore, RB1-deficient prostate tumors are particularly susceptible to ferroptosis through the E2F/ACSL4 axis, highlighting the potential of targeting ferroptosis pathways to improve radiotherapy outcomes[43].

Radiotherapy is particularly notable for its targeted delivery of high-energy particles to tumor sites, effectively inhibiting carcinogenesis, inducing cytotoxic responses, and modulating the tumor immune microenvironment (TIME)[15,44,45]. Although ROS accumulation primarily regulates molecular and metabolic processes, ROS accumulation also has a crucial role in immune activation. ROS induce damage-associated molecular patterns (DAMPs), making PCa cells more recognizable to the immune system. The increased expression and release of MHC-I in the immune microenvironment enhance antigen presentation to T cells, thereby promoting cytotoxic T cell-mediated tumor killing[7,46]. Moreover, radiation transforms prostate tumors into an "*in situ* vaccine," increasing responsiveness to immunotherapy by upregulating PD-L1 and enhancing immune responses. However, studies have indicated that radiotherapy-induced ROS production by neutrophils may disrupt antitumor immunity. Excessive ROS infiltrating the TME can impair immune responses against the tumor[15,47]. Additionally, some PCa cells develop resistance to radiation-induced ROS. Prostate tumors are often hypoxic, which reduces ROS production from radiation and stabilizes HIF-1α, and promotes survival pathways. This finding highlights the importance of combining radiation with hypoxia modifiers to enhance ROS-mediated tumor cell killing[48,49].

Thus, understanding the mechanisms underlying ROS-induced radiosensitivity and ROS resistance is of great importance for optimizing radiotherapy outcomes.

ROS removal-associated radiotherapy resistance in PCa

While radiotherapy is an effective treatment for various cancers and can slow PCa progression, the development of radiotherapy resistance limits the overall efficacy[50,51]. A significant portion of radiation-induced DNA damage stems from ROS accumulation, which destabilizes the genome and induces oxidative DNA damage. Oxidative stress, resulting from an imbalance between ROS and antioxidants, disrupts physiologic and pathologic processes by oxidizing proteins, lipids, and DNA[44,52].

Key ROS species include O^{2-}), H_2O_2, OH, and O_2, with ·OH being particularly reactive and capable of inflicting direct cellular damage. The success of radiotherapy largely depends on ROS levels because elevated concentrations enhance antitumor effects. However, ROS scavengers within tumors counteract oxidative stress, reducing radiosensitivity and promoting mechanisms of radioresistance[53].

In this review several key molecular mechanisms and processes that regulate ROS production and contribute to radiation resistance are discussed.

Nuclear factor erythroid 2-related factor 2 (Nrf2)/kelch-like ECH-associated protein 1 (Keap1) complex degradation and its role in radiation resistance

Nrf2 is a pivotal regulator of ROS homeostasis and is closely linked to tumor progression and therapeutic resistance[54]. This 605-amino-acid transcription factor, containing a leucine zipper domain, has a crucial role in maintaining cellular redox balance by regulating antioxidant defenses[55]. Under normal conditions Nrf2 is sequestered in the cytoplasm through an interaction with Keap1, which serves as an adaptor for Cul3-containing E3 ubiquitin ligase, thereby promoting Nrf2 ubiquitination and proteasomal degradation. However, oncogenic mutations, such as K-Ras^{G12D}, B-Raf^{V619E}, and Myc^{ERT2}, elevate basal Nrf2 transcription, reducing intracellular ROS levels and fostering a more reduced intracellular environment, thereby promoting tumor survival[54]. The Keap1-Nrf2 complex is disrupted upon exposure to radiation-induced ROS, allowing Nrf2 to translocate into the nucleus, where Nrf2 activates the transcription of antioxidant response element (ARE)-dependent genes that protect against oxidative damage. While this mechanism is essential for normal cellular defense, tumors

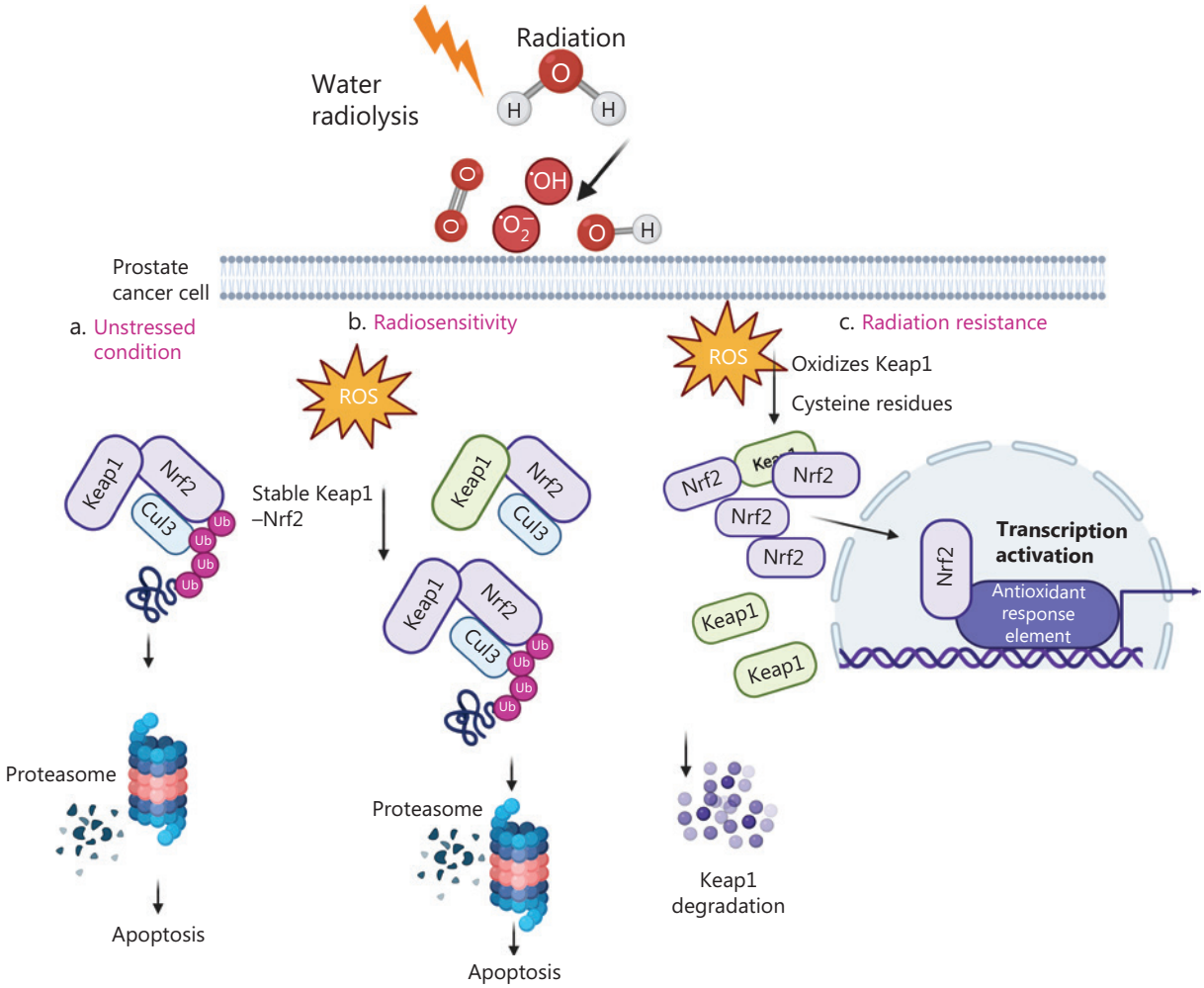


Figure 2 Keap1–Nrf2 pathway: Regulation of antioxidant gene activation. Different cellular responses occur under various conditions following radiation-induced water radiolysis: (a) Under unstressed conditions, Nrf2 binds to Keap1 in the cytoplasm and undergoes ubiquitin-mediated proteasomal degradation, preventing antioxidant gene activation and resulting in cell apoptosis; (b) Under radiosensitive situation, Nrf2 remains bound to Keap1, maintaining low basal antioxidant activity and promoting apoptotic cell death; (c) Under radiation resistance conditions, ROS oxidize specific cysteine residues on Keap1, leading to the disruption of the Keap1–Nrf2 complex. Freed Nrf2 translocates into the nucleus, where Nrf2 activates transcription of ARE, enhances cellular defense against oxidative damage, and promotes radiation resistance. Nrf2, nuclear factor erythroid 2-related factor 2; Keap1, kelch-like ECH-associated protein 1; ROS, reactive oxygen species; ARE, antioxidant response element.

exploit Nrf2 activation to enhance radiotherapy resistance by counteracting ROS-induced cytotoxicity[56,57] (**Figure 2**).

PCa cells have developed multiple strategies to manipulate the Keap1-Nrf2 axis, leading to enhanced ROS detoxification and resistance to radiotherapy-induced oxidative stress. Hu et al.[58] demonstrated that the inhibitor of apoptosis-stimulating protein of p53 (iASPP), a known binding partner and transcriptional repressor of NF-κB/p65, exerts anti-ROS effects independent of p53 by stabilizing Nrf2. iASPP competitively binds to Keap1 *via* a DLT motif, preventing Keap1-mediated Nrf2 degradation and promoting resistance to radiotherapy[55]. Glucose also induces Keap1-Nrf2 stabilization. Elevated glucose levels further enhance tumor resistance to oxidative stress by stabilizing the Keap1-Nrf2 complex and repressing the Nrf2/ARE pathway. This metabolic adaptation is accompanied by an increase in IL-6 and a decrease in IL-10, fostering a pro-inflammatory microenvironment that supports tumor survival[59,60].

Speckle-type POZ (SPOP) protein mutation induces radiation sensitivity

SPOP functions as an adaptor for the E3 ubiquitin ligase complex and has a critical role in cellular ubiquitination and proteasomal degradation. SPOP regulates various physiologic

and pathologic processes through interactions with histone-associated proteins. Among key genetic alterations in PCa, the SPOP mutation is one of the most frequently observed, making SPOP a potential biomarker for personalized treatment strategies[61]. SPOP mutations contribute significantly to PCa progression, occurring in 4%–28.6% of cases[62,63]. Previous studies have shown that patients with metastatic castration-resistant prostate cancer (mCRPC) harboring SPOP mutations often have a concurrent CHD1 deletion, which has been linked to increased sensitivity to abiraterone treatment[64,65]. Additionally, silencing SPOP using siRNA in PCa cells enhances sensitivity to radiation therapy by impairing ROS-activated DDR pathways. This dysregulation compromises DDR by downregulating RAD51 and CHK1, two key factors in HR, leading to increased radiosensitivity[62]. Beyond DDR, SPOP mutations also influence the TME. A subset of treatment-refractory CRPC patients with SPOP mutations exhibit upregulation of a 29-gene non-canonical STING (NC-STING) signature[7,9,16,66]. Recent preclinical studies demonstrated that SPOP normally targets and destabilizes STING1 protein but SPOP mutations lead to upregulated NC-STING-NF-κB signaling, promoting macrophage-driven TME remodeling and tumor growth. SPOP mutations are also linked to genomic instability. Among these SPOP mutation, the S119N mutation (serine 119 to asparagine) is associated with radiosensitivity. PCa cells carrying this mutation exhibit hypersensitivity to radiation, loss of the IR-induced G2/M checkpoint, and persistent γ-H2AX accumulation, indicating impaired DDR and increased genomic instability[67] (**Figure 3**).

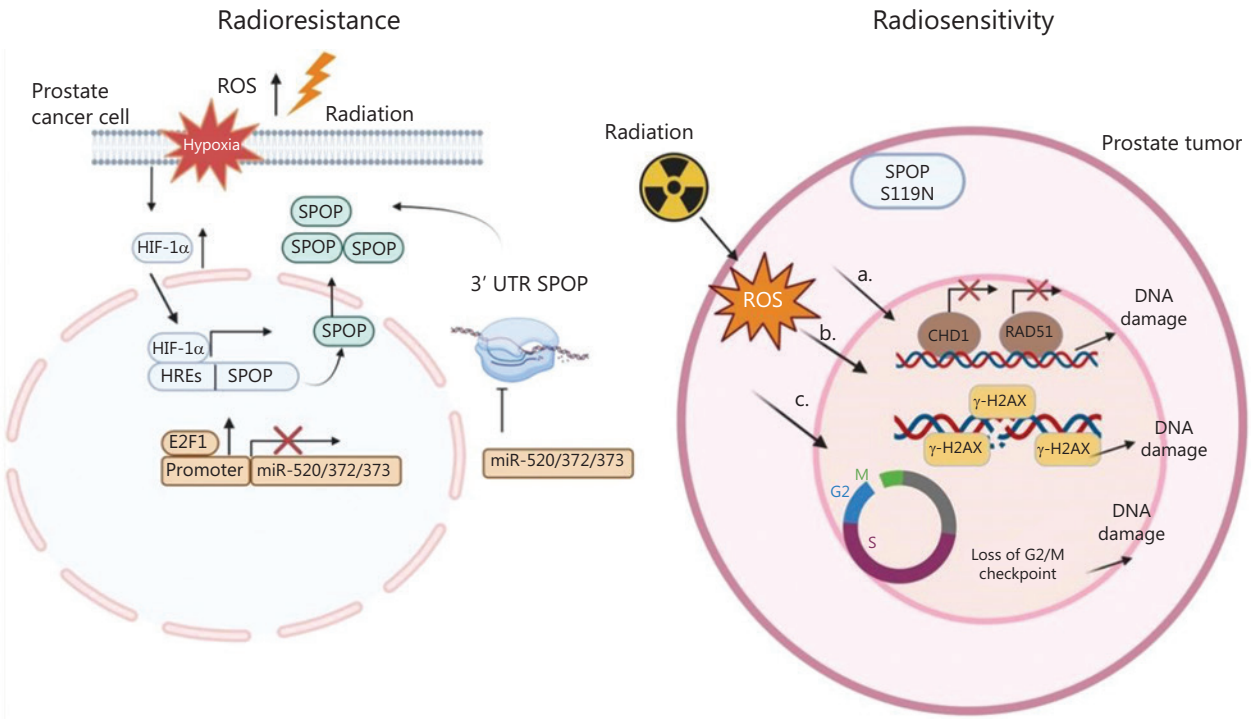


Figure 3 Impact of SPOP mutation on DDR and radiosensitivity in prostate cancer. Radiation induces hypoxia through the accumulation of ROS in radiation-resistant prostate tumors, leading to increased expression of HIF-1α. Upon nuclear translocation, HIF-1α forms heterodimers and binds to HREs to initiate target gene transcription. HIF-1α is assumed to regulate SPOP expression by interacting with an HRE located in the SPOP promoter region. Concurrently, overexpression of the transcription factor, E2F1, by ROS upregulation suppresses the transcription of miR-520/372/373 by binding to the promoter regions. Downregulation of these microRNAs prevents the inhibitory interaction with the 3′ UTR of SPOP mRNA, relieving post-transcriptional repression. Together, these mechanisms contribute to SPOP overexpression, enhancing DDR pathways and promoting radiation resistance. In radiosensitive prostate cancer cells, SPOP mutations, particularly the clinically relevant S119N variant, enhance radiation sensitivity through multiple mechanisms: (a) downregulation of key HR repair factors, including RAD51 and CHD1, leading to impaired HR-mediated DNA repair; (b) sustained γ-H2AX accumulation, reflecting persistent DNA DSB and genomic instability; (c) loss of the G2/M cell cycle checkpoint, resulting in the accumulation of unrepaired DNA damage. Together, these effects compromise DDR pathways and contribute to enhanced radiosensitivity. HIF-1α, hypoxia-inducible factor-1α; 3′ UTR, 3′ untranslated region; HR, homologous recombination; SPOP, Spop speckle-type BTB/POZ protein; DSB, double strand break; DDR, DNA damage response.

Preclinical models further support the association between SPOP mutations and higher tumor burden, as well as enhanced sensitivity to radiation therapy. Given the diverse functions of SPOP mutations across different models, further research is needed to clarify the role in ROS regulation, DDR impairment, and therapeutic resistance. These findings are further supported by preclinical PCa models, in which SPOP mutations are associated with higher tumor burden and increased sensitivity to radiation therapy[63]. Given the varied functions of SPOP observed across different research models and results, further exploration of SPOP functions is needed to clarify its roles. The current clinical trials aiming to overcome the radiation resistance in PCa are summarized in **Table 1**.

NCT05689021

NCT05689021 is a phase II clinical trial involving patients with CRPC harboring SPOP gene mutations. The study is evaluating the efficacy of a fixed-dose combination of abiraterone acetate and niraparib (CJNJ-67652000) in combination with prednisone. The primary objective is to assess radiologic progression-free survival (PFS), while a secondary objective is to determine the time to PSA progression. The trial includes 30 participants and aims to investigate whether CJNJ-67652000 with prednisone enhances tumor cell eradication in metastatic PCa compared to administration of these drugs separately[68]. This clinical trial is still ongoing.

Bcl-2 overexpression alters radiation sensitivity

The Bcl-2 family of pro-survival proteins regulates the intrinsic apoptotic pathway by modulating mitochondrial outer membrane permeabilization (MOMP), leading to the release of intermembrane space proteins, caspase activation, and apoptosis[59,69,70].

Elevated Bcl-2 levels can serve as a prognostic marker for PCa that is resistant to radiotherapy because Bcl-2 is often higher in tumors that progress after radiation compared to tumors treated with radical prostatectomy. Assessing Bcl-2 expression with pre-treatment PSA levels may help identify HRPC patients who are more likely to benefit from taxane-based chemotherapy[9,70,71]. Notably, Bcl-2-positive patients have longer cause-specific survival than Bcl-2-negative patients but overexpression of Bcl-2, which is often driven by the PI3K/NF-κB pathway, is associated with PCa progression[58].

Studies have explored Bcl-2 inhibition as a strategy to overcome radioresistance. In a preclinical model of enzalutamide (Enz)-resistant PCa, increased Bcl-2 expression was targeted using the Bcl-2 inhibitor ABT263, enhancing sensitivity to Enz in Enz-sensitive and -resistant cells. This effect was achieved by inducing ROS production and inhibiting USP26 activity, leading to the degradation of AR and ARv7 proteins[72].

Bcl-2 overexpression also drives aggressive behavior and resistance in PCa cells but treatment with the Bcl-2 inhibitor, HA14-1, can sensitize these cells to gamma radiation[73]. Sequential treatment with HA14-1 and radiation synergistically induces cell death by enhancing ROS production, JNK activation, and apoptotic pathways. This combination significantly increases apoptosis in radioresistant cells, indicating that ROS and JNK are key mediators in caspase-dependent and -independent cell death[74] (**Figure 4**).

Table 1 Summary of current clinical trials aiming to overcome radiation resistance in prostate cancer

ClinicalTrials ID	Antigen target	Clincial phase	Study type	Number of patients	Response	Patients type
NCT05689021	SPOP	Phase II	Interventional	30	On going	Castration-resistant prostate carcinoma; Metastatic prostate adenocarcinoma stage IVB; Prostate cancer AJCC V8
NCT00085228	Bcl-2	Phase II	Interventional	11	Completed	Prostate cancer
NCT00666666	Bcl-2	Phase 2	Interventional	55	Completed	Adenocarcinoma of the prostate; Stage IV prostate cancer
NCT04021394	EMT	Not applicable	Observational	31	Completed	Prostate cancer
NCT02022904	EMT	Not applicable	Interventional	0	Withdrawn	Prostate cancer
NCT02025413	EMT	Not applicable	Observational	46	Completed	Metastatic progressive breast cancer; Metastatic progressive castration-resistant prostate cancer

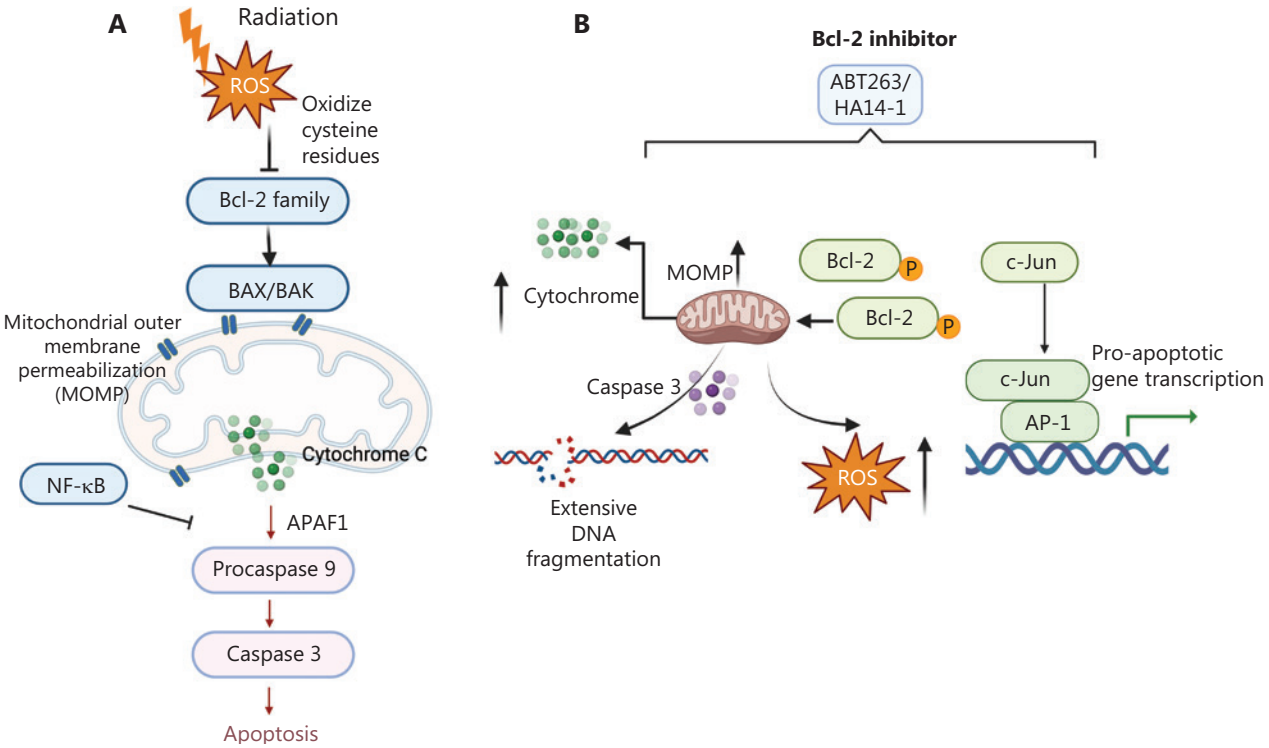


Figure 4 Mechanisms of intrinsic apoptotic pathway and Bcl-2 inhibitor action in overcoming radiation resistance. (A) The intrinsic apoptotic pathway is activated by intracellular stress. ROS induced by radiation oxidize cysteine residues on Bcl-2 family proteins, altering their activity and promoting BAX/BAK-mediated MOMP. This effect results in the release of pro-apoptotic proteins from the mitochondrial intermembrane space, including cytochrome c, which binds to APAF1 to assemble the apoptosome and activate downstream caspases. (B) Bcl-2 inhibitors (e.g., ABT263 and HA14-1) counteract radiation resistance primarily by neutralizing anti-apoptotic Bcl-2 activity, resulting in increased MOMP. Elevated MOMP promotes the release of cytochrome c, extensive DNA fragmentation through activation of caspase-3, and increased ROS levels. In parallel, Bcl-2 inhibition facilitates the phosphorylation and nuclear translocation of c-Jun, which associates with AP-1 to drive pro-apoptotic gene transcription. Bcl2, B-cell lymphoma 2; BAX, Bcl2-associated X protein; BAK, Bcl2 antagonist/killer; MOMP, mitochondrial outer membrane permeabilization; APAF1, apoptotic protease-activating factor 1; ROS, reactive oxygen species; c-Jun, Jun proto-oncogene.

NCT00085228

NCT00085228 is a randomized phase II clinical trial evaluates the efficacy of combining docetaxel with oblimersen compared to docetaxel alone in the treatment of hormone-refractory prostate adenocarcinoma. Chemotherapy-naïve patients with PSA progression and testosterone levels ≤ 0.5 ng/mL were assigned to receive docetaxel (75 mg/m^2 on day 1) or oblimersen (7 mg/kg/day) *via* continuous intravenous infusion on days 1–7 with docetaxel (75 mg/m^2) administered on day 5 every 3 weeks for up to 12 cycles[75].

The results indicated a confirmed PSA response in 46% of patients receiving docetaxel alone (n = 57) and 37% of patients receiving the docetaxel–oblimersen combination (n = 54). A partial response, as defined by RECIST criteria, was observed in 18% and 24% of patients in the respective groups. However, the addition of oblimersen was associated with an increased incidence of grade ≥ 3 fatigue, mucositis, and thrombocytopenia. Severe adverse events were reported in 22.8% of patients receiving docetaxel alone and 40.7% of patients receiving combination therapy[75].

The identification of patients who would benefit most from oblimersen in clinical settings remains undetermined. Given that apoptotic failure may result from molecular mechanisms beyond Bcl-2 overexpression, the subgroup of patients most likely to benefit from oblimersen therapy are patients in whom chemoresistance is specifically linked to Bcl-2 overexpression[75]. Although this trial included a total of only 11 patients, future studies with larger cohorts are

necessary to validate these findings. Additionally, strategies to mitigate the increased toxicity of the combination regimen should be explored to enhance clinical applicability[75].

NCT00666666

NCT00666666 is a phase II clinical trial that enrolled 55 patients with a median age of 61 years who were initiating ADT for metastatic PCa. Patients received ADT with a luteinizing hormone-releasing hormone (LHRH) agonist and bicalutamide, initiated 6 weeks prior to the administration of oral AT-101 (20 mg/day for 21 d per 28-d cycle). Fluorescence *in situ* hybridization (FISH) with confocal microscopy was performed in a subset of patients to assess treatment efficacy and CHD1 association. Computed tomography (CT) scans were conducted within 28 d of starting AT-101 and repeated every 12 weeks[76].

A total of 10 patients (18%) discontinued treatment due to toxicity, while 12 patients (22%) experienced serious adverse events (SAEs), including 7 (13%) who had multiple SAEs. The study hypothesized that overcoming a key resistance mechanism to apoptosis would increase the proportion of patients achieving undetectable PSA from 48% to 68%. However, the combination of AT-101 and ADT failed to achieve this target. In an intention-to-treat analysis, 31% of patients attained undetectable PSA levels, while an additional 25% normalized the PSA levels to < 4 ng/mL[76].

The study population included Caucasian and African American patients, allowing for a more diverse representation of clinical outcomes across racial groups. However, the high toxicity of AT-101 remains a significant limitation with 33% of patients developing neuropathy, leading to early termination of the trial for some participants. Future research should focus on optimizing AT-101 dosing or exploring alternative formulations to reduce toxicity, thereby improving patient adherence and the overall therapeutic potential of this combination strategy[76].

Epithelial-mesenchymal transition (EMT) and radiation resistance

EMT is a process in which epithelial cells lose polarity and intercellular adhesion, gaining migratory and invasive properties. This transformation gives cells mesenchymal stem-like qualities, enabling differentiation into various lineages. Alterations in the EMT phenotype are associated with radiotherapy resistance and tumor recurrence in PCa[77]. EMT is regulated by signaling pathways, such as Wnt, TGF-β, and MAPK, which activate transcription factors that influence EMT and contribute to cancer stem cell (CSC) formation[78]. There is an inverse relationship between CSC stemness and intracellular ROS levels. Reducing ROS scavengers within CSCs increases ROS concentrations, which enhances cellular radiosensitivity[52]. The interplay between EMT, CSC characteristics, and ROS regulation highlights the critical role of oxidative signaling in cellular plasticity and treatment response[79].

CD44, a glycoprotein involved in adhesion and migration, is a key marker for CSCs. Overexpression of CD44v6 induces radiotherapy resistance, making CD44v6 a potential therapeutic target to enhance radiosensitivity through ROS upregulation[80,81]. Targeting CD44 with agents (e.g., salinomycin or siRNA) inhibits EMT and reduces PCa invasiveness, suggesting that CD44+CSCs drive EMT *via* TGFβ1-CD44 signaling. Inhibition of CD44 also decreases glucose consumption, increases ROS levels in PC-3 cells and sensitizes PC-3 cells to docetaxel[82].

Key genes in EMT, like aldehyde dehydrogenase (ALDH), contribute to radiotherapy resistance by enhancing DNA repair and activating the WNT/β-catenin pathway. Studies have shown that inhibiting WNT/β-catenin with XAV939 or β-catenin knockdown sensitizes PCa cells to radiation[83].

Clinical trials targeting EMT and circulating tumor cells in different cancers are ongoing, assessing the potential therapeutic efficacy.

NCT04021394

NCT04021394 is an observational clinical trial designed to evaluate whether the existing methods for measuring CTCs are feasible and whether CTCs accurately reflect prognosis. Epithelial tumor cells can downregulate epithelial markers (e.g., E-cadherin) and upregulate mesenchymal markers (e.g., N-cadherin, vimentin, and MMPs) during the EMT, enhancing the ability of epithelial and mesenchymal markers to intravasate into the bloodstream as CTCs. As a result, CTCs serve as crucial biomarkers in PCa, strongly correlating with metastatic disease and poor outcomes, driving by the EMT. However, the standard CellSearch® assay fails to detect CTCs in approximately 35% of patients with mCRPC. This detection failure may result from the true absence of CTCs or phenotypic changes, such as the EMT, enabling cancer cells to evade detection[84].

Studies have indicated that EMT is associated with ADT and castration resistance, resulting in a more aggressive cancer phenotype. It has also been shown that mesenchymal CTCs,

particularly hybrid epithelial-mesenchymal forms, are often undetectable by standard assays. However, the presence of mesenchymal CTCs is linked to poorer outcomes. Preclinical models suggest that mesenchymal tumors shed more CTCs with higher metastatic potential than epithelial tumors[5].

These findings underscore the limitations of current CTC detection methods and emphasize the need for improved technologies capable of capturing a broader range of CTC phenotypes. Enhanced detection methods could provide better prognostic and therapeutic insights for PCa management[85].

NCT02022904

NCT02022904 is an interventional clinical trial that aims to evaluate novel CTC detection technologies. The primary objective of the pilot phase is to assess the effectiveness of capturing CTCs using mesenchymal-marker-based near infrared-emissive polymersomes (NIR-EPs), prostate-specific membrane antigen (PSMA)-based NIR-EPs, and epithelial cell adhesion molecule (EpCAM)-based NIR-EPs. The EMT suppresses epithelial markers, such as EpCAM, E-cadherin, and cytokeratins. Transcription factors, like SNAIL, SLUG, ZEB1, and TWIST, repress EpCAM expression, limiting the sensitivity of conventional EpCAM-based detection methods. If these novel approaches demonstrate effectiveness, the novel methods will be further evaluated in a larger comparative study[86].

NCT02025413

NCT02025413 is an interventional clinical trial involving 46 patients with metastatic progressive breast cancer and mCRPC. The primary objective of the preliminary lead-in phase is to determine whether CTCs in patients with mCRPC or metastatic progressive breast cancer can be effectively captured using a novel mesenchymal-marker-based ferrofluid targeting N- or O-cadherin. In the subsequent comparative phase with a focus on PCa, the primary goal is to evaluate and compare the CTC non-detection rate between conventional methods and these novel detection technologies[87].

Conclusions

Radiation therapy remains a cornerstone of PCa treatment with approximately one-half of patients receiving radiotherapy as the initial therapy. This modality leads to curative outcomes in approximately 40% of cases due to advances in treatment techniques[1]. However, despite these improvements, many patients still have radiotherapy resistance, resulting in late-stage tumor relapse and metastasis[88]. Understanding the underlying mechanisms of radiotherapy resistance is essential for identifying new therapeutic targets for PCa[51]. This review highlights the pivotal role of ROS in driving both tumor progression and the development of radiotherapy resistance[21]. Key molecular elements are described herein, including the Nrf2/Keap1 complex, which regulates ROS levels and contributes to cellular redox homeostasis and the importance of Bcl-2 overexpression in promoting radiotherapy resistance by modulating mitochondrial function[70]. Additionally, the EMT process, which enhances ROS resistance and supports the formation of CSCs, was shown to further contribute to treatment failure[55,58]. Recent advances in targeting Keap1 degradation and inhibiting EMT offer promising strategies to overcome radiotherapy resistance and hinder disease progression[89]. For example, dimethyl fumarate, an oral agent, activates the Nrf2 pathway and induces cell death by inhibiting Keap1 degradation[60]. Other compounds, such as 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) and sulforaphane, have shown potential in clinical trials for promoting Nrf2 activation and combating resistance. Furthermore, pro-oxidants, like imerxon, PEITC, and B2G, have demonstrated efficacy in overcoming ROS-resistant pathways[55,60].

By targeting ROS-related signaling pathways, these promising strategies, combined with ongoing research into novel inhibitors, have the potential to significantly improve radiotherapy outcomes and patient survival in PCa[89,90].

For example, dimethyl fumarate, an orally agent, has shown efficacy in clinical settings by activating the Nrf2 pathway and inducing cell death through inhibition of Keap1 degradation[91]. Other Keap1 degradation inhibitors, such as CDDO, a synthetic triterpenoid, have also shown potential in recent clinical trials. Looking ahead, future clinical strategies should focus on a balanced modulation of ROS to maximize the therapeutic benefits while minimizing potential resistance mechanisms[89]. Given the dual role of ROS in both promoting and suppressing cancer, a combination approach that integrates ROS-enhancing pro-oxidants (e.g., imerxon, PEITC, and B2G) with selective ROS-scavenging agents may provide a more refined therapeutic strategy. Additionally, while Nrf2 pathway activation has shown promise in overcoming resistance, it is crucial to determine which subsets of PCa patients would benefit most from such interventions because excessive Nrf2 activation may inadvertently support tumor survival[92].

From a translational perspective, prioritizing ROS-modulating pathways that target CSCs and EMT may yield the most clinically relevant breakthroughs. Furthermore,

future clinical trials should explore optimal sequencing strategies, such as integrating ROS-targeted therapies with immune checkpoint inhibitors or metabolic reprogramming approaches, to enhance treatment efficacy[52,82]. These advances, combined with ongoing research and the mechanism-based discovery of novel inhibitors, hold significant potential for overcoming radiotherapy resistance and improving PCa therapy outcomes.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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