Alterations in *BRCA2* as Determinants of Therapy Response in Prostate Cancer

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ABSTRACT: Prostate cancer (PCa) is one of the leading causes of cancer diagnoses and cancer-related deaths in the United States. Mutations or deletions in the genes involved in the DNA damage response (DDR) are common in aggressive primary PCa (germline alterations) and further enriched in advanced therapy-resistant PCa (somatic alterations). Among the DDR genes, *BRCA2* is the most commonly altered (~ 13%) in advanced therapy-resistant PCa. Patients with *BRCA2*-altered PCas are exquisitely sensitive to poly (ADP-ribose) polymerase (PARP) inhibitors (PARPis). Indeed, two PARPis-olaparib and rucaparib have recently gained U.S. Food & Drug Administration approval for the treatment of advanced PCas harboring a *BRCA2* mutation. This review seeks to explore the role of *BRCA2* in DNA damage repair, the pathogenesis and progression of *BRCA2* mutant PCa, and the utility of radiation therapy, targeted therapies, and platinum-based chemotherapies for patients with *BRCA2* alterations.

KEY WORDS: prostate cancer, BRCA2 mutations, PARP inhibitors, platinums, radiation therapy

I. INTRODUCTION

Prostate cancer (PCa) represents a significant health-care burden in the United States, with an estimated 268,490 new cases and 34,500 cancer related deaths in 2021.[1] A majority of PCas are clinically localized and indolent in nature with five-year cancer-specific survival rates > 98% and can be managed with active surveillance, surgical resection with radical prostatectomy (RP) or radiation therapy (RT).[1–3] Patients who fail local therapy or those who present with *de novo* metastatic disease are treated with androgen-deprivation therapy (ADT) consisting of medical castration via the use of gonadotropin-releasing hormone/luteinizing hormone related hormone (GnRH/LHRH) agonists or orchiectomy. Although the majority of patients initially respond to ADT, ADT is not curative in the metastatic setting and progression to castration resistant PCa (CRPC) is common.[4] Chen and Sawyers showed that CRPC maintains androgen receptor (AR)-dependence, as evidenced by the subsequent development and U.S. Food & Drug Administration (FDA) approval of second-generation agents targeting AR signaling, including those targeting precursors of androgens (such as the CYP17 inhibitor abiraterone acetate) and those directly targeting the AR as competitive antagonists (such as enzalutamide, apalutamide, and darolutamide).[4–11] Although these agents have significantly altered the therapeutic landscape of advanced PCa, resistance to these agents and progression is inevitable. Thus, there is a compelling unmet need for new targeted therapies in advanced PCa.

Whole-genome sequencing of patient tumor DNA has yielded significant insight into the molecular underpinnings and common targetable aberrations in both clinically localized and advanced PCa, such as *AR* upregulation, *TMPRSS2-ERG* fusions, and mutations in oncogenes or tumor suppressors conferring cellular survival.[12–14] Importantly, recent genomic analyses have implicated genes involved in the DNA damage response (DDR), as common alterations in both primary and aggressive PCa. Whole exome and transcriptome analyses of 150 metastatic CRPC samples from the International Stand Up to Cancer/Prostate Cancer Foundation Team (SU2C-PCF) identified genomic alterations affecting DDR genes in ~ 23% of metastatic CRPCs.[15] Analyses of biopsies using whole exome, mRNA sequencing, and DNA methylation analysis by The Cancer Genome Atlas (TCGA) indicated that 19% of 333 primary PCas harbor alterations in genes involved in DDR.[16] A more recent genomic

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survey of 1013 PCas identified DDR mutations in 10% of primary and 27% of metastatic PCas.[17,18] Furthermore, analyses of patients screened for the PROfound clinical trial (www.clinicaltrials.gov no. NCT02987543) identified DDR genomic alterations in 28% of metastatic biopsies.[19–22] Due to the high prevalence of mutations in DDR genes in PCa, the National Comprehensive Cancer Network (NCCN) has recommended germline testing for all men with high-risk localized PCa and in those with metastatic disease.[23]

BRCA2 is the most commonly altered DDR gene in both primary (~ 3–8%) and advanced PCa (~ 13% in CRPC).[15,16,24] *BRCA2* encodes the breast cancer type 2 susceptibility protein, which is an essential player in the DDR response to toxic double-stranded DNA (dsDNA) breaks.[25] Mutations or deletions of *BRCA2* are well characterized in cancer and are associated with an enhanced risk for developing breast, ovarian, prostate, and other cancers.[26] This review seeks to cover the multifaceted roles of *BRCA2* in DDR, the pathogenesis and progression of *BRCA2* mutant PCa, and explore both the utility of radiation therapy, targeted, and platinum-based chemotherapies for patients with *BRCA2* alterations.

II. DDR MECHANISMS

The DDR pathway is an essential, conserved, and complex cellular response that occurs when genomic damage is detected leading to efficient and effective DNA damage repair.[27–30] Although single-stranded DNA (ssDNA) break repair occurs more commonly, double-stranded DNA (dsDNA) breaks confer significantly greater cytotoxicity. In fact, in some contexts, a single unrepaired dsDNA break (DSB) is sufficient to cause cancer-promoting chromosomal translocations or induce apoptosis.[31] Additionally, repair of DSBs are the primary determinant of a cell's sensitivity to RT.[32] When a DSB is first recognized, a vast network of DDR signaling cascades are triggered, inducing temporary cell cycle arrest. Depending on the damage, signaling cascade, and cell cycle stage, DDR occurs via either non-homologous end joining (NHEJ) or romologous recombination repair (HR). If the DNA damage is excessive and cannot be repaired, the cell undergoes apoptosis.[33]

A. NHEJ

NHEJ is the primary mechanism of repair for IR-induced DSBs in mammalian cells and can occur at any phase in the cell cycle (see the schematic in Fig. 1A). In NHEJ, the Ku80/Ku70 heterodimer has sequence-independent affinity for broken ends of DNA and serves as the sensor of DNA damage. Ku80/Ku70 then recruits and activates the DNA-PK catalytic subunit (DNA-PKcs), which then acts as a bridge to maintain the proximity of the two ends of broken DNA.[34] Endonucleases process the broken ends, DNA polymerases fill in the gap, and DNA ligase IV seals the DNA and completes the repair.[35,36] This process, while rapid, can lead to loss of information at the site of repair in the form of small insertions or deletions, due to the lack of a homologous template strand. Thus, NHEJ is considered an error-prone method of repair with low fidelity.[34,37]

B. HR

HR is the secondary pathway for repair of IR-induced DSBs, although it is the predominant repair pathway for endogenous DSBs following replication fork collapse.[38] In contrast to NHEJ, HR utilizes the homologous sister chromatid as a template in the repair of dsDNA breaks, and therefore can only occur during post-replicative phases of the cell cycle (late S and G_2) when this template is available. As shown in Fig. 1B, the basic process by which HR occurs first involves the recognition of the dsDNA break. Nucleases (MRE11 of the MRE11/Rad50/NBS1 (MRN) complex, Exo1, Sae2/CtIP, and Dna2) excise a section of the 5′-strand at the break to expose a long stretch of 3′-ssDNA. This ssDNA is stabilized by replication protein A (RPA) which binds to prevent hairpin loop formation and is subsequently replaced by RAD51, which is loaded with the help of the BRCA1/BRCA2/PALB2 complex. RAD51 in combination with the ssDNA forms a recombinogenic nuclear filament that serves as a probe

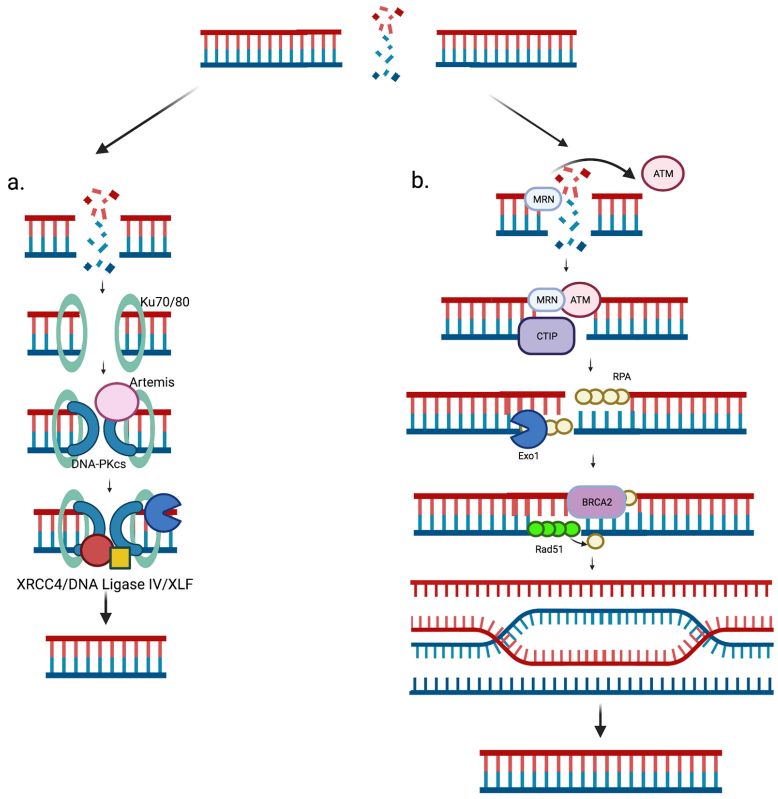

FIG. 1: Pathways of double–strand DNA break repair. (A) The NHEJ pathway is an error–prone repair pathway that functions throughout the cell cycle. (B) HR is an error–free repair pathway that requires intact homologous DNA as a repair template and is active in the later S and G_2 phases. Figure created with BioRender.

for homologous sequences in the sister chromatid. Following DNA strand invasion and generation of a Holliday junction, the damaged DNA is faithfully repaired by copying information from the homologous template.[25,39–43]

C. Role of BRCA2 in DDR

In healthy cells, BRCA2 plays an essential role in HR, mainly through its interaction with the protein Rad51, which eventually helps form the nucleofilament necessary for sister chromatid strand invasion and Holliday junction/D-loop formation.[39,41,44–48] The role of BRCA2 in HR was clearly established by reconstitution experiments, where transient expression of BRCA2 into the BRCA2-deficient pancreatic cancer cell line, Capan-1 resulted in significantly increased HR rates.[49] BRCA2 is critical for the translocation of Rad51 to the nucleus, enhances RPA protein dissociation from ssDNA, and facilitates Rad51 assembly onto single strand overhangs.[50–53] Additionally, BRCA2 prevents ATP-hydrolysis and subsequent inactivation of Rad51.[52,54] Finally, BRCA2 has been shown to prevent inaccurate and unnecessary binding of Rad51 to dsDNA.[52,55] Thus, the primary function of BRCA2 in HR is to recruit and enable Rad51 function to the sites of DNA damage.

Additionally, BRCA2 plays roles in preventing the nucleolytic degradation of stalled replication forks, in protection of telomere integrity, and in protection against deleterious R-loop formations.[56–60] Importantly, BRCA2 has a well characterized role in the repair of intra-strand cross-links (ICLs), a type of lesion in which two complementary strands of DNA become covalently linked to one another.[61,62] In this pathway, BRCA2 has also been shown to be

important in recruitment of HR proteins PALB2/FANCN and FANCD2.[63–65]

D. BRCA2 and Synthetic Lethality

In normal cells, poly (ADP-ribose) polymerase (PARP) participates in excision repair mechanisms to repair ssDNA breaks.[66,67] PARPis exert their efficacy by exploiting cellular synthetic lethality.[67] When PARP is inhibited and ssDNA breaks are subsequently allowed to persist in the genome, replication forks are unable to proceed through the breaks, causing them to stall and collapse (Fig. 2). This collapse converts the ssDNA breaks into highly toxic dsDNA breaks.[67,68] Such breaks are mainly repaired through HR, which relies on functioning BRCA2.[69] Thus, treatment with a PARPi in the context of BRCA2 loss promotes apoptosis in the cells harboring these deleterious mutations and consequently cause synthetic lethality. Clinically, these data are supported by the recent FDA approval of PARP inhibitors (PARPis) for patients with mCRPC harboring a pathogenic *BRCA2* mutation.[19–22] Additionally, the importance of BRCA2 in ICL repair has led to an avenue for chemical exploitation via the use of platinum therapies, which cause DNA cross-links.[70–72]

III. BRCA2 IN PROSTATE CANCER

A. Germline *BRCA2* Mutations in Prostate Cancer

The prevalence of *BRCA2* mutations in primary PCa is ~ 3–8%.[16] To date, hundreds of unique germline mutations have been identified in *BRCA2*, and germline *BRCA2* mutations can be found throughout the *BRCA2* transcript (Fig. 3A).[73,74] The majority of the patients who have a germline *BRCA2* mutation

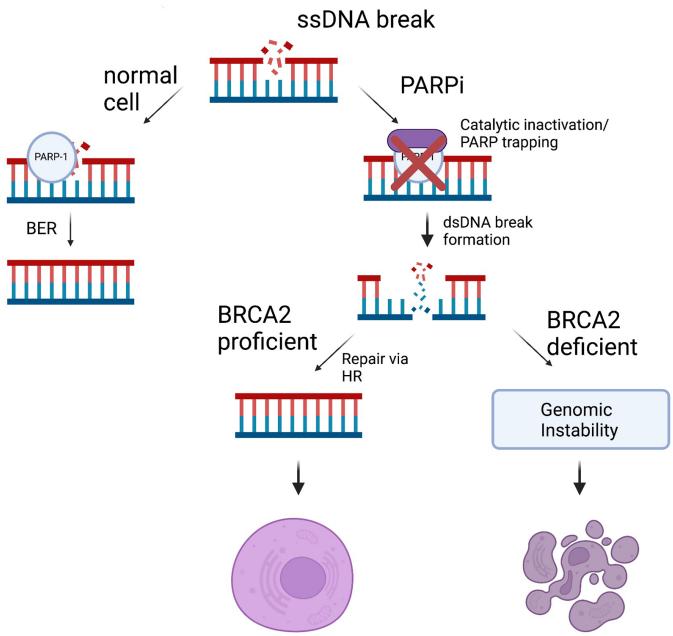

FIG. 2: Synthetic lethality. Pathways underlying PARP1-BRCA2 synthetic lethality: PARP-1 is involved in repair of single-strand DNA breaks through base excision repair (BER) mechanisms (left). In the presence of PARPis, trapped PARP1/DNA nucleoprotein complexes impair the progression of replication forks and result in double–strand DNA breaks (right). In BRCA2-proficient cells, repair occurs through homologous recombination (HR). Because BRCA2-deficient cancer cells lack HR, the double strand DNA breaks are not repaired, leading to genomic instability and cell death. Thus, PARPis are selectively toxic to the BRCA2-defective cancer cells, creating synthetic lethality. Figure created with Bio Render.

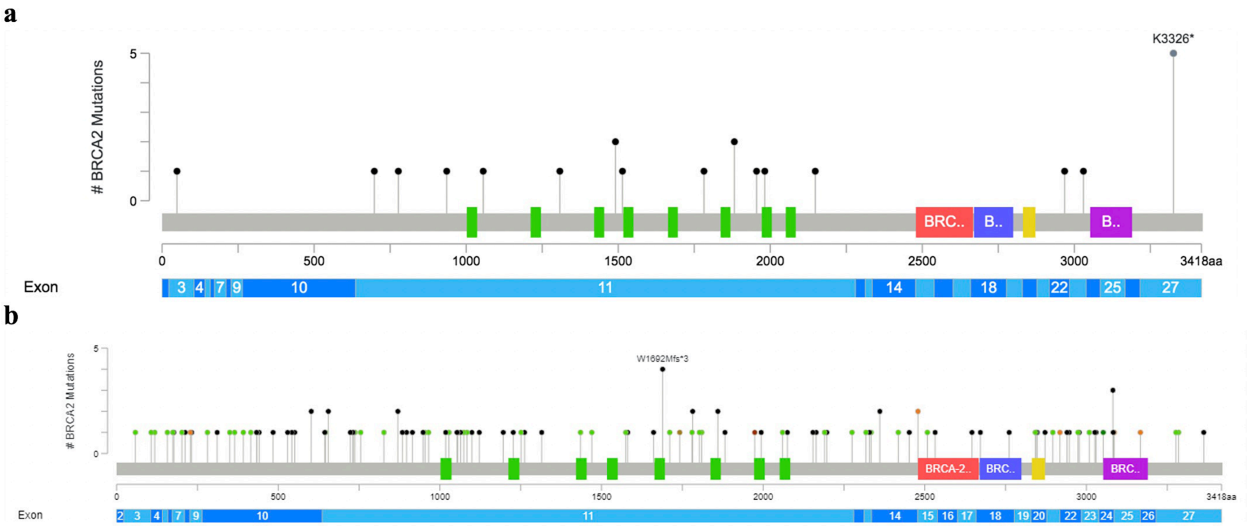

FIG. 3: Distribution of *BRCA2* mutations in prostate cancer datasets (data from cBioPortal). Graphical summary of *BRCA2* mutations from prostate cancer studies in cBioPortal database mapped across the gene.[73,74] (A) Distribution of the germline alterations of *BRCA2* in prostate cancer datasets. (B) Distribution of somatic *BRCA2* alterations in prostate cancer datasets.

have a unique mutation specific to them and their families. Two population-specific pathogenic germline *BRCA2* mutations have been identified in PCa: the Icelandic founder *999del5* mutation and the Ashkenazi *BRCA2* 6174delT mutation. The Icelandic *999del5* mutation results in a frameshift mutation that results in an early truncation of translation at codon 273 and subsequent loss of function.[75,76] The Ashkenazi *BRCA2* 6174delT mutation causes a frameshift mutation and is found in 1% of the Ashkenazi Jewish population.[77,78] In addition, a germline variant of unknown pathogenic significance, p.K3326* is highly represented in the TCGA analyses of primary PCa.[16] Thus, the true magnitude and importance of germline *BRCA2* alterations is unclear, given the incomplete characterization of the pathogenic significance of each alteration.

There is a significantly increased risk of developing PCa in patients with a germline *BRCA2* mutation, with one study estimating a 4.65 higher relative risk of PCa [95% confidence interval (CI) = 3.48–6.22] in patients with a *BRCA2* mutation.[26] *BRCA2* mutations are also associated with a higher risk of early onset PCa: with estimates ranging from an 8.6-fold higher risk by age 65, to a 23-times higher risk for the development of PCa by age 56.[79,80] Alterations also lead to increased aggressiveness of PCa with higher Gleason score at initial presentation, increased risk of intraductal PCa which confers a poor prognosis, increased genomic instability, high copy number alterations, and a mutational profile that mimics a metastatic signature even in the presence of localized PCa.[81–85] Finally, *BRCA2* mutations may portend an increased risk of metastasis and of dying from the disease.[82,86,87]

B. Somatic *BRCA2* Mutations in Prostate Cancer

A significant number of men develop somatic mutations in *BRCA2* throughout the course of their PCa treatment, although the exact proportion of patients varies in literature. In the SU2C-PCF cohort, 23% of metastatic CRPC patients harbored a mutation in DDR genes, with ~ 13% of patients harboring a mutation in *BRCA2* and 6.6% of patients harboring a confirmed somatic mutation.[15] Interestingly, ultra-high-depth exomic DDR sequencing identified somatic *BRCA2* mutations in 52.6% and 42.4% of African-American and Caucasian-American PCa patients, respectively.[88] Analysis of the Catalogue of Somatic Mutations in Cancer (COSMIC) database

and cBio Portal shows that pathogenic *BRCA2* somatic mutations occur throughout the entire *BRCA2* transcript in PCa (Fig. 3B), and are mainly comprised of missense and nonsense mutations and deep deletions (Fig. 4).[73,74,89] Importantly, purely somatic mutations in *BRCA2* show similar clinical and molecular phenotypes to tumors harboring one germline and one somatic mutation.[90]

C. *BRCA2* and Responsiveness to Radiation Therapy

The relationship between *BRCA2* and RT sensitivity is well established in the preclinical setting. The human pancreatic cancer cell line Capan-1, which harbors the Ashkenazi 6174delT mutation, displays RT sensitivity on colony formation assay with doses as low as 1 Gy.[91] Additionally, mouse embryonic stem cells with a BRCA2 C-terminal truncation mutation show hypersensitivity to γ-irradiation.[92] In the *in vivo* setting, mouse embryonic fibroblasts (MEFs) with biallelic *BRCA2* mutations showed increased sensitivity to γ-irradiation.[93] Additionally, BRCA2 deficient tumors formed from Capan-1 cells in nude mice demonstrated increased sensitivity to RT and enhanced necrosis after RT compared with wild-type controls.[91]

In the clinical setting, patients with Fanconi's anemia (of which a portion harbor biallelic mutations in *BRCA2*) demonstrate hypersensitivity to irradiation.[94–96] On the basis of these findings, the logical extrapolation would be that tumors in patients with germline or somatic *BRCA2* mutations would be more sensitive to RT, although normal surrounding tissue in patients with germline *BRCA2* mutations could also be more sensitive to RT. This

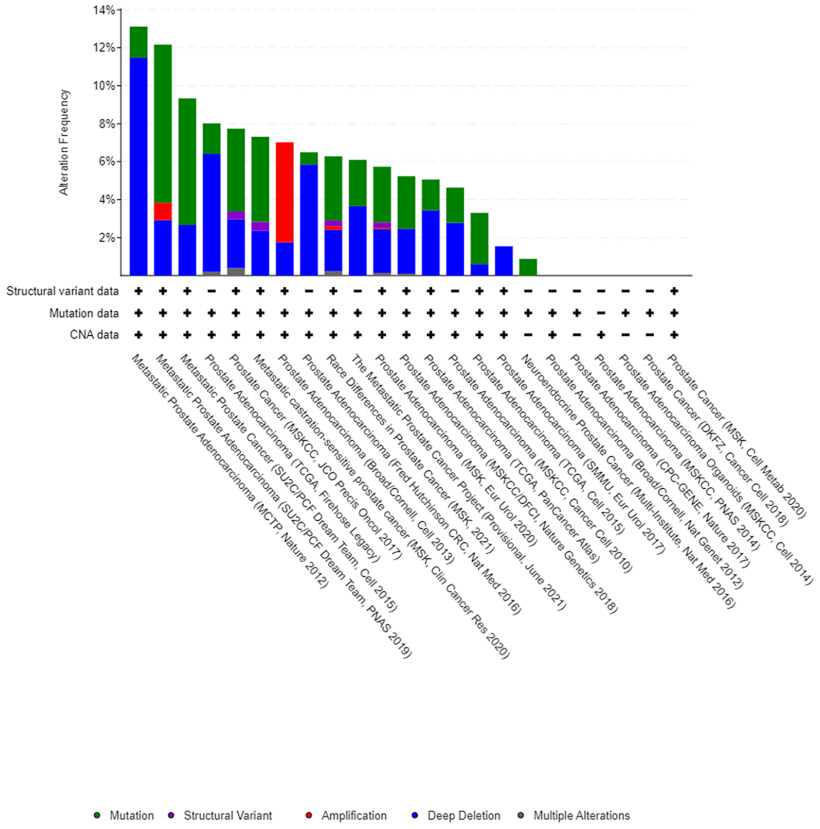

FIG. 4: Incidence of *BRCA2* mutations in various cohorts (data from cBioPortal). Summary of prostate tumor samples with *BRCA2* gene alterations in multiple studies and patient cohorts. The most commonly noted alterations are deep deletions and mutations. Figure created via the cBioPortal database.[73,74]

could increase the risk for increased radiation-induced toxicity, including potentially higher risks of RT-induced secondary malignancies.

However, a retrospective case-control study of women with breast cancer undergoing adjuvant RT identified no increased ipsilateral tumor recurrence after RT (with a median follow-up of 13.4 years) in *BRCA1/2* carriers versus sporadic controls.[97] Importantly, this study did not demonstrate a higher overall survival in *BRCA2* carriers and suggests that these tumors are not more sensitive to RT. These findings have been noted in other studies, with neither increased responsiveness to RT, nor enhanced risk of radiation-induced secondary malignancies or toxicities.[98–102]

D. Management of *BRCA2* Altered Patients with Low- and Intermediate-Risk Prostate Cancer

For patients with clinically localized PCa management, options typically include active surveillance, surgical extirpation or radiotherapy.[103] One important caveat to note is that the strategies for the management of patients with low- and intermediate-risk PCa with *BRCA2* alterations are largely derived from retrospective analyses, most of them focused on germline *BRCA1/2* mutation carriers.

For patients with low-risk PCa undergoing active surveillance, *BRCA2* germline carriers are nearly twice as likely to undergo tumor upstaging in subsequent biopsies than patients without known DDR alterations (78% vs. 40% at 10 years).[104] Although these results are derived from a small cohort of *BRCA2* patients ($n = 11$), the question of whether standard active surveillance protocols are appropriate for germline *BRCA2* carriers needs further exploration. This potentially highlights the need for more rigorous surveillance in PCa patients with germline *BRCA2* alterations however, the optimal schedule needs to be defined.

For patients undergoing definitive therapeutic treatment with surgery or RT, retrospective analyses in small patient cohorts indicate a higher propensity for development of metastasis in patients with *BRCA2* alterations. The 10-year metastasis-free survival for PCa patients treated with surgery was 91% and 67% in *BRCA2* wild-type vs. *BRCA1/2* carriers, respectively. With radiation, 10-year survival dropped to 80% for non-carriers and 39% for PCa patients harboring a *BRCA1/2* alteration.[105,106] Although some provocatively cite the apparent favorable outcomes with surgery vs. RT seen in this study, the authors caution that the patients treated with RT had a higher tumor burden and a more aggressive histology upon initial therapy. Thus, substantial imbalances in patient risk profiles likely skewed favor towards the surgically treated cohort. Additionally, the caveats of retrospective studies and small patient numbers should be considered.

Randomized comparisons between surgery and RT specifically for *BRCA2* PCa carriers are unlikely, due to the challenges of cross-modality trials in PCa and the low frequency of carrier status in unselected patients. Regardless, given poor outcomes regardless of local modality, we hypothesize that *BRCA2* carriers may require intensified systemic adjuncts to address their systemic progression risk, independent of local therapy modality. In this regard, with the integration of genomic biomarkers into many contemporary planned trials of high and unfavorable intermediate risk and relapsed PCa, the prognostic significance of *BRCA2* carrier status treated with RT will be better defined. Moreover, these trials will be helpful to assess if *BRCA2* mutant patients would benefit from systemic therapy intensification strategies.

In the interim, the finding of high rates of metastatic progression amongst those men with a *BRCA2* carrier status in PCa may require special considerations for staging imaging for those treated with RT. Although abdominopelvic staging with CT/MRI and bone scans are recommended for patients with high and unfavorable intermediate risk PCa, their sensitivity is low, and they may miss early nodal metastases or bony micro-metastases. The advent of more sensitive imaging modalities, such as PET-PSMA, may increase the detection of metastatic disease.[107] Given the lack of pathologic assessment of nodes and immediate biochemical outcome feedback after treatment with RT, as compared with surgery, it may be worth considering whether those with *BRCA2* carrier alterations be considered for advanced PET staging at lower thresholds.

Aside from outcome, a theoretical concern about the use of RT as the primary treatment modality for PCa in *BRCA2* mutation carriers is the risk of secondary malignancy development in neighboring non-cancerous tissue, due to impaired DSB repair. Difficulties in designing studies to address this concern include not only obtaining large clinical datasets and adequate follow-up length, but also the increased propensity of patients with germline DDR mutations to develop second malignancies irrespective of RT exposure.[82,108] At present, there is not enough data to recommend against RT for such patients.[98–101] Notably, data from breast cancer *BRCA1/2* carriers treated with adjuvant RT support its safety, despite such women often being diagnosed at much earlier age than men with PCa. These considerations are tempered by the differential hormonal milieu and differences in radiating the post-operative breast fields and the primary prostate.

E. Management of *BRCA2* Altered Patients with Metastatic Prostate Cancer

For patients with metastatic hormone-sensitive prostate cancer, multiple studies indicate that patients with *BRCA2* alterations have a shorter time to progression to CRPC from initiation of continuous ADT.[109–111] Multivariate analyses of the PROREPAIR-B trial indicated that germline *BRCA2* mutations are a negative prognostic factor for cause-specific survival (CSS) in patients with metastatic CRPC, with CSS in *BRCA2* patients being half-that of non-mutated counterparts (hazard ratio = 2.11; 95% CI = 1.06–4.18). Additionally, patients with germline *BRCA2* mutations had significantly worse outcomes if treated with initial taxane chemotherapy as opposed to an androgen signaling inhibitor. This study stands as a testament to the limitations of conventional chemotherapy or AR-targeted therapies in in the management of *BRCA2* altered mCRPCs.[110]

The sensitivity of *BRCA2* mutant breast and ovarian cancers to platinum therapies, which exploit the role of BRCA2 in ICL repair, is well-established.[112–114] However, data on platinum efficacy in *BRCA2* mutant PCa is limited to retrospective and anecdotal case studies.[70–72] These limited observations form the basis for multiple clinical trials evaluating these agents in this space (www.clinicaltrial.gov, Nos. NCT04038502, NCT03652493, NCT02311764, NCT02955082, and NCT02598895).

There is considerable evidence suggesting therapeutic potential of PARPis in the management of *BRCA2* mutant prostate cancers. In cells with *BRCA2* mutations, PARPis cause accumulation of toxic dsDNA breaks, leading to genetic instability, chromosomal rearrangements, and cell death through synthetic lethality and PARP trapping, as depicted in Fig. 2. In clinical settings, PARP-inhibitor therapy has proven effective in improving progression-free survival in *BRCA2* mutant PCa patients. Two PARPis are FDA approved for use in patients with mCRPCs with *BRCA1/2* alterations: olaparib based on results from the TOPARP A/B and PROfound clinical trials, and rucaparib based on the TRITON2 study.[19,21,22,115] The phase III PROfound trial demonstrated significant improvement in overall survival, radiographic progression-free survival, and objective response rate with olaparib compared with second generation antiandrogens in patients with *BRCA2* mutations.[19,116] The phase II TRITON study also indicated that rucaparib significantly improved objective response rate and prostate-specific antigen response in *BRCA1/2* carriers. Additional PARPis, such as niraparib (which gained breakthrough status for heavily pretreated mCRPCs in 2019) and talazoparib are currently under clinical investigation for use in *BRCA1/2* mutant PCa.[117–119] All these PARPis leverage the synthetic lethality enabled by *BRCA2* mutation in PCa. It is important to recognize that while *BRCA2* mutant PCa respond to PARPis, the response is often of limited duration, with inevitable disease progression. The most common mechanism of resistance of *BRCA2* mutant PCa to PARPi treatment are reversion of the *BRCA2* mutation, which abrogates the synthetic lethality.[20,120,121]

To enhance the utility of PARPis, combination therapies with AR targeting agents are being explored, due to well-documented cross-talk between the pathways.[122–124] Cross-talk between AR signaling and PARP has been documented through PARP

effects on AR-dependent transcription, and AR regulation of DDR gene expression.[123,125] Therefore, the use of PARPis can be used to exploit these vulnerabilities. Several ongoing phase III trials aim to investigate the potential synergy between PARPis and AR signaling inhibitors in prostate cancer patients, without regard to DDR status (www.clinicaltrials.gov, Nos. NCT04455750, NCT04179396, and NCT04734730).

IV. CONCLUSIONS AND FUTURE DIRECTIONS

Increased emphasis on genetic testing of men with clinically localized PCa has led to the identification of patients with clinically actionable germline or somatic mutations in DDR genes such as *BRCA2*. Progress has been made in developing personalized therapies for patients harboring a *BRCA2* mutation with the approval of olaparib and rucaparib, and the understanding of the greater efficacy of platinum-based chemotherapies.

Several questions remain unanswered:

1. Because mutations in *BRCA2* are not limited to hotspot mutations, the pathogenic basis of each *BRCA2* variant/mutation and their effect on HR is not known.
2. Molecular bases for the differences in tumor aggressiveness and therapy responsiveness between germline and somatic *BRCA2* alterations is unclear. The frequency of pathogenic *BRCA2* alterations and need for aggressive screening in these patients remains undefined.
3. The ideal management of patients with clinically localized PCa and *BRCA2* mutations remains to be determined. In the limited available data, these patients have a high risk of progression to metastatic disease after localized treatment, be it surgery or radiation.
4. To determine the utility and toxicity of RT for treatment of patients with *BRCA2* mutant PCa, prospective clinical trials with close follow-ups are needed. However, the low frequency of relevant germline mutations in the clinically localized population will challenge classical randomized trials of such strategies or comparisons to surgery-based treatment.
5. Integration of DDR gene analysis into ongoing prospective trials across modalities and consideration as a stratification factor are indicated to evaluate and improve the outcomes of these men.
6. Although PARPis have dramatically enhanced the management of *BRCA2* altered metastatic PCa, their responses are neither durable nor curative. Alternative synthetic lethality strategies to target somatic *BRCA2* mutations using agents that target either NHEJ or increase DNA adducts may offer more durable responses. Combination therapies with agents that further enhance cell killing of *BRCA2* altered CRPCs are desperately needed.
7. The lack of PCa models with *BRCA2* alterations is a major impediment to these studies and are desperately needed.[83,126]
8. Finally, agents that induce "BRCA-ness" in PCa cells can further enhance the utility of PARPis to PCa that do not have a DDR alteration.

The present study may help in our understanding of how *BRCA2* alterations affect DDR responses in PCa cells, influence the pathogenesis and progression of affected patients, and affect the utility of therapies across the spectrum of disease.

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