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– FOCUS ISSUE –

Prostate Cancer

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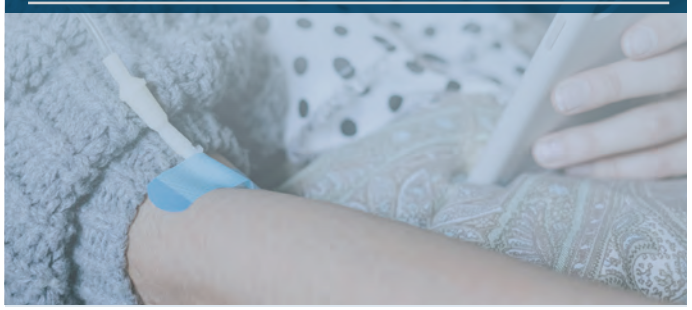

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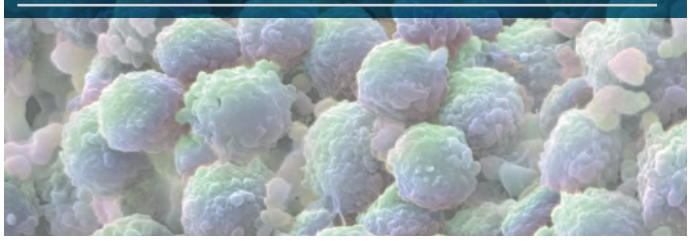

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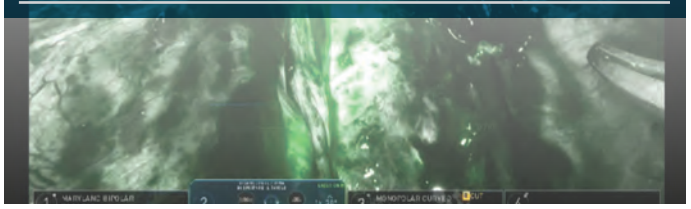

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AUA/SUO2024 APC RECAP

Genetic Testing of Prostate Cancer Patients in the Urology Clinic Setting

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In the mid 1990s, several genes were discovered that when mutated, increased the risk of inheriting certain cancers. These were the *BRCA1* and *BRCA2* genes associated with hereditary breast and ovarian cancers. Over the last 10 years, understanding this family of related DNA repair pathway genes has become important in the management of prostate cancer from screening through treatment of advanced disease.

While these inherited germline mutations may be identified in a relatively small percentage of patients, finding these pathogenic genes can have a major impact on the individual and their family. It is no longer sufficient to ask a man being screened or treated for prostate cancer about relatives just with prostate cancer. In the clinic setting, it is essential to ask for a more extensive family history to identify relatives with breast, ovarian, and pancreatic cancer, and gastrointestinal or other Lynch syndrome–associated tumors. If these tumors are present in other family members, it suggests that there may be an inherited germline mutation increasing cancer risk with further genetic testing and counseling warranted.

The most common inherited germline alterations that have been associated with increased prostate cancer risk are mutations in the *BRCA2* gene. While mutations in this DNA repair pathway gene are the most common in advanced prostate cancer, dozens of other altered genes have been described, such as *BRCA1*, *ATM*, and *CHEK2* to name a few.[1] Most of these mutated genes found in prostate cancer pathways do not directly cause prostate cancer but allow the cancer to progress, mostly by interfering with DNA repair. Germline mutations can be detected in 11.8% of metastatic vs 4.6% localized prostate cancer, with later data suggesting rates up to 25% in metastatic castration-resistant prostate cancer (mCRPC).[2]

While these mutated genes can be inherited, the mutations implicated in prostate cancer can also arise de novo in tumors. These identified noninherited pathogenic genes are referred to as somatic mutations. Both germline and somatic mutations can be detected in the tumor. Any mutations found in the germline or tumor can be important in guiding therapy of advanced disease. While inherited germline mutations can be detected with blood testing or a buccal swab, analysis of any mutations in the tumor itself requires tissue biopsy of the primary tumor, a metastasis, or through newer liquid biopsy techniques.

A variety of commercial assays are available that can analyze both solid tumor biopsies and liquid biopsy circulating tumor cell free DNA. This somatic tumor testing can reveal additional actionable mutations in advanced prostate cancer. These include the identification of mutations in homologous recombination repair (HRR) genes such as *BRCA2* and others, mismatch repair genes (*MLH1*, *MSH2*, *MSH6*), and tumor mutational burden. All of these suggest potential treatment options for advanced prostate cancer including metastatic hormone-sensitive prostate cancer and mCRPC.

Somatic testing can identify a large panel of mutated genes that indicate agents such as poly (ADP-ribose) polymerase (PARP) inhibitors could be used in the setting of mutated HRR genes. In the setting of mismatch repair gene abnormalities or high tumor mutational burden, immunotherapeutic agents such as pembrolizumab can be considered. The utility of commercial somatic tumor assays is often further enhanced by providing treatment options that include single agents, combination agents, and investigational options based on current clinical trials.

Table. Advanced Prostate Cancer AUA/Society of Urologic Oncology Guidelines Genetic Testing Considerations[5]

• mHSPC: Offer germline testing, and consider somatic testing and genetic counseling.
• mCRPC: Offer germline (if not already performed) and somatic genetic testing to identify DNA repair deficiency, MSI status, TMB, and other potential mutations that may inform prognosis and familial cancer risk, as well as direct any targeted therapies.
• Offer a PARP inhibitor: With deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC following prior treatment with enzalutamide or abiraterone and/or a taxane-based chemotherapy. Platinum-based chemotherapy is an alternative to PARP inhibitor.
• Mismatch repair deficient or MSI-H mCRPC: Offer pembrolizumab.

Abbreviations: HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; MSI, microsatellite instability; MSI-H, microsatellite instability-high; PARP, poly (ADP-ribose) polymerase; TMB, tumor mutational burden.

One of the most important advances in the treatment of mCRPC is the use of PARP inhibitors. PARP enzymes are important for repairing single DNA strand breaks. The PARP mechanism is important in malignant prostate cancer cells by allowing the malignant cell to continue to grow under certain conditions. DNA HRR genes, such as *BRCA2*, *BRCA1*, *ATM,* and others, make proteins that repair double-stranded DNA breaks. When these HRR genes are mutated, as can be seen in advanced prostate cancer, errors in double-strand DNA repair genes can result in neoplastic growth.[3] PARP inhibitors (olaparib, rucaparib, niraparib, talazoparib) interfere with single-strand DNA repair breaks, limiting the ability of a malignant cell harboring the mutated HRR DNA repair genes from growing. This mechanism of action of PARP inhibitors has been called "synthetic lethality." The newest use of PARP inhibitors includes combining these agents with others, such as androgen receptor pathway blockers.

Genomic profiling by germline and somatic tumor testing are now effective precision medicine tools to optimize patient care with expanding roles in daily patient care. There is an unmet need to increase the use of genetic testing by urologists. Recent data suggest that only 1% of men with a history of prostate cancer reported undergoing specific germline testing compared with over 50% of patients with breast or ovarian cancer, with measures such as digital web tools being developed to improve these statistics.[4]

The Table summarizes the 2023 update of the AUA/Society of Urologic Oncology Advanced Prostate Cancer Guidelines that provide recommendations for the use of genetic testing in advanced disease including metastatic hormone-sensitive prostate cancer and mCRPC.[5] Family history and confirmation of inherited germline mutations can inform screening and treatment options in localized and advanced disease. Advances in understanding genetic alterations in advanced prostate cancer have provided many more targeted options to men beyond traditional hormonal ablation and chemotherapy. ■

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AUA/SUO2024 APC RECAP

Immune Therapy in Metastatic Castration-Resistant Prostate Cancer

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The treatment landscape for metastatic castration-resistant prostate cancer (mCRPC) continues to evolve rapidly. The 2023 update to the AUA/Society of Urologic Oncology guidelines for patients with mCRPC details the treatment options, including chemotherapy (docetaxel, cabazitaxel, or platinum-based therapy), oral hormonal therapies (abiraterone acetate plus prednisone or enzalutamide), radium-223,^{177}Lu-PSMA-617, or sipuleucel-T.[1] The National Comprehensive Cancer Network guidelines also recommend germline and/or somatic testing to identify genetic mutation(s) and microsatellite instability status, as this may qualify patients for management with novel immunotherapeutic agents.[2]

Immunotherapy for advanced cancer has led to improvement in survival with several cancers including head and neck cancers, renal cell carcinoma, melanoma, and lung cancer.[3] In particular, immune checkpoint inhibitors such as pembrolizumab have shown excellent efficacy and safety through their targeting of PD-1 (programmed death protein 1)/PD-L1 (programmed death ligand-1)[4] and CTLA-4 (cytotoxic T-lymphocyte–associated antigen 4).[5] However, the results in mCRPC have been relatively underwhelming, as prostate cancer is recognized as an immunologically "cold" tumor.[6,7] Early trials with ipilimumab in the post-chemotherapy and chemotherapy-naïve settings did not show any survival benefit; however, there was some indication that patients on therapy for more than 1 year may have improved survival and longer progression-free survival.[8,9] Pembrolizumab has also been studied in mCRPC as a monotherapy in several trials, notably in KEYNOTE-199. This was a phase 2 study to determine safety and efficacy in 3 groups, all of whom had received docetaxel and at least 1 targeted endocrine therapy: (1) patients with PD-L1–positive disease; (2) patients with PD-L1–negative disease; and (3) patients with bone-predominant disease, regardless of PD-L1 expression.[10] The objective response rate was 5% in cohort 1 and 3% in cohort 2, and median survival was 9.5 months, 7.9 months, and 14.1 months, respectively, with only 5% of patients discontinuing treatment.[10] Several trials using a combination of immune checkpoint inhibitors have shown similar modest improvements in overall survival and progression-free survival including CheckMate 650,[11] CheckMate 9KD,[12] and STARVE-PC.[13]

The most significant results appear to be in tumors with high tumor mutational burden, tumors with mutations in genes involved in homologous recombination repair such as BRCA 1 and 2, CHEK2, ATM, those with deficiencies in mismatch repair pathways, and/or high microsatellite instability. These genetic alterations are common in mCRPC and may be particularly sensitive to poly-(adenosine diphosphate-ribose) polymerase inhibition.[14] Early evidence of this activity was reported by Mateo and colleagues in the TOPARP-A trial published in 2015, where they investigated olaparib in men with previously treated mCRPC. Thirty-three percent of patients had a significant response, which was associated with homozygous deletions or mutations in BRCA 1 and 2, ATM, CHEK2, and Fanconi's anemia genes.[15] This, among several other studies, led to the approval of olaparib and rucaparib as standard therapies for patients with mCRPC who harbor deleterious genetic alterations in the genes of interest.

The first Food and Drug Administration–approved immunotherapy for mCRPC was in 2010 with advent of sipuleucel-T after publication of the IMPACT trial.[16] Sipuleucel-T is an autologous cellular immunotherapy where a patient's peripheral blood mononuclear cells are activated with a recombinant prostatic acid phosphatase fusion protein before infusion. This resulted in a modest 4.1-month improvement in median survival (HR = 0.78); however, subsequent subset analysis showed an even greater improvement (13.1 months) in men who were treated in the lowest quartile of PSA below 22.1 ng/mL.[16,17] Sipuleucel-T remains a recommended therapeutic option for patients with minimally symptomatic or asymptomatic mCRPC.[2]

The future for patients with mCRPC remains hopeful, with several clinical trials for immunotherapy on the horizon (Table). Many of these trials utilize a combination approach to address both the immune and hormonal milieus. As oncologists investigate and discover new treatment paradigms, emphases on clinical efficacy and quality of life will be paramount. ■

Table. Metastatic Castration-Resistant Prostate Cancer Trials in Recruitment in the US

Trial name	Drug	Study phase	Primary end point(s)	Secondary end points
NCT04071236	M3814, avelumab	I, II	MTD, rPFS	
NCT05502315	Cabozantinib + nivolumab	II	rPFS	
NCT04221542	AMG 509	I	AE, DLT	OR, PSA response
NCT06100705	Bipolar androgen therapy + sipuleucel-T	II	Immune response to PA2024	rPFS, OS

Abbreviations: AE, adverse events; DLT, dose-limiting toxicities; MTD, maximum tolerable dose; OR, objective response; OS, overall survival; rPFS, radiographic progression-free survival.

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AUA/SUO2024 APC RECAP

AUA/SUO Advanced Prostate Cancer Guidelines: Update on Nonmetastatic Castration-Resistant Prostate Cancer

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The treatment of castration-resistant prostate cancer (CRPC) has enjoyed a renaissance over the past decade, with a plethora of new treatments that have delayed the progression of disease; maintained or improved quality of life; and, most impressively, extended survival. Most of these efforts were derived from clinical trials that enrolled patients with metastatic CRPC, and almost exclusively those patients were eligible for treatment based on radiographic findings that resulted from conventional imaging. It was in that context that the enigma of nonmetastatic castration-resistant prostate cancer (M0 CRPC) was defined in that these patients had a rising PSA (2.0 or greater) despite a castrate level of testosterone on androgen deprivation therapy (ADT) and the absence of metastatic disease on conventional imaging.[1] Nuanced in this definition is the absence of metastatic disease based on conventional imaging: CT, MRI, or nuclear medicine bone scan. So, beginning in 2018 and continuing through 2020, 3 novel second-generation antiandrogens were trialed in phase 3 randomized placebo-controlled trials in patients with M0 CRPC, and this led to the Food and Drug Administration approval of enzalutamide, apalutamide, and darolutamide for the treatment of men in this disease state. Importantly, the approval of these agents was based on a new but meaningful intermediate end point: metastasis-free survival (MFS).[2] By allowing the trials to demonstrate an MFS primary outcome, the agents were able to be approved much faster than if an overall survival benefit had been mandated, and this undoubtedly extended the survival of thousands of men with M0 CRPC by allowing these medications with indications for M0 CRPC to get to market much more rapidly than would have otherwise happened.

> "The enzalutamide group's median overall survival was 67 vs 56.3 months in the placebo group, corresponding to a 27% reduction in the risk of death.[4]"

Three randomized controlled trials were conducted using novel second-generation nonsteroidal antiandrogen agents. The PROSPER trial was an international, placebo-controlled randomized controlled trial that studied the impact of enzalutamide on MFS in patients with M0 CRPC.[3] All patients in the study had a PSA doubling time (PSADT) of less than 10 months. Patients were then randomized in 2:1 fashion to receive either 160 mg per day of enzalutamide or placebo. In both arms, patients continued to receive ADT. The enzalutamide cohort experienced more than twice the duration of MFS vs placebo (36.6 vs 14.7 months), corresponding to a 71% improvement in the risk of metastasis or death. In absolute terms, at the time of the initial analysis, nearly half of the placebo group had died vs only 23% of the enzalutamide group. In 2020, mature overall survival results from the trial were reported. The enzalutamide group's median overall survival was 67 vs 56.3 months in the placebo group, corresponding to a 27% reduction in the risk of death.[4]

In the phase 3 SPARTAN trial, investigators randomized 1207 participants with M0 CRPC in 2:1 fashion to receive ADT plus apalutamide (240 mg per day) vs ADT plus placebo.[5] A total of 806 patients were assigned to receive apalutamide. In a similar design to PROSPER, all patients in SPARTAN exhibited PSADT of less than 10 months. Once again, MFS was the primary end point. ADT plus apalutamide demonstrated a 72% improvement in the risk of developing metastasis, with an MFS interval of 40.5 months for the apalutamide group vs 16.2 months for the ADT plus placebo group. An update to this trial with overall survival results demonstrated that ADT and the addition of apalutamide in M0 CRPC resulted in a 22% reduction in the risk of death over ADT and placebo, corresponding to 14 months of improved survival.[6]

Darolutamide was the third novel antiandrogen agent to be approved for use in M0 CRPC. Its mechanism of action is similar to that of apalutamide and enzalutamide in terms of its ability to inhibit androgen receptor binding, translocation, and androgen receptor–activated transcription.[7] However, its unique chemical structure reduces the ability of darolutamide to cross the blood-brain barrier, an effect that may have implications on tolerability and adverse event rate.[8] The phase 3 ARAMIS trial was similarly designed to PROSPER and SPARTAN and examined similar primary MFS end points.[9] All patients met M0 CRPC criteria by conventional imaging standards, had a PSADT of less than 10 months, were randomized in 2:1 fashion vs placebo, and continued ADT. Patients in the darolutamide arm received 600 mg by mouth twice daily. The total number of patients in the study was 1509 (955 in the darolutamide arm vs 554 in the placebo arm). At the planned initial analysis, patients in the darolutamide group received a 22-month MFS advantage over placebo. When mature overall survival data were ultimately released, patients taking darolutamide experienced a 31% decrease in the risk of death, corresponding to 6% more patients being alive at 3 years with darolutamide.[10]

> "ADT plus apalutamide demonstrated a 72% improvement in the risk of developing metastasis, with an MFS interval of 40.5 months for the apalutamide group vs 16.2 months for the ADT plus placebo group."

With the 3 agents currently approved for M0 CRPC having similar efficacy at prolonging time to metastasis, radiographic progression, and overall survival, the next question naturally raised has become how to select the most appropriate agent for patients.[11] Again, we lack randomized head-to-head comparative studies to guide us, and one approach has been to select the treatment based on the adverse effect profiles gleaned from each of the phase 3 trials. This, however, should be interpreted with caution as it lacks the rigor and standardization of a true comparative analysis. A surrogate for adverse event severity measured across PROSPER, SPARTAN, and ARAMIS was the treatment discontinuation rates due to adverse events. For enzalutamide, 17% (n = 158) of patients in the intervention arm discontinued therapy, citing an adverse event as the primary reason. A total of 51 patients (5% of the enzalutamide cohort) were determined to have died due to an adverse event.[4] This compares with apalutamide, which saw 15% (n = 120) treatment discontinuation due to adverse events.[6] Fewer patients

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in the SPARTAN trial died due to an adverse event on apalutamide (3.0%; n = 24). Darolutamide appears to carry the lowest rate of treatment discontinuation due to an adverse event, with an overall attrition rate of 8.9%.[10]

Treatment of patients with M0 CRPC continues to evolve. Recognizing that the disease state exists in part because of limitations with enhanced imaging that existed during the trials in this disease state, future recommendations will have to reconcile efficacy and outcomes in the setting of oligometastatic disease. The ability to detect and treat small-volume metastatic disease continues to improve with advances in prostate-specific membrane antigen positron emission tomography technology.[12] Currently, AUA/SUO guidelines advocate for the treatment of M0 CRPC patients with a PSADT of 10 months or less. Among those patients with slow PSA doubling times, observation and periodic restaging with positron emission tomography imaging and PSA monitoring may be appropriate. The decision to treat and choice of agent in the M0 CRPC space must also consider patient-specific factors, given the limitations of comparative data. In keeping with the AUA/SUO Advanced Prostate Cancer Guidelines, ADT is continued during treatment with enzalutamide, apalutamide, or darolutamide.[1] Finally, the frequent involvement of our multidisciplinary care team consisting of colleagues from medical and radiation oncology, as well as clinical research support staff, is paramount to ensuring these complex patients receive evidence-based and guideline-concordant care while having access to the latest clinical trials. ■

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ASCO2024 HIGHLIGHT

Is Quality of Life Impacted for Patients With High-Risk Biochemical Recurrence When Enzalutamide Is Prescribed?

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Nonmetastatic hormone-sensitive biochemical recurrence (BCR) after radical prostatectomy or radiation has a very high prevalence of prostate cancer (PC) patients given it occurs in upwards of 70,000 US patients per year.[1] Prior studies have clearly established that patients with a PSA doubling time (PSADT) ≤ 9 months are at high risk of progression to metastatic disease[2] and death from PC.[3] Until the EMBARK trial results, we had limited options for high-risk BCR patients beyond a surveillance approach or androgen deprivation therapy (ADT). Despite a paucity of evidence-based publications, intermittent or continuous early ADT alone (prior to metastases) and/or first-generation androgen receptor blockers (eg, bicalutamide) were the commonly chosen therapeutic strategies.[4]

Given this gray zone of evidence-based trials, the EMBARK trial was completed after 8 years of global site participation with over 1000 subjects. EMBARK was a global phase 3 trial assessing whether intensified ADT (adding enzalutamide or enzalutamide monotherapy) could improve outcomes for high-risk BCR vs ADT alone. Patients with nonmetastatic BCR (by conventional imaging) with a PSADT ≤ 9 months and PSA ≥ 1 ng/mL post prostatectomy or PSA ≥ 2 ng/mL above the nadir for those without prostatectomy were randomized to enzalutamide + ADT, ADT alone, or enzalutamide alone. As previously reported,[5] enzalutamide with or without ADT delayed metastasis-free survival with trends toward improved overall survival, though results for overall survival are immature; however, these patients are being followed and we'll hopefully report in the near future. Furthermore, global quality of life (QoL) was preserved as assessed by patient-reported outcomes (PROs) completed every 12 weeks.[6] This led the Food and Drug Administration to approve enzalutamide for high-risk BCR in November 2023, its inclusion into the National Comprehensive Cancer Network guidelines in April 2024, the European Medicines Agency's approval in April 2024, and inclusion into European Association of Urology guidelines in the same month.

> "Remarkably, for global QoL as well as for nearly every subdomain of QoL analyzed, we found no statistically significant nor clinically meaningful benefit to stopping treatment."

Notably, a unique aspect of EMBARK is that if the PSA was < 0.2 at week 36, then at week 37 treatment for all 3 arms could be suspended. The rationale was to balance oncological benefits (more therapy) with improved QoL (less therapy). As previously presented,[5] the treatment suspension occurred more often in the enzalutamide arms (> 90% in enzalutamide + ADT and > 85% in enzalutamide monotherapy) vs

→ Continued on page 7

IS QUALITY OF LIFE IMPACTED FOR PATIENTS WITH HIGH-RISK BIOCHEMICAL RECURRENCE

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ADT alone (67%). At the ASCO (American Society of Clinical Oncology) 2024 annual meeting, the question we assessed was the impact of stopping treatment on QoL. We analyzed data from the PROs every 12 weeks for those who received the treatment suspension and for as long as they remained on treatment suspension. Using the last time point before suspension (week 36) as the new baseline, we assessed what happens to QoL when treatment is suspended through week 109 (ie, over 2 years in the study). After week 109, the majority of patients in all 3 arms had gone back on treatment and thus the number of patients left was small, thereby leading to wide confidence intervals and unreliable estimates.

Remarkably, for global QoL as well as for nearly every subdomain of QoL analyzed, we found no statistically significant nor clinically meaningful benefit to stopping treatment. This was even true in the enzalutamide monotherapy arm, wherein testosterone levels are elevated during treatment, and thus our results do not reflect any possible lingering effects of ADT to suppress testosterone. While perhaps counterintuitive, intriguingly, when looking back at the impact of initially starting treatment, we also saw no impact of treatment on global QoL. As such, if the initial treatment does not negatively impact QoL, it makes sense that stopping treatment does not improve QoL. Said in another way, enzalutamide for high-risk BCR does not negatively affect QoL and thus stopping it does not improve QoL.

One exception to the above general rule was in hormonal symptoms, which rapidly improved (at the next PRO measurement 12 weeks later) in all 3 treatment arms. As these are the some of the most bothersome symptoms patients get from enzalutamide, it is reassuring that with enzalutamide the likelihood of receiving treatment suspension is very high and patients can be reassured that those symptoms rapidly resolve when stopping therapy.

In summary, our recent ASCO 2024 presentation adds to the narrative that enzalutamide with or without ADT for high-risk BCR improves oncological outcomes without negatively affecting QoL. Given these data, it further supports the conclusion that enzalutamide is the new standard of care for high-risk nonmetastatic BCR. ■

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AUA2024 BEST VIDEO

Near-Infrared Fluorescence: An Intraoperative Tool to Manage Lymphorrhea After Radical Prostatectomy

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> "The procedure consisted of the following: (1) ICG injection before the beginning of the surgery; (2) robotic trocars placement; (3) intraoperative lymphangiography using NIRF imaging; (4) lymphatic leakage identification; (5) double clips application and sealing of the leaking lymphatic vessels; (6) drainage placement; (7) peritoneum reconstruction."

Introduction and Objectives

Near-infrared fluorescence (NIRF) imaging with indocyanine green (ICG) has emerged as a safe and feasible tool for an enhanced surgical experience. NIRF/ICG assists in the identification of key anatomical landmarks and surgical targets, either for oncological or nononcological scopes. According to the site of distribution (ie, bloodstream, lymphatic stream, organs' parenchyma), the diffusion pattern of ICG emphasizes the areas of interest (ie, blood vessels, lymphatic vessels, nodal stations). Specifically, the purpose of the current video was to describe the intraoperative use of NIRF/ICG to manage a case of massive lymphorrhea, which occurred after robot-assisted radical prostatectomy.

Materials and Methods

We present the case of a 72-year-old man who underwent Retzius-sparing robot-assisted radical prostatectomy and extended pelvic lymphadenectomy in March 2021. After 6 months, the patient presented to the emergency department with asthenia, dyspnea, and weight loss. CT scan showed severe ascites. No suspected abdominal lesions were detected. The patient underwent a complete clinical evaluation without evidence of pathological findings. Lymphoscintigraphy with ^{99m}Tc nanocolloid detected a deficit of lymphatic superficial drainage, with tracer accumulation in the inguinal region and abdomen. A massive lymphorrhea due to lymphatic drainage damage was suspected. Therefore, the patient was submitted to robot-assisted explorative laparoscopy and real-time lymphangiography with ICG. Intuitive da Vinci Xi system was used, given the availability of Firefly vision. One milliliter of diluted ICG was injected subcutaneously in the interdigital space and on the sole of each foot, 15 minutes before the surgery. The procedure consisted of the following: (1) ICG injection before the beginning of the surgery; (2) robotic trocars placement; (3) intraoperative lymphangiography using NIRF imaging; (4) lymphatic leakage identification; (5) double clips application and sealing of the leaking lymphatic vessels; (6) drainage placement; (7) peritoneum reconstruction.

Results

The postoperative follow-up period was uneventful. The output of each drainage gradually decreased to 0 cc in 10 days. At 6 months after surgery, a CT scan revealed no residual lymphorrhea. An asymptomatic pelvic lymphocele of approximately 5 cm was detected. PSA was undetectable at the last follow-up.

Use the QR code to access the video.

> "Real-time lymphangiography with ICG allowed accurate intraoperative identification of the lymphatic leakage, which had resulted in massive lymphorrhea."

Conclusion

Real-time lymphangiography with ICG allowed accurate intraoperative identification of the lymphatic leakage, which had resulted in massive lymphorrhea. Future studies are warranted to corroborate the role of NIRF/ICG in such a clinical scenario. ■

AUA2024 BEST POSTER

Neutrophil-Derived Extracellular Vesicles: Mediators of Bladder Toxicity in Radiotherapy-Treated Prostate Cancer

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Prostate cancer (PCa) affects approximately 12.5% of men in the US during their lifetime,[1] and radiotherapy (RT) remains a mainstay of PCa management in clinical practice. RT is used alone or in combination with hormone therapy and/or surgery in more than 50% of PCa cases.[2] Despite its clinical benefits, RT causes persistent radiation cystitis (RC) and related forms of late bladder toxicity in roughly 25% of treated patients.[3,4] There is no Food and Drug Administration–approved preventative therapy for this debilitating form of radiotoxicity, which is characterized by hematuria, leading to a pronounced decline in quality of life and decisional regret in many cases. The discovery of biomarkers capable of predicting RC in PCa patients before it develops has the potential to inform treatment planning and elucidate the molecular basis for this condition, enabling the design of appropriate pharmacological interventions that can mitigate the risk of this devastating bladder radiotoxicity.

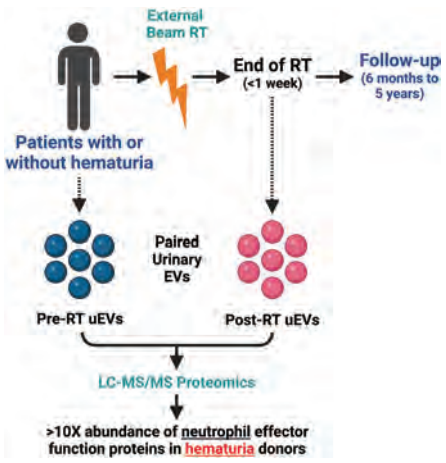

Figure 1. Urinary extracellular vesicles (uEVs) collected both pre and post radiotherapy (RT) demonstrated a high abundance of neutrophil effectors function proteins in the patients who developed hematuria compared to those who did not, suggesting potential roles of neutrophils and extracellular vesicles (EVs) thereof in late bladder toxicities. LC-MS/MS indicates liquid chromatography–tandem mass spectrometry. Created with BioRender.com.

Extracellular vesicles (EVs) are small, membrane-enclosed vesicles released from all nucleated cells that contain a variety of biologically active macromolecular cargoes specific to their cells of origin. Our group recently reported that urinary EV (uEV) particle counts increased significantly at the end of RT in PCa patients who developed subsequent hematuria 6 months to 5 years post RT, whereas such induction by RT was not found in patients who did not develop hematuria over the course of similar follow-up.[5] This suggests that uEVs may serve as a valuable biomarker for predicting future RC risk, potentially enabling timely and earlier intervention for at-risk patients to mitigate the development of late bladder toxicities. Given the functional role of EVs in many biological systems, we performed a differential proteomics analysis of paired uEV samples collected before RT and at the end of RT from 6 PCa patients, 3 of whom developed post-RT hematuria and 3 who did not. This approach revealed the enrichment of neutrophil-related proteins in the uEVs from the donors who developed hematuria, with some of these proteins having been enriched even before RT (Figure 1), raising the tantalizing possibility of predicting RC risk even before RT. Given these findings and a growing body of evidence suggesting a link between neutrophil functions and adverse post-RT outcomes in cancers and other preclinical settings,[6-8] we conducted a series of in vitro analyses aimed at clarifying the effects of irradiation on neutrophils.

We generated neutrophil-like cells suitable for experimental use by using either dimethyl sulfoxide or all-trans retinoic acid to differentiate human promyelocyte-like HL60 cells for 5 days, confirming their successful differentiation based on flow cytometry and quantitative reverse transcription polymerase chain reaction analyses of neutrophil markers. We then evaluated the longitudinal responses of these cells to irradiation in an effort to determine whether irradiation can directly activate neutrophils or induce their release of EVs. Following irradiation (2 Gy or 10 Gy), differentiated HL60 (dHL60) cells exhibited time-dependent changes in neutrophil effector gene expression that coincided with increased oxidative burst activity and the release of significantly higher numbers of EVs. Strikingly, the co-culture of these irradiated dHL60s with SV-HUC bladder urothelial cells led to a significant decline in SV-HUC cell viability and higher rates of apoptotic urothelial cell death, while the knockout of the *RAB27A* gene required for EV biogenesis or the use of the Rab27a inhibitor Nexinhib20 reversed this irradiated neutrophil-mediated cytotoxicity, supporting a role for neutrophil-derived EVs and their cargoes as mediators of urothelial damage (Figure 2).

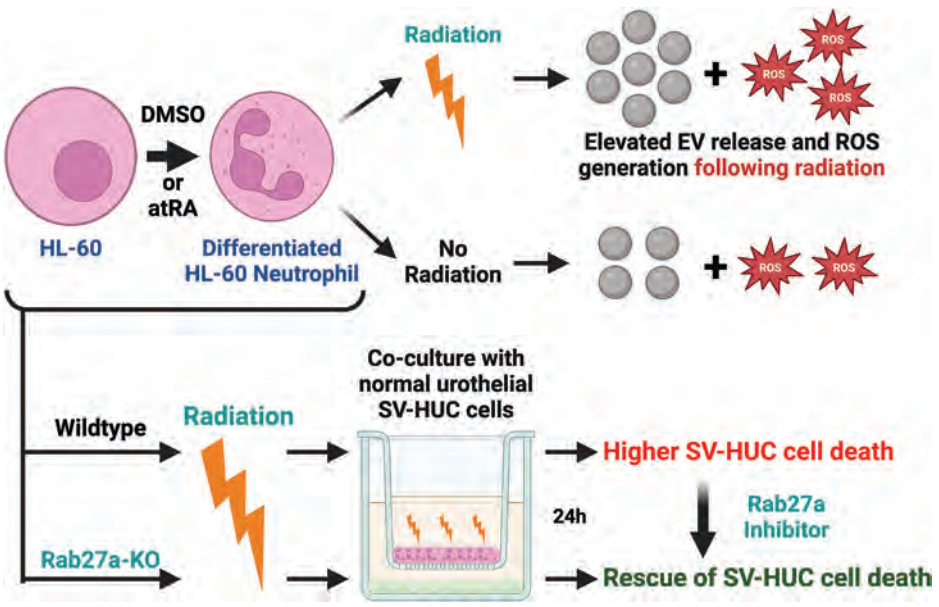

Figure 2. Extracellular vesicle (EV) release and reactive oxygen species (ROS) generation were significantly elevated following the radiation of differentiated HL-60 neutrophils. Co-culturing irradiated HL-60 neutrophils with normal urothelial SV-HUC cells induced death of the latter cell type as evidenced by Annexin V/PI staining, which could be rescued by knocking out Rab27a, a key gene in the extracellular vesicle biogenesis pathway or the use of a small molecule inhibitor against it. Created with BioRender.com.

Our in vitro findings support a functional link between RT-associated neutrophil EV release and late bladder toxicity in PCa patients, suggesting that neutrophil-derived EVs may offer value as predictive biomarkers for RC and that neutrophils or their EV release pathways may be viable targets for efforts to prevent this form of radiotoxicity. Given our enticing data and the growing interest in neutrophils as RT-related biomarkers in various cancers,[9] we are in the process of conducting further detailed bioinformatics analyses of our uEV and matched serum EV proteomic datasets from PCa patients with and without late hematuria and corresponding functional analyses that we hope will inform efforts to

> "Despite its clinical benefits, RT causes persistent radiation cystitis (RC) and related forms of late bladder toxicity in roughly 25% of treated patients.[3,4]"

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NEUTROPHIL-DERIVED EXTRACELLULAR VESICLES

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mitigate the risk of late bladder radiotoxicity, ultimately leading to better patient outcomes. ■

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AUA2024 BEST POSTER

Design and Validation of Hydrogel Transperineal Prostate Biopsy Simulator With Real-Time Quantitative Assessment

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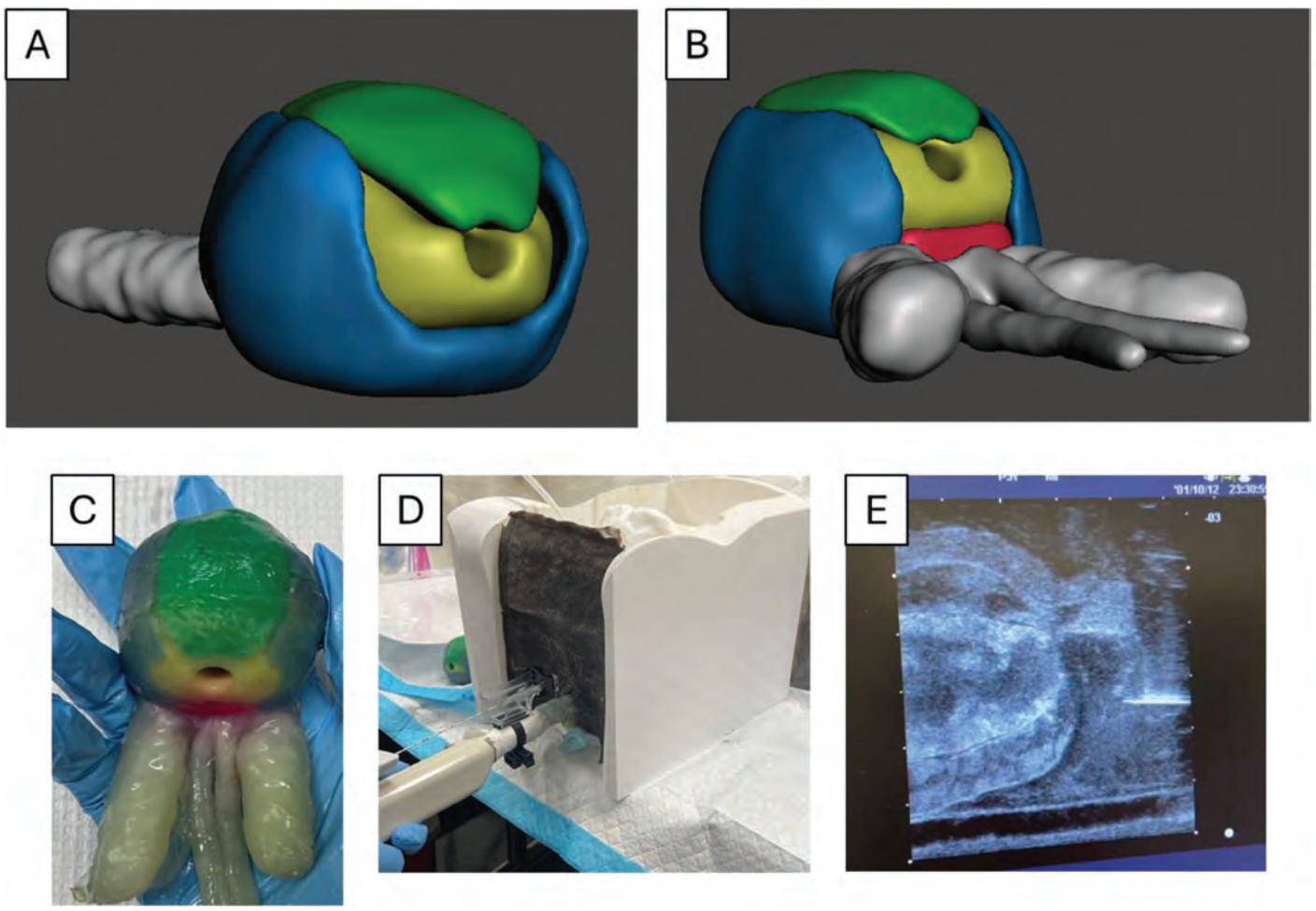

Figure 1. 3D design and hydrogel simulator. Two views of 3D rendering of the prostate with color-coded zones: peripheral (blue), yellow (transition), green (anterior), red (central; A and B); hydrogel prostate (C); full hydrogel simulator (D); and ultrasound appearance of hydrogel simulator (E).

Prostate biopsy remains the gold standard for histologic confirmation of prostate cancer diagnosis, with over 1 million biopsies performed yearly in the US and Europe and many requiring repeated biopsies over their lifetime.[1,2] The transrectal approach continues to be ubiquitous despite the virtual elimination of infection and sepsis without the need for antibiotic prophylaxis for the transperineal approach. There has been a slow adoption of the technique due to the perceived need for anesthesia due to lower pain tolerance and the lack of a training platform.[3] The PREVENT trial demonstrated that transperineal biopsy (TPBx) can be completed in office-based settings with comparable cancer detection rates and low infection risk compared to the transrectal approach[1]; therefore, there is a need for a training platform that reinforces correct transperineal technique and spacing of biopsies to optimize zonal sampling. 3D printing offers a unique tool for surgical education, allowing for customizable and patient-specific models. Combined with hydrogel molding, realistic simulators can be developed for surgical simulation, training, and education. Using our previously validated and published approach of 3D printing and hydrogel molding, we developed a non-biohazardous training model with built-in metrics for real-time feedback during TPBx training.

Previously, we developed a high-fidelity simulator for transrectal ultrasound biopsy[4] and modified this for the transperineal approach. Archival 3T MRI images were selected from a prospective database and segmented to incorporate essential anatomy: perineum, prostate, seminal vesicles, vas deferens,

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DESIGN AND VALIDATION OF HYDROGEL TRANSPERINEAL PROSTATE BIOPSY SIMULATOR

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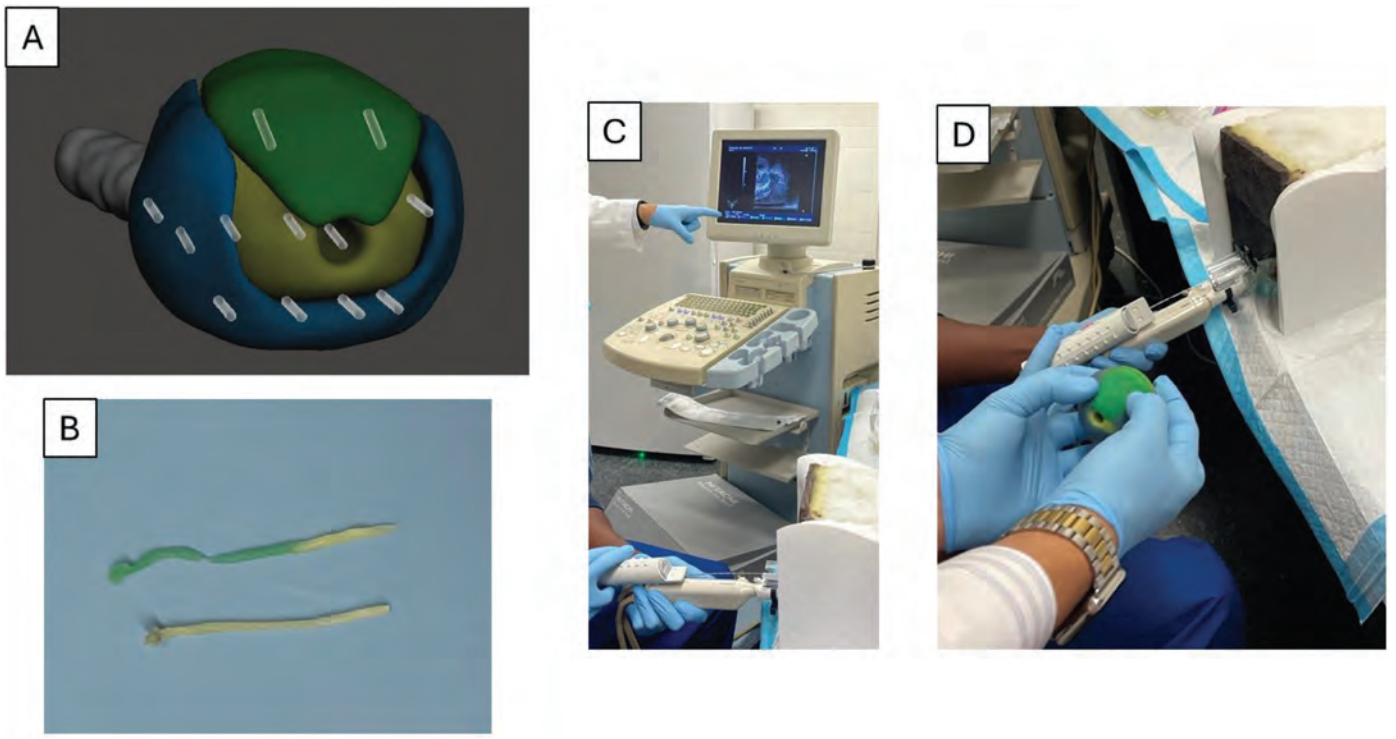

Figure 2. Transperineal biopsy simulation. Map of 12 target biopsy cores (A); an example of partially correct (green and yellow) vs incorrect (yellow) core for the anterior zone (B); instructor teaching trainee (C) and instructor using hydrogel model to demonstrate zones and target with trainee (D).

bladder, urethra, rectum, pubic bone, pelvic diaphragm, and ischiocavernosus muscles. Using the 10-sector template, the 3D computer-aided design was modified to include 4 different color-coded zones that provide immediate feedback after biopsy: transition zone, central zone, peripheral zone, and anterior zone (Figure 1, A and B). Tissue tensile strength was modeled after a series of cadaver mechanical tests (Instron Universal Testing System).[5] Additional mechanical testing was completed comparing the model and cadaver using a novel needle force mechanical system.[6] A hydrogel model was then created for simulations with realistic ultrasound echogenicity and the various anatomical components (Figure 1, C-E).

Six experts and 4 novices completed TPBx on the model targeting a 12-core template (Figure 2, A and B). Colored biopsy cores were collected and measured for accuracy, core length, and number of attempts. Novices were trained by an expert prior to collecting biopsy cores for assessment (Figure 2, C and D). Experts successfully biopsied the cores at a higher accuracy than novices (80% vs 67%, $P < .001$) and superior length (12.1 vs 7.9 mm, $P < .001$), but with no difference in the number of attempts ($P = .14$). The base posterior, lateral, and anterior cores demonstrated the greatest difference in core length among experts and novices ($P < .05$, .01, and .05, respectively; Figure 3). In addition, the experts assessed the model via survey using a 5-point Likert scale. The results concluded the model adequately replicated ultrasound appearance (82%), procedural realism (71%), and educational effectiveness (86%).

This high-fidelity hydrogel simulator provided a portable nonbiohazardous training platform for transperineal prostate biopsy. Participants rated the model highly for realism and educational effectiveness. Real-time feedback was provided to participants in the form of accuracy (core color), precision (correct color core percentage), and quality (length of core). This model can be modified to accommodate any preferred prostate template and adapted to variable prostate anatomy while blunting the learning curve to facilitate adoption. Our next step includes a multicenter validation study and including lesions for targeted biopsy to train in this technique and encourage further adoption of the transperineal approach for prostate biopsy. ■

> "This high-fidelity hydrogel simulator provided a portable nonbiohazardous training platform for transperineal prostate biopsy. Participants rated the model highly for realism and educational effectiveness."

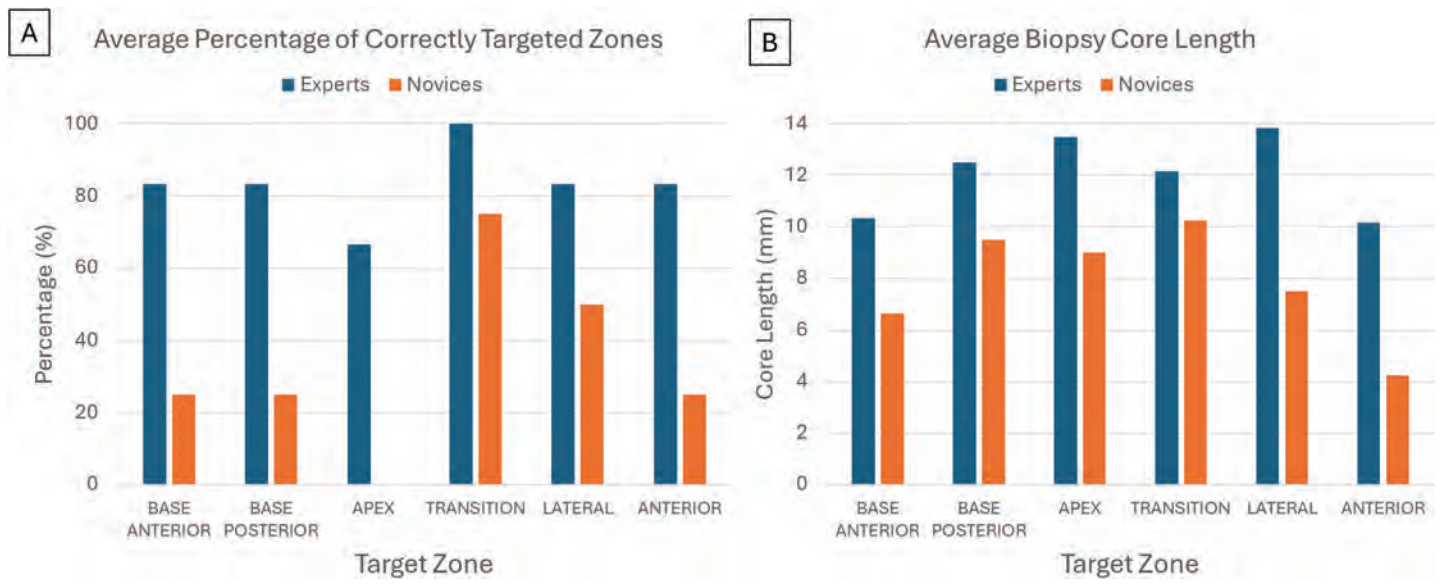

Figure 3. Biopsy assessment comparing novices and experts: the average number of correctly targeted zones (A) and the average biopsy core length (B).

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AUA/SUO2024 APC RECAP

The Role of Next Generation Imaging for Advanced Prostate Cancer

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Historically, patients with advanced prostate cancer have been imaged using conventional imaging, including nuclear medicine bone scan and CT scans. These images were widely available, economical, and familiar to urologists, who used them for decades in clinical practice. Importantly, conventional imaging was used in clinical trials to define patient selection and stratification. However, next generation imaging has been developed with the goal of improving prostate cancer detection. The widespread adoption of prostate-specific membrane antigen (PSMA) positron emission tomography (PET) has brought about a new era of imaging. With this change, the guidelines have shifted from considering novel PET scans after negative conventional imaging to now preferentially recommending PSMA PET.

There are currently 3 approved next generation PET imaging modalities, including C-11 choline PET, F-18 fluciclovine, and PSMA PET. Choline PET was the first approved prostate cancer PET imaging technique that relies on cellular membrane synthesis, which is increased in prostate cancer cells. However, choline PET has limited access due to a very short half-life (20 minutes) and the need for an on-site cyclotron. The next approved PET imaging technique was fluciclovine. This is a synthetic amino acid PET that has increased uptake in prostate cancer cells due to increased metabolism. Minimal urinary excretion makes fluciclovine PET ideal for detection of recurrence after prostatectomy. Lastly, PSMA PET has become widely adopted after its approval. It relies on detection of a transmembrane glycoprotein overexpressed on prostate cancer cells. There are 2 approved PSMA PET agents, F-18 piflufolastat (DCFPyL) PSMA and Ga-68 PMSA-11. Studies comparing PSMA PET to other next generation imaging techniques have found that PMSA PET has a higher sensitivity.

The first PSMA PET agent approved by the Food and Drug Administration (FDA) was gallium 68 PSMA-11 PET in December 2020. The approval was initially limited to sites in California based on studies from the University of California, San Francisco and the University of California, Los Angeles. The first study was a prospective trial of 635 men with biochemical recurrence after radical prostatectomy, radiation therapy, or both. PSMA PET successfully localized recurrent cancer in 75% of patients.[1] The second study was a phase 3 study, once again at the University of California, San Francisco and the University of California, Los Angeles that evaluated 277 men with intermediate- or high-risk prostate cancer undergoing PET prior to radical prostatectomy. The positive study found that PSMA PET detected lymph node disease with a specificity of 95%.[2]

The next approved PSMA PET agent was F-18 PSMA PET, which was approved based on the OSPREY and CONDOR studies in 2021. In the OSPREY study, men with high prostate cancer undergoing prostatectomy and those with suspected recurrent cancer were evaluated.[3] In total, 385 patients were evaluated and the primary end point for prostate cancer specificity was met. In the CONDOR trial, 208 men at risk for recurrence after radical radiation therapy were evaluated. The study successfully found the correct localization occurrence in up to 87% of men.[4] The proPSMA study compared PSMA PET to conventional imaging.[5] It evaluated 302 men with high-risk prostate cancer randomized to PSMA PET or conventional imaging. The study found that PSMA PET was significantly more accurate and resulted in lower radiation exposure.

With the FDA approval of PSMA PET there have been updates to advanced prostate cancer guidelines that recommend PSMA PET preferentially. The updated AUA guidelines recommend PSMA PET for patients with biochemical recurrence after local treatment. The guidelines also recommend PSMA PET for patients with castrate-resistant prostate cancer who may have metastases. In patients with metastatic castrate-resistant prostate cancer, guidelines suggest PSMA PET may help identify patients who are candidates for novel PSMA-targeted treatments. The guidelines also clarify that conventional imaging is not needed prior to PSMA PET. Both the National Comprehensive Cancer Network and European Association of Urology guidelines express caution that PSMA PET may cause a Will Rogers phenomenon, moving patients with worse prognosis to higher-risk groups, thereby appearing to improve the outcomes of both.

The adoption of PSMA-targeted imaging has also allowed for the development of a new field of treatment called theranostics. This is the combination of both therapy and diagnostics. Theranostic treatments use radiolabel ligands as both a predictive biomarker and therapeutic agent. The first approved theranostic treatment for prostate cancer occurred in 2022 with the FDA approval of lutetium. This is a β-particle radioligand therapy targeting PSMA-expressing cells. The approval of lutetium was based on the VISION Trial, a phase 3 trial of lutetium plus standard of care compared to standard of care alone.[6] The study found that lutetium improved progression-free survival and overall survival compared to standard of care alone.

Over the last 4 years, there has been a rapid transition from conventional imaging to next generation PSMA PET imaging for patients with advanced prostate cancer. PSMA PET has been found to be more sensitive for the detection of prostate cancer, both in pretreated and recurrent states. Because historical studies have used conventional imaging to define the clinical states of advanced prostate cancer, future clinical trials evaluating the impact of new imaging will be important to determine the benefit. PSMA PET has provided a new treatment modality using the theranostic agent luteum in patients with a history of castration-resistant prostate cancer. ■

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ERRATUM

Emerging Treatments in Bladder Cancer: Erratum

AUANews, July 2024, Volume 29, Issue 7, Page 4.

Formatting errors in Table 1 in the article have been corrected and some values were updated to reflect recent data. The revised table is available online: https://auanews.net/issues/articles/2024/july-2024/emerging-treatments-in-bladder-cancer

PROSTATE CANCER

The Impact Genetics Plays in the Diagnoses and Treatment of Prostate Cancer: What This Means for Patients

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Since Tom was diagnosed in 2015, the landscape has expanded for prostate cancer (PCa) diagnostics. Cancer treatments continue to advance. What this means to the patient is having targeted treatments with the ability to kill cancerous cells, while minimizing the damage to surrounding tissue. Treatments must try to exploit features that are unique to cancer cells, such as a specific protein that, like prostate-specific membrane antigen, is expressed on the cancer cell surface.

There has been a paradigm shift in treating cancers based on the genomic code of the tumor. What this means to the patient is that researchers can identify key genetic mutations associated with disease progression and tailor treatments accordingly.

What's exciting to us is that research and clinical trials mean that our knowledge base is expanding all the time. What this means to the patient is that new therapies have brought the field closer to the goal of being able to implement precision oncology therapy for every patient.

Existing genomic technologies can "read" and interpret DNA (the molecule that carries genetic information for the development and functioning of an organism) to map unique cancer mutations and match these to precision medicines, which target the mutations in the cancer.

Right now, all men with localized high-risk, recurrent, or advanced disease should discuss germline testing. This test analyzes noncancer cells (like blood samples) to look for mutations that were inherited and are present in every cell of the body since birth. Also, patients with strong family history should be considered for testing, since the testing can help diagnose hereditary cancer predisposition syndrome and provide information about a patient's likelihood of a future cancer diagnosis.

GENETIC OR GERMLINE TESTING	BIOMARKER OR SOMATIC TESTING
Inherited, or hereditary, mutations	Acquired mutations
Inherited - passed from parent to child	Not passed from parent to child
Inherited gene mutations exist in every cell of the body	Acquired gene mutations exist only in the tumor itself
10% of prostate cancer is thought to be caused by inherited, germline mutations	90% of prostate cancer is thought to be due to non-inherited, acquired mutations
Provides eligibility for targeted cancer therapies	Provides eligibility for targeted cancer therapies
May provide information on family member's risk of developing certain cancers	Does not provide information on cancer risk in other family members
Identified through a blood or saliva sample	Identified by testing the tumor itself or tumor cells that are circulating in the blood

Figure 1. Education on genetic testing should include both germline and somatic testing, both before and after genetic testing. Reprinted with permission from ZERO.

By contrast, somatic testing analyzes cancer cells to look for alterations in the genes of the tumor that have occurred over time. Currently, somatic testing is indicated for patients with metastatic PCa since the results can help identify those patients who might benefit from other therapies, such as targeted therapies or immunotherapies.

Patient advocacy groups such as ZERO Prostate Cancer encourage patients to get care adherent to National Comprehensive Cancer Network and AUA guidelines. ZERO educates patients on when they should be tested so they can talk with their doctors. An educated patient is an empowered patient. Ideally, patients who meet National Comprehensive Cancer Network criteria should get genetic counseling.

Education on genetic testing should include both germline and somatic testing (Figure 1), both before and after genetic testing. Often, specialized counseling needs to be considered, especially in the cases of positive germline alterations. For such cases, a genetic counselor can play an important role in the pre- and posttest education as well as in possible cascade testing where family members are also tested to rule out hereditary syndromes.

Molecular profiling via somatic testing at the time of metastatic disease can help with more personalized therapy, leading to better outcomes. Biomarker testing for mutations associated with HRR (homologous recombination repair pathway), such as BRCA1 and 2 or ATM, plays an important role. These genetic markers help in the understanding of the individual profile, which influences both prognosis and treatment strategies, including more targeted treatments. In general, the preferred method is testing the available tumor tissue from a biopsy or surgery. However, when tumor tissue is not available, a liquid biopsy (which finds circulating tumor DNA) can be considered.

The process of comprehensive testing including both germline and somatic testing is complex and requires additional resources (Figure 2). Often, these tests are not conducted at the institutions where patients received their care, and the samples are sent out to external genetic companies to analyze

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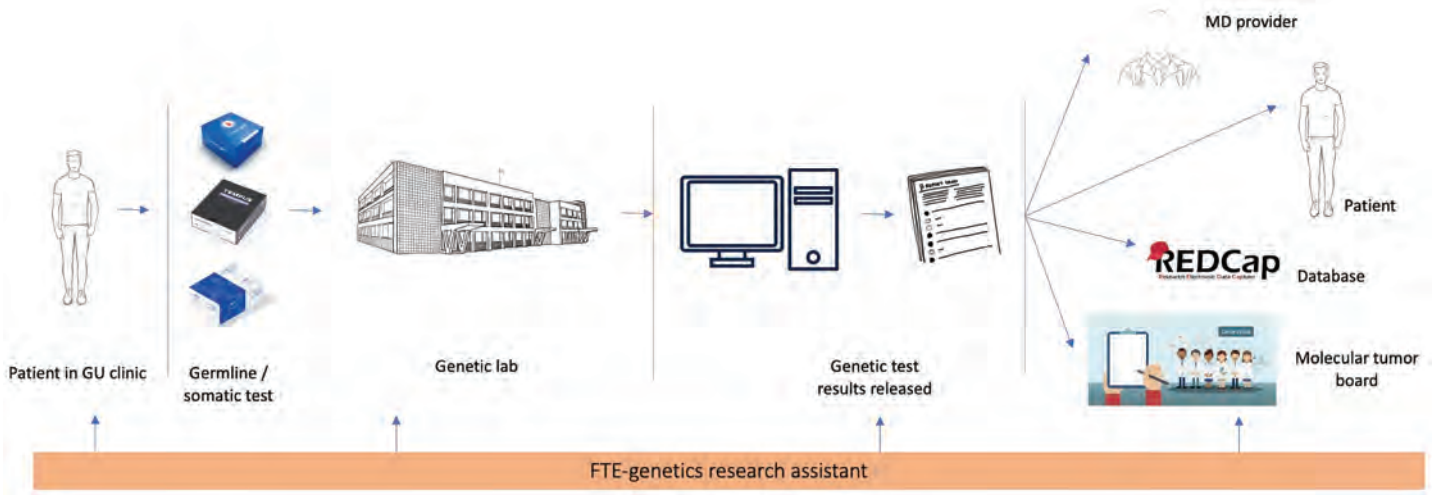

Figure 2. Genetic testing model at genitourinary (GU) clinics at University Hospitals Seidman Cancer Center. FTE indicates full-time equivalent. Courtesy of Pedro Barata, MD, MSc, FACP.

THE IMPACT GENETICS PLAYS IN THE DIAGNOSES AND TREATMENT OF PROSTATE CANCER

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the samples. For example, at University Hospitals Seidman Cancer Center and many other institutions there is a multidisciplinary team, including a genetic test assistant, that can help in this process. Currently, less than 50% of patients with PCa are offered genetic testing due to several barriers[1-3]:

- Cost-effectiveness of genetic testing and shortage of genetic clinics especially in low- and middle-income countries
- Availability of genetic counseling for patients with advanced PCa in the early stages after diagnosis
- Limited genetic panels such as BRCA (breast cancer gene) and ATM (ataxia-telangiectasia mutated gene) panels only
- Challenges in sample selection: blood vs tumor vs circulating DNA
- Tissue availability

What This Means to the Patient

Genetic mutations in the DNA of cancer cells can help detect aggressive cancer subtypes, determine the progression of the disease, and manage the PCa more effectively.

Unmet Needs

- Define your risk
- Determine if you can pass it on
- Somatic testing may determine how the tumor was developed and identify the molecular makeup of the tumor, which can provide access to specific targeted therapies that otherwise would not be considered
- Avoid certain treatments
- Better prognostic information about the tumor
- Trust

The inclusion of genetic testing and counseling for HRR mutations will be critical for improving patient outcomes with advanced PCa.[4]

Takeaways

Clinicians should discuss treatment options with patients with advanced PCa based on life expectancy, comorbidities, preferences, and tumor characteristics.

Clinicians should encourage engagement with professional or community-based resources, including patient advocacy groups.

The opportunity of genetic testing should be considered and discussed with patients diagnosed with PCa, especially those diagnosed with high-risk, recurrent, or metastatic disease.

Genetic alterations such as mutations in the DNA of cancer cells can help define prognosis and predict response to targeted therapies, thus impacting the management of PCa more effectively. ■

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Emerging Role of PARP Inhibitors in Advanced Prostate Cancer Treatment

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For patients with advanced prostate cancer, germline and somatic profiling have enabled new treatment strategies. DNA damage repair mechanisms have been a specific focus of precision medicine, with one potential target being homologous recombination repair (HRR) genes including BRCA1, BRCA2, and ATM.[1] Poly (ADP-ribose) polymerase (PARP) inhibitors are a class of drugs that work by targeting cancer cells that already have deficient HRR genes. PARP enzymes also play a role in repairing DNA. One mechanism by which PARP inhibitors work is synthetic lethality. Cancer cells with HRR deficiencies (such as a BRCA-mutated cell) rely heavily on PARP-mediated repair mechanisms to survive. When a PARP inhibitor is added, there is simultaneous loss of PARP activity along with the defective HRR, leading to lethal DNA damage and cell death.

Currently, several PARP inhibitors have shown efficacy, as monotherapy or in combination with androgen receptor (AR) blockers, in treating patients with HRR genetic alterations who have castrate-resistant metastatic prostate cancer (mCRPC).

The phase 3 PROfound trial randomized olaparib vs abiraterone or enzalutamide in patients with mCRPC with progression on at least 1 novel hormonal agent (abiraterone or enzalutamide). One prior taxane agent was permitted but not required.[2] Patients were required to have somatic or germline HRR gene mutations. The patients were divided into cohort A (BRCA1/2 or ATM mutations) and cohort B (12 other HRR genes). The final overall survival analysis of PROfound showed a survival benefit with olaparib vs abiraterone/enzalutamide in cohort A (HR 0.69, 95% CI, 0.50-0.97).[3]

> "Multiple studies have shown benefit in improving progression-free survival with this combination therapy, including PROPel (olaparib + abiraterone), MAGNITUDE (niraparib + abiraterone), and TALAPRO-2 (talazoparib + enzalutamide)."

TRITON3 compared rucaparib or physician's choice in patients with mCRPC.[4] Eligible patients had mCRPC with a BRCA1, BRCA2, or ATM alteration and disease progression after treatment with a second-generation androgen-receptor pathway inhibitor. They received rucaparib or a physician's choice control (docetaxel or a second-generation androgen receptor pathway inhibitor). The primary outcome was median duration of imaging-based progression-free survival. In the intention-to-treat analysis, imaging-based progression-free survival was improved in the rucaparib group compared to the control group (HR 0.50, 95% CI 0.36-0.69). Interestingly, the benefit for imaging-based survival was specifically seen in the BRCA subgroup; in the exploratory data analysis of patients with an ATM alteration, the duration of imaging-based progression-free survival was similar in the rucaparib and control groups. The AUA recommends

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EMERGING ROLE OF PARP INHIBITORS IN ADVANCED PROSTATE CANCER TREATMENT

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that clinicians offer a PARP inhibitor to patients with deleterious or suspected deleterious germline or somatic recombination repair gene-mutated mCRPC following treatment with enzalutamide or abiraterone acetate and/or a taxane-based chemotherapy.

Further, combination therapy with PARP inhibitors and AR blockers has emerged as a management option in the treatment of mCRPC. The androgen receptor pathway has been shown to regulate the expression of DNA repair genes, and inhibiting signaling can impair the DNA repair mechanism in prostate cancer cells. As discussed above, PARP inhibitors already exploit deficiencies in DNA repair pathways. The combination of the two has a synergistic effect.[5]

Multiple studies have shown benefit in improving progression-free survival with this combination therapy, including PROPel (olaparib + abiraterone), MAGNITUDE (niraparib + abiraterone), and TALAPRO-2 (talazoparib + enzalutamide).

PROpel is a double-blind randomized phase 3 trial of abiraterone and olaparib vs abiraterone and placebo in the first-line treatment of patients with mCRPC.[6] The primary end point was imaging-based progression-free survival. The median imaging-based progression-free survival was significantly longer for abiraterone and olaparib than in the abiraterone and placebo arm (HR 0.66, 95% CI, 0.54-0.81). In May 2023, the Food and Drug Administration (FDA) approved the combination of olaparib with abiraterone for patients with BRCA-mutated mCRPC.

> "The AUA recommends that clinicians offer a PARP inhibitor to patients with deleterious or suspected deleterious germline or somatic recombination repair gene-mutated mCRPC following treatment with enzalutamide or abiraterone acetate and/or a taxane-based chemotherapy."

> "PARP inhibitors alone or in combination with AR blockers offer an additional promising treatment strategy for patients with castrate-resistant prostate cancer harboring somatic or germline DNA damage mutations."

MAGNITUDE is a phase 3, randomized, double-blinded study that evaluated niraparib and abiraterone acetate plus prednisone vs placebo and abiraterone acetate.[7] The primary end point, radiographic progression-free survival, was significantly longer in the niraparib and abiraterone acetate plus prednisone group compared with placebo (HR 0.53, 95% CI 0.36-0.79). Based on these results, the FDA approved the combination of niraparib and abiraterone in August 2023 for mCRPC patients with BRCA mutations.

Finally, TALAPRO-2 randomized patients to talazoparib plus enzalutamide vs placebo plus enzalutamide in patients with mCRPC.[8] The primary end point was radiographic progression-free survival, and this was significantly longer in the intervention group who received talazoparib plus enzalutamide compared to the control (HR 0.73, 95% CI 0.56-0.96). This combination has also been FDA approved for patients with mCRPC harboring HRR mutations.

Common adverse events from PARP inhibitors include anemia, thrombocytopenia, fatigue, nausea, and gastrointestinal symptoms, with anemia being one of the most commonly reported. Patients should be monitored for symptoms and undergo appropriate laboratory testing, with dose interruptions or reductions as deemed necessary.

PARP inhibitors alone or in combination with AR blockers offer an additional promising treatment strategy for patients with castrate-resistant prostate cancer harboring somatic or germline DNA damage mutations. With more widespread use of genetic testing, urologists can now tailor care as we move towards precision medicine in advanced prostate cancer. ■

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