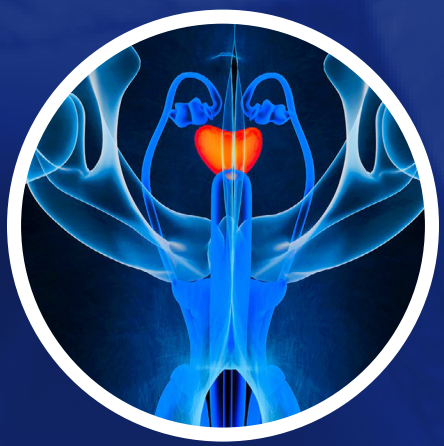
BENCH TO BEDSIDE
URO-ONCOLOGY
GU CANCERS TRIAD



Proceedings From the 5th B2B Uro-Oncology: GU Cancers Triad Meeting

October 13, 2023

Prostate Cancer

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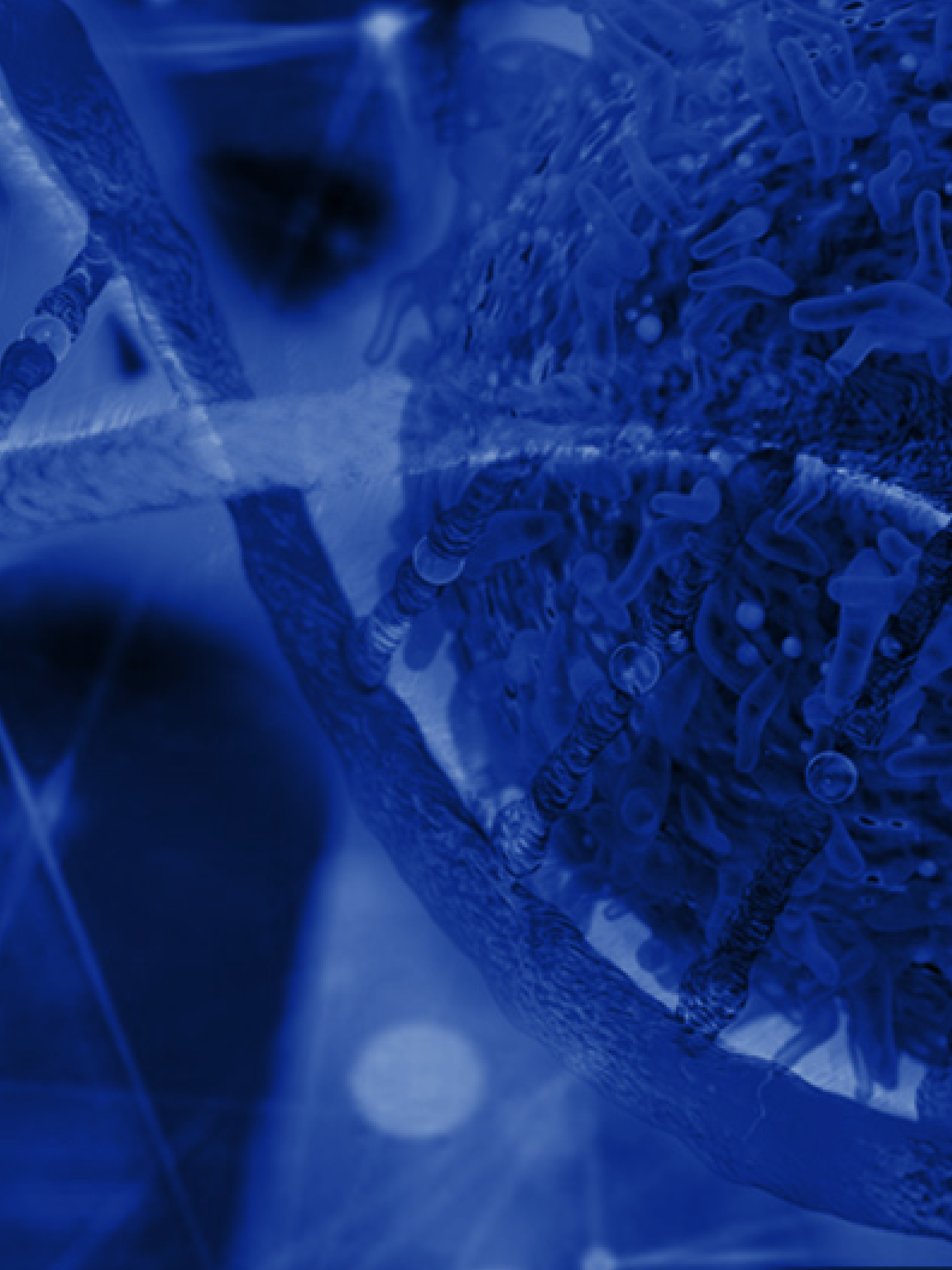

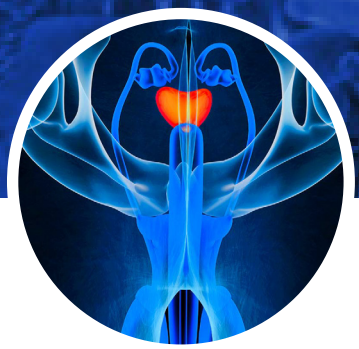

B2B: Prostate Cancer Summary

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The 5th Bench-to-Bedside Uro-Oncology: GU Cancers Triad Meeting, organized in conjunction with the 43rd Annual Congress of the Société Internationale d'Urologie, was held on October 13th, 2023, at the Istanbul Lutfi Kirdar International Convention and Exhibition Centre in Istanbul, Türkiye, and transmitted live on the *SIU@U* virtual platform. The session on prostate cancer (PCa) was chaired by Dr. Derya Tilki (Germany) and took place in the afternoon, along with 2 Genitourinary (GU) Cancers Talks. The first presentation of the afternoon focused on the impact of new robotic-assisted surgical systems on uro-oncology surgery. This was followed by talks on the use of intraoperative frozen section during radical prostatectomy and how to improve patient outcomes after surgery. Next were presentations on novel biomarkers in PCa, both in localized as well as metastatic disease, followed by a debate on patient selection for therapy with poly(ADP-ribose) polymerase (PARP) inhibitors. The session continued with talks on the next generation of androgen receptor (AR) inhibitors and a clinical trials update on radiotherapy for PCa, followed by a presentation on chimeric antigen receptor T cell (CAR-T) in GU cancers.

The afternoon sessions opened with Dr. A. Erdem Canda (Türkiye) discussing the impact of new robotic surgery systems in uro-oncology. The number of robotic systems with applications in urological surgery has expanded in recent years; currently, around 50 robotic platforms are available worldwide. Of these, most are available uniquely in China and Korea. In addition to surgical performance itself, robotic systems have improved on surgeon ergonomics, especially compared to the older laparoscopic systems. Importantly, there have been developments not only in robotic platforms for intra-abdominal urological surgery, but also for intrarenal procedures, such as the removal of stones.

While open surgery is used for many urological procedures worldwide, there has been an increase in robotic-assisted surgery in several countries, given its advantages over other surgical approaches. For instance, robotic-assisted radical prostatectomy (RARP) is now considered a standard in the United States[1]. Compared to laparoscopic radical prostatectomy, the robotic-assisted approach has a shorter learning curve and requires a minimum of 40 cases to gain robust surgical experience (compared to at least 200 for laparoscopy)[2].

Dr. Canda then focused on several examples of how new robotic surgery systems have impacted

procedures performed at the Department of Urology of Koç University Hospital. Robotic systems have additional applications in urology other than the surgical procedure itself. One example is the use of virtual reality tumour navigation using 3D-reconstructed images based on tumour segmentation on multiparametric magnetic resonance imaging (mpMRI), as well as positron emission tomography (PET)/computed tomography (CT) of the prostate to guide robotic surgery[3]. The 3D images are colour coded, highlighting tumour areas, and can be displayed on the robotic surgical system screen to guide several aspects of surgery, such as changes in plane of resection. RARP can also be improved with the use of prostatic indocyanine green (ICG) injection for extended pelvic lymph node dissection (ePLND). An initial experience from the Koç University Hospital suggests that ICG-guided ePLND might increase identification and excision of metastatic lymph nodes during RARP[4].

Urological robotic surgery is not limited to RARP only. Radical cystectomy can also be performed with robotic assistance. One technique, developed by Dr. Mevlana Derya Balbay, is endopelvic fascia sparing during robotic-assisted radical cystectomy with the reconstruction of an intracorporeal neobladder with anti-reflux properties[5]. In a recent report, all 10 patients who underwent this procedure achieved full continence during daytime and 3 required pad use for mild incontinence during nighttime.

Robotic retroperitoneal lymph node dissection (RPLND) is a less invasive approach in select cases of non-seminomatous germ cell tumours[6]. The procedure is performed with 4 to 5 ports of 1 cm in diameter, avoiding the need for large incisions in the abdomen. From the perspective of the surgeon, robotic RPLND allows better visualization of the surgical area and sparing of abdominal nerves.

Robotic-assisted renal transplantation offers an example of a non-oncological procedure that has been further developed with advances in new robotic systems. The 3D magnified vision combined with wrist instruments facilitates the performance of anastomosis, especially related to the vessels. Results from the initial experience at Koç University Hospital have not yet been published.

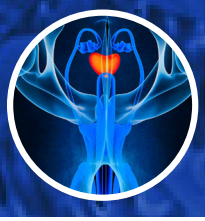
Robotic-assisted adrenalectomy is an effective approach for the treatment of adrenal diseases that is gaining popularity[7]. Dr. Canda presented the example of a 7-cm cystic adrenal mass that was easily resected through robotic assistance. Generally, robotic-assisted surgery demonstrates lower performance for the resection of masses that are 4 cm or larger.

Patients with benign prostatic hyperplasia (BPH) presenting with enlarged prostates (≥ 150 g) are generally managed by robotic-assisted simple prostatectomy at Koç University Hospital. This is a viable minimally invasive approach and is considered as a simple procedure by experienced robotic surgeons[8]. Robotics has also led to further developments in pyeloplasty (both adult and pediatric), as well as the management of complications from robotic-assisted surgery at Koç University Hospital.

During the Q&A, Dr. Canda noted that Koç University Hospital currently possesses 2 Da Vinci Xi systems, while the RMK AIMES Surgical Training Center associated with the hospital has a Da Vinci X system.

Next, Dr. Tarik Esen (Türkiye) discussed the use of intraoperative frozen section during radical prostatectomy. Nerve-sparing radical prostatectomy presents a delicate balance between reducing the positive surgical margin (PSM) rates and improving oncological outcomes while achieving better functional outcomes and quality of life (QoL) for patients, such as improved urinary continence and erectile function. The European Association of Urology (EAU) guidelines currently recommend offering nerve-sparing surgery only to patients with risk of extracapsular extension (ECE) on that side (strong recommendation). Conversely, surgeons should consider avoiding nerve-sparing surgery when there is a risk of ipsilateral ECE (weak recommendation)[9].

The ability to detect ECE may impact the feasibility of performing a nerve-sparing surgery. Conventional imaging with transrectal ultrasound and CT has limited accuracy in detecting ECE[10]. For mpMRI, a meta-analysis of 75 studies has suggested an overall sensitivity of 57% and specificity of 91% for ECE. The accuracy increases at high field strength (3 Tesla)[11]. mpMRI also has low sensitivity for focal or microscopic



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ECE[12]. Alternatively, prostate-specific membrane antigen (PSMA) PET/CT has contradictory outcomes across different studies. In a study of 21 patients, staging with PSMA PET/CT prior to radical prostatectomy performed with sensitivity of 90% and specificity of 90.9% for ECE[13]. Another study of 49 patients comparing PSMA PET/CT vs. mpMRI found similar interreader agreement for sensitivity (mean: 58% vs. 61%, respectively) and specificity (mean: 81% vs. 81%, respectively) for ECE prediction[14]. Even when combined with mpMRI, PSMA PET appears to have limited performance in detecting ECE[15].

Given the limitations of imaging, intraoperative frozen section is still considered the gold standard for pathological assessment of surgical margins[16]. The idea to perform frozen section during radical prostatectomy dates back to the year 1999, when the technique was shown to improve nerve sparing without compromising oncological control[17]. Despite its advantages, the sensitivity of frozen section during radical prostatectomy (42%) is not sufficiently high to be performed routinely[18]. Therefore, the use of frozen section analysis has been limited only to areas of high suspicion for PSM evaluation.

The neurovascular structure-adjacent frozen-section examination (NeuroSAFE) technique was first described in a consecutive series of 11 069 radical prostatectomies at the Martini Klinik (Hamburg, Germany), of which 49% were conducted with NeuroSAFE[19]. Compared to non-NeuroSAFE procedures, NeuroSAFE radical prostatectomies improved the frequency of nerve-sparing (97% vs. 81%) and reduced the PSM rate (15% vs. 22%) in all PCa stages. NeuroSAFE also performed with a high accuracy of 97%[19]. NeuroSAFE has also been associated with higher safe-R scores, a composite measure of margin status and laterality of nerve-sparing used to assess and report oncological outcomes of radical prostatectomy[20].

More recently, the efficacy and safety of NeuroSAFE during RARP is under evaluation in the NeuroSAFE PROOF randomized controlled trial (NCT03317990). In the feasibility study, NeuroSAFE RARP performed with sensitivity of 100% and specificity of 92.7% on the basis of neurovascular bundle (NVB). Compared to standard RARP, NeuroSAFE RARP required longer operation time and incurred an additional cost of £1000 per surgery[21]. Additional studies have suggested that NeuroSAFE improves nerve-sparing, both unilaterally and bilaterally, and reduces PSM rates[22,23]. NeuroSAFE has also been associated with improved biochemical recurrence (BCR)-free survival[22] and urinary continence after radical prostatectomy[24].

Despite these advantages, there are several concerns regarding the limitations of NeuroSAFE. These include the assessment of PSM on the apical, basal, or anterolateral side; the added cost with NeuroSAFE as well as the need for additional pathology workup; the longer operation times required; and the questionable oncological benefits observed in trials and through clinical experience[25].

In a study of 208 patients led by Dr. Esen, NeuroSAFE RARP resulted in lower PSM rates compared to RARP alone, both for pT2 (7.5% vs. 15.6%) and pT3 (21.6% vs. 55.0%) disease[26]. NeuroSAFE RARP also resulted in higher bilateral NVB preservation compared to RARP alone (81.1% vs. 66.3%), but BCR rates were comparable with both approaches (2.2% vs. 2.5). The best differential benefit with NeuroSAFE RARP was observed in D'Amico high-risk patients with ECE identified on mpMRI or PSMA PET[26].

Novel approaches are also under investigation and show promise for improving intraoperative assessment of radical prostatectomy specimens. These include ex vivo digital microimaging with fluorescence confocal microscopy[27], antibody-based dual probe difference specimen imaging[28], and PSMA PET/CT of resected specimens[29].

Presently, the data on intraoperative frozen section during radical prostatectomy are limited. The current evidence suggests that the NeuroSAFE technique might reduce PSM rates and increase NVB rates, especially in high-risk patients. Further research, including prospective randomized clinical trials, is needed to evaluate the impact of intraoperative frozen section on oncological and functional outcomes.

During a Q&A, Dr. Esen commented on the experience with NeuroSAFE at his institution. Presently, he and his team are able to perform one NeuroSAFE radical prostatectomy procedure per day. They work

with a team of 3 uro-pathologists, who were amenable to the introduction of the technique in the hospital. One of the limitations of NeuroSAFE is that if PSM are detected on initial intraoperative frozen section, additional resection and pathological assessment often identifies no tumour tissue in resected specimens. This emphasizes the importance of collaboration between surgeons and pathologists and highlights that a complete resection of the NVB may not be required, as they are most times tumour-free upon intraoperative frozen section.

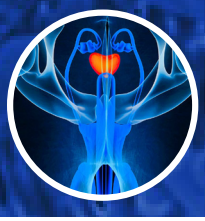
In the subsequent presentation, Dr. Kirsten L. Greene (United States) discussed strategies for improving patient outcomes and QoL after prostatectomy. Incontinence remains one of the most feared side effects of radical prostatectomy and is profoundly affected by the surgical technique. Back in the 1970s, the anatomical structures underlying urinary continence, such as the dorsal venous complex, the urinary sphincter, and the course of the cavernous nerve, were not fully described and their respective functions not well understood. This limited knowledge of continence anatomy and function had an impact on the surgical technique at the time. Radical prostatectomy was associated with high blood loss, as well as severe incontinence and erectile dysfunction. Given the poor outcomes of surgery, radiotherapy was the preferred treatment approach for PCa. It was only after the description of the dorsal venous complex by Drs. Patrick Walsh and William Reiner in 1979[30] that the surgical technique and outcomes of radical prostatectomy started to improve.

Despite several advances in technique and robotic-assisted surgery in the last 50 years, incontinence after surgery remains a main concern of PCa treatment. Data from the CEASAR trial suggest that compared to active surveillance, androgen deprivation therapy (ADT), and radiotherapy, patients who undergo radical prostatectomy have clinically meaningful worse continence 5 years after treatment[31]. These results are recapitulated through patient-reported outcomes from the ProtecT trial[32]. Within 6 years of follow-up, patients treated with radical prostatectomy had poorer outcomes for urinary function, including higher pad use daily, worse score on International Consultation on Incontinence Questionnaire (ICIQ), and greater impact on QoL[32].

There are some basic surgical principles for improving continence outcomes after radical prostatectomy. Recreating anterior urethral support with a periurethral suspension stitch during RARP has been demonstrated to improve continence from 35% to 61% 3 months after surgery[33]. Bladder neck preservation (i.e., bladder neck and urethra are the same diameter) and reconstruction have shown high 3-month continence rates, with better 1-week continence achieved with the preservation approach[34]. Continence recovery 1 week after surgery has also been demonstrated to improve with the urethral-fixation technique during open surgery[35].

Retzius-sparing prostatectomy has been performed over the last 10 years and involves preservation of structures anterior to the prostate by performing the surgery through a posterior opening. A recent meta-analysis revealed that 1-week and 3-month continence rates are significantly improved with Retzius-sparing RARP compared to the standard anterior approach[36]. Interestingly, continence rates are similar with both techniques at 6 months. Similar results have also been observed in a randomized controlled trial[37]. Despite the potential advantages, Retzius sparing may result in higher PSM rates[36]. This can be mitigated as the surgeon becomes more experienced with the technique.

Good candidates for the Retzius-sparing approach may include patients undergoing surgery in combination with radiation; those who are ≥ 70 years of age, in whom the return of continence is slower; and patients in whom extensive extraperitoneal surgery or mesh should be avoided. Some of the most challenging aspects of the Retzius-sparing approach are identifying the lateral area next to the prostate where the prostate curvature becomes visible, and finding the plane between the prostate and bladder neck. Anterior dissection is where PSM are usually identified during the learning curve. Dr. Greene also pointed out that Retzius sparing results in a small bladder neck, which may explain the improved continence rates observed with this approach.



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The hood technique is an anterior approach that preserves periurethral tissue in the space of Retzius and later allows for reconstruction of the detrusor apron when the surgeon sews this tissue to the bladder. Results of a prospective clinical study with the hood technique compared to retrospective studies using the Retzius-sparing approach revealed similar continence benefit but lower PSM rates[38]. Like the Retzius-sparing approach, the hood technique also involves a learning curve. This technique requires a different dissection approach and does not allow control over the dorsal venous complex, which may result in more bleeding obscuring the field of view. Increased anterior PSM rate may also occur as the surgeon approaches the anterior apex of the prostate.

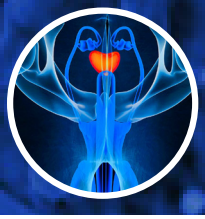
Reconstruction of the extraperitoneal space may provide an alternative to both the Retzius-sparing and hood techniques. Anterior bladder suspension to the anterior abdominal wall is a simple, easy, and quick technique that may optimize continence outcomes after surgery. This may occur because the anatomical position of the bladder neck relative to the pubic symphysis may be a predictor of early urinary continence recovery[39,40]. The degree of descent of the bladder neck may also play a role in postsurgical continence. In a study at Dr. Greene's centre, lower degree of bladder descent and improved continence were seen to correlate significantly with Retzius-sparing and anterior suspension techniques compared to standard radical prostatectomy (data unpublished). While preliminary, these results suggest that improved outcomes may be associated with preservation of bladder neck tension as well as reconstruction of bladder neck support with anterior bladder suspension.

Changes in the pelvic anatomy, such as urethral length, position of the bladder neck and membranous urethra, and urethral closing pressure caused by radical prostatectomy, may have an impact on continence[41]. In fact, dynamic MRI findings have demonstrated that resting urethral closing pressure is higher and membranous urethral length is longer after Retzius-sparing radical prostatectomy compared to the anterior approach, which may contribute to improved continence[42]. Another study has demonstrated that continent patients postprostatectomy had significantly more movement of the membranous urethra and the puborectalis muscle compared to incontinent patients postprostatectomy[43]. These studies suggest that the location of the bladder neck may interact with the pelvic muscles to impair continence. Understanding the interaction between pelvic muscles may help to determine approaches to recover continence. It may also become possible to identify patients preoperatively who are at higher risk of incontinence after radical prostatectomy and may benefit from early or preoperative pelvic floor physical therapy or even another management approach, such as radiotherapy.

Dr. Greene outlined the different surgical considerations that may optimize continence outcomes postprostatectomy. These include maintaining or recreating urethral support; preserving or reconstructing the bladder neck; preserving the vasculature to the sphincter; and preserving or reconstructing the detrusor apron. Resuspending the bladder may have a similar impact on continence as using the Retzius-sparing and the hood approaches. In addition, maintaining the angles for urethral closing pressure and promoting pelvic floor physical therapy and prehabilitation are also important.

Over the years, increased experience with the Retzius-sparing approach has led to a better understanding of the underlying anatomy and function of continence. It is now understood that preservation of pelvic support should be one of the main priorities during surgery, as all structures in the pelvis play an important role in continence. The focus with new techniques should be on preservation of the anatomy and no longer on radical resection. Surgeons should be guided to have a better understanding of the pelvic anatomy, preserve it as much as possible during surgery, and work alongside multidisciplinary teams to rehabilitate patients postsurgically.

In a Q&A, Dr. Greene explained that it is possible to perform a wide resection with the Retzius-sparing approach even in high-risk PCa to ensure negative surgical margins. She also noted that randomized controlled trials for surgical technique, including bladder neck preservation, are few. Similarly, the role of urethral length in postprostatectomy continence has primarily been evaluated through retrospective



cohorts and case series. Dr. Greene also commented that not only the length of the membranous urethra but also indentation of the sphincter closure at rest may have a role in predicting continence outcomes after surgery. Interestingly, the degree of nerve sparing with Retzius-sparing/anterior suspension does not appear to impact continence compared to standard anterior prostatectomy. Based on her experience, Dr. Greene believes that the location and suspension of the bladder neck play a more important role in continence outcomes than preservation of the cavernous nerves.

Next, Dr. Derya Tilki discussed the Stockholm3 test for detection of localized PCa. The Stockholm3 test is a blood-based test for risk stratification before MRI. It combines plasma concentration of different proteins, including total and free prostate-specific antigen (PSA); genotyping information of 101 single nucleotide polymorphisms (SNP); and clinical patient data, such as age, family history of PCa, and information on previous biopsies. A proprietary algorithm generates a risk score for clinically significant PCa: low and normal risk (≤ 10%) and increased risk (≥ 11%). Currently, Stockholm3 has been validated in primary detection and for secondary testing upon elevated PSA levels. Studies are ongoing to validate its utility in active surveillance.

Stockholm3 has been extensively validated when compared to other blood-based and urine-based biomarkers. Studies have evaluated the role of Stockholm3 prospectively in more than 75 000 patients combined[44–48]. One study of 532 patients tested the utility of Stockholm3 plus mpMRI as a reflex test for men with elevated risk of PCa based on PSA. Compared to PSA plus systematic biopsies, Stockholm3 plus mpMRI reduced the number of biopsies by 38% and the number of clinically nonsignificant PCa by 42%, and increased the sensitivity for clinically significant PCa by 10%. When compared to PSA plus mpMRI, Stockholm3 plus mpMRI reduced the number of unnecessary biopsies by 54% and performed with a relative sensitivity of 92% for clinically significant PCa[45].

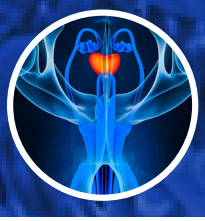
A population-based screening study in Sweden enrolled 12 750 men, of whom 2293 were identified as elevated risk on PSA testing (≥ 3 ng/mL) or Stockholm3 score (≥ 11) and were randomized to receive either systematic prostate biopsies or MRI-targeted and systematic biopsy in MRI-positive patients. Compared to PSA plus MRI, Stockholm3 plus MRI provided identical sensitivity in detecting clinically significant PCa and led to a reduction of MRI by 36%, as well as reduction of unnecessary biopsies by 18%[48].

The clinical utility of Stockholm3 in primary care was evaluated in an observational study of 4748 patients in a centre in Norway. General practitioners were asked to replace PSA testing with Stockholm3 as a standard procedure for PCa diagnosis. The implementation of Stockholm3 led to an increase of 89% in detection of clinically significant PCa on biopsy. Additionally, a decrease of 26% in detection of clinically nonsignificant PCa on biopsy was observed. Altogether, these led to a 23% to 28% reduction of direct healthcare costs[46].

A prospective multicentre validation of Stockholm3 was recently published[49]. The study was conducted in 2 centres in Switzerland and 1 centre in Germany, and included 343 patients who were referred for biopsy on the basis of an elevated PSA and/or abnormal digital rectal examination (DRE) followed by mpMRI. Of those, 336 patients underwent mpMRI and 89% had Prostate Imaging Reporting and Data System (PI-RADS) ≥ 3. All patients underwent systematic, targeted, and perilesional biopsies. The study showed that if the Stockholm3 cut-off of 11% had been used, 21% of prostate biopsies could have been omitted. While 8% of clinically significant PCa could have been missed with this approach, only 2.8% would be grade group > 2. In this study, the area under the curve (AUC) was 0.77 for Stockolm3 vs. 0.66 for PSA.

A retrospective validation of Stockholm3 was conducted with data from 405 patients from 2014 to 2017 at the Martini Klinik. Patients were selected for biopsy based on PSA or DRE and underwent systematic (10 to 12 core) biopsy. Compared to PSA as biopsy criterion, Stockholm3 at a score cut-off of 15 could have reduced unnecessary biopsies by 52% while detecting 92% of clinically significant cases. In this study, Stockholm3 performed with an AUC of 0.80 vs. 0.63 for PSA[50].

Stockholm3 is under validation in North America in the prospective, observational SEPTA study



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(NCT04583072). This study includes a multi-ethnic cohort of 2152 patients. Recruitment closed as of July 2023 and results are expected within the next year.

During a Q&A, Dr. Tilki noted that insurances policies in Europe do not cover biomarker testing, unlike in the United States. In Germany, the cost of Stockholm3 is €350. At the Martini Klinik, an MRI of the prostate costs €850. The concept of Stockholm3 is to reduce the number of unnecessary MRIs and, consequently, the number of unnecessary biopsies related to false-positive MRIs. Dr. Tilki explained that currently her group in Germany, in collaboration with the Koç University Hospital, is assessing the performance of Stockholm3. She emphasized that the test is used before the diagnosis of PCa and may have a role in active surveillance of low-risk disease, as seen in the studies discussed during her presentation.

The next presentation was by Dr. Himisha Beltran (United States), who discussed novel biomarkers in metastatic PCa. Biomarkers play an important role in all stages of the PCa disease continuum. Understanding how to integrate clinical and molecular features will likely improve risk stratification and treatment selection. Several prognostic biomarkers have been identified in metastatic PCa. Clinical prognostic biomarkers in this setting include the presence of liver metastases as well as the volume of disease. For metastatic castration-resistant PCa (mCRPC), circulating tumour cell (CTC) count and circulating tumour DNA (ctDNA) fraction can be used as a surrogate for tumour burden. Genomic prognostic biomarkers include losses in tumour suppressor genes (*RB1, TP53, PTEN*) as well as germline mutations (e.g., *BRCA2*). On PET imaging, fluorodeoxyglucose (FDG) volume may also have a role in mCRPC prognosis. These prognostic biomarkers may guide treatment intensification to optimize outcomes in mCRPC.

Alternatively, predictive biomarkers in metastatic PCa may help to predict which subset of patients may benefit more from a certain treatment. For instance, patients with *BRCA1/2* alterations may show better response to PARP inhibitor therapy, whereas those with mismatch repair alterations or microsatellite instability (MSI)/high tumour mutational burden (TMB-H) may benefit more from immunotherapy. A positive PSMA PET can identify patients for treatment with lutetium-PSMA-617 (LuPSMA-617). These predictive biomarkers demonstrate the importance of testing in clinical practice to guide treatment decision-making and personalized care. Most guidelines now broadly endorse germline and somatic DNA testing for metastatic PCa, particularly because of the predictive implications of these biomarkers for treatment selection. Some studies are also investigating the utility of genomic biomarkers in earlier disease settings. One example is GUNS (NCT04812366), a genomic umbrella neoadjuvant study that is investigating treatment selection in patients with high-risk localized PCa based on genomic profiling.

Several PARP inhibitors have been approved in combination with an AR pathway inhibitor (ARPI) as first-line treatment for mCRPC or as monotherapy post-ARPI therapy. Most of these treatments have been approved in biomarker-selected patients. However, each trial that led to the approval of PARP inhibitor plus ARPI combinations[51–53] or PARP inhibitor monotherapy[54,55] in mCRPC used a different approach to assess genomic alterations. Therefore, it is challenging to make broad inferences across trials. Dr. Beltran noted that *BRCA1/2* alterations are consistently seen across different approaches, but more information is needed to determine which genes should be tested and which alterations may be predictive of treatment response.

Additionally, trials so far have offered little guidance for testing in clinical practice, such as which tissue should be tested and the timing of testing. Many of these trials used primary tumour in patients with mCRPC, usually from archival tissue. This is a non-invasive approach that allows early detection of DNA repair alterations. However, testing may be limited by the age and quality of the tissue. Metastatic tumour biopsies are invasive but allow capturing of acquired alterations and phenotypic changes through testing. On the other hand, liquid biopsies, especially ctDNA testing, are an emerging noninvasive option to test for DNA repair alterations linked to PARP inhibitor response as well as MSI alterations. Germline testing from blood or saliva is indicated for all patients with mCRPC and cannot be replaced with somatic tumour testing. Germline

testing influences not only patient treatment, but also has implications for the patient's family.

Several studies have demonstrated concordance of > 80% in DNA repair gene mutations, such as *BRCA* mutations, between metastatic biopsy and ctDNA [56–59]. In a study evaluating the Foundation Medicine ctDNA testing in 3334 patients with mCRPC, 94% had detectable ctDNA. Of those, 72 of 837 patients had *BRCA1/2* mutations detected in tumour tissue and 67 were also identified in ctDNA[60]. Of note, this study did not report copy number alterations such as *BRCA2* deletions, which are associated with increased response to PARP inhibitor treatment.

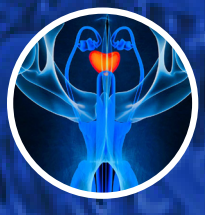
Clonal hematopoiesis of indeterminate potential (CHIP) refers to acquired mutations in white blood cells that are sometimes reported in ctDNA studies. These mutations, which are found in normal white blood cells, increase with age. It is important to recognize that clonal hematopoiesis can involve genes such as *ATM* and *TP53*, which may confound results of ctDNA testing and result in a false positive test. For instance, a case series of 69 men with advanced PCa found that 7 (10%) had CHIP variants in genes, most frequently in *ATM*, used for PARP inhibitor treatment indications approved by the US Food and Drug Administration (FDA)[61].

Currently, a positive PSMA PET is used to select patients with mCRPC for treatment with LuPSMA-617. Some patients with mCRPC do not express PSMA, highlighting the importance of refining PET biomarkers to improve patient selection. Patient selection for PSMA-directed therapy likely depends not only on PSMA expression to allow PET imaging, but also on other biomarkers of response (tumour and drug features, as well as drug mechanism) and mechanisms of resistance that can guide next therapy.

In TheraP, a randomized phase 2 trial investigating LuPSMA-617 vs. cabazitaxel in mCRPC post ARPI and docetaxel, patients were selected based on PSMA and FDG-PET. Patients with discordant PET scans (e.g., PSMA high/FDG low) were excluded. The odds of PSA response to LuPSMA-617 compared to cabazitaxel were significantly higher for patients with standardized uptake value (SUV) mean ≥ 10 compared with those with SUVmean < 10 (odds ratio [OR] 12.19 [95% confidence interval [CI] 3.42 to 58.76] vs. 2.22 [1.11 to 4.51][62]. Similar results have also been observed in the VISION trial[63]. These results suggest that quantification of PSMA uptake on PET imaging may be useful to help better select patients for treatment, although these parameters are not routinely reported by nuclear medicine. Also in TheraP, patients who were PSMA positive and high-volume disease on FDG-PET (≥ 200 mL) had the worst prognosis for radiographic progression-free survival (rPFS)[62].

A recent study led by Dr. Beltran demonstrated that metastases in the liver have lower and more heterogenous PSMA expression, which might explain the inferior outcomes of patients with liver metastases treated with LuPSMA-617[64]. PSMA expression is dynamic in individual patients. For those undergoing ARPI therapy, PSMA expression may increase with acute AR inhibition, but rapidly decrease with treatment response. PSMA expression may also increase in AR-driven mCRPC, but may be lost in patients with late-stage mCRPC. However, there are currently no clinical studies that serially measure PSMA dynamics. In preclinical models for metastatic hormone-sensitive PCa (mHSPC), treatment with enzalutamide was shown to decrease PSMA expression[65]. In the ENZA-p trial (NCT04419402), which is evaluating enzalutamide plus LuPSMA-617 vs. enzalutamide in mCRPC, serial imaging and liquid biopsies are being conducted. These may provide a prospective assessment of PSMA dynamics in mCRPC in association with tumour features.

PSMA expression is lost in 15% to 20% of patients with mCRPC[66,67]. The mechanisms underlying loss of PSMA expression are not well understood. They may include loss of differentiation, loss of AR, epigenetic changes, or other mechanisms. Some PCa may change phenotype and transition from the typical adenocarcinoma to small cell neuroendocrine PCa[68], leading to loss of PSMA expression. Preclinical research has demonstrated that AR indirectly regulates PSMA expression: AR-positive PCa expresses PSMA and AR-negative PCa does not express PSMA[65]. This loss of PSMA expression is also seen in AR-negative small cell neuroendocrine PCa[69,70]. Glucose transporters are upregulated in small cell neuroendocrine PCa and



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AR-negative castration-resistant PCa (CRPC)[71], which may explain the discordant PSMA/FDG-PET findings observed in clinical trials and be associated with poor prognosis[72].

There are many other potential biomarkers of response to PSMA-directed therapy. Several questions related to genomics and other features are under investigation in the context of clinical trials with respect to radiation resistance and other PSMA-directed therapies.

Studies are needed to provide a better understanding of mechanisms of resistance to LuPSMA-617. Hypothetically, if the tumour is still PSMA positive, alternative PSMA-directed therapies could be used, such as actinium-225. If the tumour is PSMA negative, alternative targets may be evaluated to guide treatment. In a retrospective study, it was observed that a subset of patients who progressed after LuPSMA-617 still had PSMA-positive tumours and responded to actinium-PSMA-617 (AcPSMA-617)[73].

For patients who are PSMA negative or those who progress after treatment with LuPSMA-617, several cell surface targets (e.g., prostate stem cell antigen [PSCA], FAPI, STEAP1, KLK2, CEACAM5, DLL3) and imaging agents are currently under investigation.

A number of biomarker tools exist in metastatic PCa. Predictive genomic biomarkers have revolutionized treatment decision-making for patients with mCRPC; therefore, testing for predictive biomarkers is now considered standard of care (SOC). However, there are several open questions regarding access to testing, the best test to use, the level of evidence, cost effectiveness, and how currently available biomarkers can be refined to optimize treatment. Understanding changes in biomarker dynamics is also important and will help to guide the evolving management of metastatic PCa.

During a Q&A, Dr. Beltran explained that patients with biallelic alterations in *BRCA* genes are more likely to respond to PARP inhibitor treatment. However, no trials have used this criterion for patient selection and most commercial tests do not report biallelic loss. Based on clinical trials, any pathogenic mutations in *BRCA* genes can be used as predictive biomarkers for treatment with PARP inhibitors. On the other hand, the current evidence suggests that *ATM* alterations do not confer good response to PARP inhibitors. Other agents are in development to specifically target *ATM* alterations. Dr. Beltran also noted that PSMA PET has not yet been evaluated to predict response to other systemic therapies aside from PSMA radioligand therapy. Despite the limited resources available, she sees great value in using serial PSMA PET for monitoring response to treatment.

Subsequently, there was a debate on patient selection for PARP inhibitor therapy, moderated by Dr. Tilki. Dr. Sevil Bavbek (Türkiye) defended why this treatment approach should be offered to all patients with PCa, whereas Dr. Yüksel Ürün (Türkiye) explained why PARP inhibitors should be reserved for biomarker-positive patients.

In PCa, approximately 10% of primary tumours and 25% of metastases have an alteration in at least 1 gene involved in DNA damage repair (DDR)[74,75]. Homologous recombination repair (HRR) is one of the most important processes to maintain genome stability and prevent oncogenesis by repairing DNA double-strand breaks. Among several genes, *BRCA1/2* encode proteins that are essential for the HRR pathway. HRR-deficient cells are highly sensitive to PARP inhibition. PARP inhibitors prevent PARP1 and PARP2 from repairing DNA single-strand breaks. These are converted into double-strand breaks that HRR-deficient cells cannot repair effectively, leading to DNA damage, cell cycle arrest, and cell death. This mechanism is called synthetic lethality, which is more pronounced in cells with *BRCA1/2* mutations[76].

Clinical trials investigating PARP inhibitor monotherapy have shown clinical efficacy in *BRCA*-mutated mCRPC. Other HRR genes, however, have shown conflicting results[54,55,77,78]. There are different aspects to PARP inhibition. Aside from mutations, other processes, such as epigenetic alterations and changes in expression of microRNAs or transcription factors, could in principle impair HRR and confer sensitivity to PARP inhibition[79].

PARP inhibitor sensitization can potentially be achieved by combining a PARP inhibitor with another

treatment, such as ARPI, chemotherapy, or radiotherapy. Biologically, PARP1 interacts with AR and AR signalling. PARP1 has also been shown to promote ligand-independent AR activation, suggesting a role in treatment resistance and disease progression to CRPC[80]. In preclinical models, enzalutamide followed by enzalutamide plus olaparib promoted DNA damage–induced cell death and inhibited clonal proliferation of PCa cells in culture, as well as suppressed the growth of PCa xenografts in mice[81].

Two phase 3 clinical trials investigating the combination of a PARP inhibitor with an ARPI as first-line treatment in patients with mCRPC have recently been reported. PROpel examined olaparib plus abiraterone vs. placebo plus abiraterone. Patients were enrolled irrespective of HRR mutation (HRRm) status and subsequently assigned to subgroups based on tumour tissue and/or ctDNA testing[82]. Olaparib plus abiraterone significantly improved median rPFS in the intent-to-treat (ITT) population, both by investigator assessment and by central review. Prolonged median rPFS benefit was observed across subgroups, including HRRm (hazard ratio [HR] = 0.50; 95% CI, 0.34 to 0.73) and non-HRRm (HR = 0.72; 95% CI, 0.60 to 0.97)[82].

In TALAPRO-2, talazoparib plus enzalutamide was compared to placebo plus enzalutamide as first-line treatment for mCRPC[52]. Similar to PROpel, this trial enrolled all comers, irrespective of HRR alterations, in cohort 1. HRRm status was prospectively analyzed using tumour tissue and ctDNA. Talazoparib plus enzalutamide significantly improved rPFS in the ITT population. This benefit was also observed both in HRRm (HR = 0.46; 95% CI, 0.30 to 0.70) and non-HRRm patients or those of unknown status (HR = 0.70; 95% CI, 0.54 to 0.89)[52].

A number of clinical trials are under way to examine the role of PARP inhibitor monotherapy in earlier PCa settings or in combination with other treatments in advanced PCa. Like PROpel and TALAPRO-2, none of these trials use HRRm status as a criterion for enrollment.

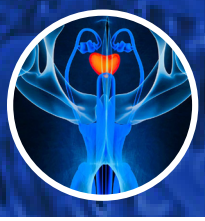
While initial data on PARP inhibitor monotherapy in mCRPC showed activity exclusively in HRR-deficient patients, Dr. Bavbek noted that there is efficacy in all patients despite HRRm status with a PARP inhibitor combined with an ARPI. Therefore, PARP inhibitor combinations should not be limited to HRR-deficient patients before the results of ongoing clinical trials irrespective of HRRm status become available.

Next, Dr. Ürün took the podium to explain why PARP inhibitors should be reserved for HRR-deficient patients. There are several studies exploring the synergy between PARP inhibitor and ARPI therapy to slow tumour growth and enhance treatment efficacy. In first-line mCRPC, PROpel (olaparib plus abiraterone)[82], MAGNITUDE (niraparib plus abiraterone)[53], and TALAPRO-2 (talazoparib plus enzalutamide)[52] have recently reported results. The phase 3 CASPAR (rucaparib plus enzalutamide) is ongoing.

As previously discussed, PROpel met its primary endpoint of improved median rPFS with the combination of olaparib and abiraterone. While subgroup analysis demonstrated consistent rPFS improvement, the magnitude of benefit differed across subgroups. Overall survival (OS) was not significant with olaparib plus abiraterone in the ITT population. However, exploratory subgroup analysis suggested a potential OS benefit in patients with HRRm and, specifically, *BRCA* mutations[82].

The initial trial design of MAGNITUDE included biomarker testing to allocate patients into 2 cohorts, one HRRm positive and the other HRRm negative, prior to randomization to either niraparib plus abiraterone or placebo plus abiraterone. The HRRm-negative cohort closed early due to futility[53]. In the HRRm-positive cohort, longer rPFS was observed with niraparib plus abiraterone vs. placebo plus abiraterone (16.5 vs. 13.7 months; HR = 0.73; 95% CI, 0.56 to 0.96; $P = 0.022$)[53].

In TALAPRO-2, 2 cohorts were included in the trial design. Cohort 1 (N = 805) included all comers, who were prospectively assessed for HRR alterations prior to randomization. Cohort 2 (N = 399) included only HRRm patients[83]. In this cohort, treatment with talazoparib plus enzalutamide resulted in a 55% risk reduction of progression or death compared to placebo plus enzalutamide (HR = 0.45; 95% CI, 0.33 to 0.61; $P < 0.0001$)[84]. Looking at gene subgroups, patients with *BRCA* alterations had the largest rPFS benefit with talazoparib plus enzalutamide[84].



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Overall, all phase 3 trials reported to date show varying trends regarding efficacy of a PARP inhibitor plus ARPI combination as first-line treatment of mCRPC in the ITT population. However, results appear consistent across trials for the treatment combination only in patients with *BRCA* alterations. Moving forward towards a precision medicine approach, it is important to optimize outcomes by tailoring treatment to patients who are more likely to benefit. Patients who are biomarker positive appear more susceptible to the combined effects of a PARP inhibitor with an ARPI, and clinical trials demonstrated better response in patients with *BRCA1/2* mutations. While it is important to maximize efficacy, it is also important to avoid unnecessary treatment for patients who are unlikely to respond. Lastly, clinicians should also be mindful of adequate patient selection for cost-effectiveness of treatment and avoiding the development of early drug resistance in non-responsive patients.

During a Q&A, Dr. Ürün explained that routine genomic testing is generally advised for patients with high-risk localized PCa, as well as those with metastatic PCa. In Türkiye, ARPIs are reimbursed and most patients receive either abiraterone or enzalutamide to treat mHSPC, which impacts subsequent treatment of mCRPC. PARP inhibitors, even as monotherapy, are not reimbursed and cannot be prescribed to all patients. Because of these constraints, Dr. Ürün mostly prescribes PARP inhibitor monotherapy to patients with *BRCA1/2* mutations. However, Dr. Ürün actively participates in clinical trials, holding the conviction that optimal management for cancer patients is best achieved within the framework of such trials. He advocates strongly for the increased encouragement of patient participation in clinical trials.

Dr. Bavbek addressed the differences in the results observed in the HRR-negative cohort in MAGNITUDE, which closed early due to futility, and in the ITT population of PROpel, which did not select for HRR alterations and demonstrated benefit with the treatment combination. She noted that there may be differences in the technology and procedure used for genomic testing as well as the interpretation of those results in each trial that could explain such differences in the results. Better expertise in genomic testing and analysis is necessary to assess these data. She emphasized that the primary endpoint of improved rPFS was met in both PROpel and TALAPRO-2, which enrolled all comers. OS is not as relevant to interpret the implications of these trials because crossover was allowed between treatment arms, which compromises the assessment of OS. While PARP inhibitor combinations are not yet approved in Türkiye, Dr. Bavbek suggested that they should be used upfront for all patients with mCRPC based on the results of PROpel and TALAPRO-2. Because the optimal sequencing of treatment for mCRPC is controversial, Dr. Bavbek added that clinicians should aim to select the best first-line therapy available based on the current clinical data, despite the cost of treatment with PARP inhibitors.

After the debate, Dr. Martin E. Gleave (Canada) presented on the next generation of ARPIs in PCa. ADT is the cornerstone of treatment for metastatic PCa as it targets the AR pathway, which is the main oncogenic driver of PCa. While significant responses have been seen with ADT in most patients, acquired treatment resistance leading to CRPC remains a challenge in the management of PCa.

Several mechanisms, which are heterogeneous and dependent on the genomic context, play a role in the development of castration resistance to ADT. Of these mechanisms, reactivation of AR activity is critical for clinical practice. It may occur through steroidogenesis, intertumoural production of androgens, or genomic alterations in the AR itself. This improved understanding of the molecular underpinnings of reactivation of AR activity has led to the development of novel ARPIs (abiraterone, apalutamide, and enzalutamide), which are now SOC for the treatment of mHSPC in combination with ADT[85–87].

Nevertheless, treatment-induced genomic alterations in AR are also drivers of castration resistance. Over time, continued treatment with ARPIs leads to several alterations in the AR, such as AR overexpression, altered coregulator expression, AR gain-of-function mutations, and emergence of AR splice variants, such as AR-V7, which is constitutively active[88]. Collectively, these genomic alterations drive resistance to ARPIs, underlying the need for alternative approaches to target the AR.

One potential approach is targeting the AR N-terminal domain (NTD). Anitens are small-molecule inhibitors that bind irreversibly to the AR NTD. EPI-7386 is an aniten that demonstrated promising pharmacokinetic properties in preclinical investigation[89]. However, results of a phase 1a clinical trial have revealed poor PSA response to EPI-7386[90]. Because PSA is a pharmacodynamic indicator of AR suppression, the lack of PSA response with EPI-7386 suggests that this compound is not adequately targeting the AR. This should be an early signal indicator of limited efficacy in clinical trials.

Another potential approach under investigation is targeting the AR DNA-binding domain (DBD). VPC-14449 is a novel AR DBD small-molecule inhibitor identified in silico at the University of British Columbia, Canada, that demonstrated promising activity both in vitro and in vivo[91,92]. VPC-14449 inhibits the AR but not other nuclear receptors, and antagonizes CRPC cells as well as enzalutamide-resistant PCa cell lines. While initial attempts failed to develop a pharmacokinetically stable molecule, VPC-14449 has now been licensed to a startup that is applying generative artificial intelligence (AI) to overcome the medical chemical challenges of drug engineering.

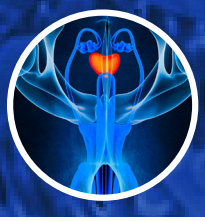
Proteolysis targeting chimera (PROTAC) degraders are a new class of drug agents. The investigational PROTAC ARV-110 (bavdegalutamide) is composed of an AR ligand attached to an E3 ligase recognition moiety. ARV-110 binds to the AR ligand-binding domain (LBD) and recruits E3 ligase, subsequently leading to AR ubiquitination and degradation by the proteasome. This compound has demonstrated encouraging activity in a phase 1/2 trial[93]. Interestingly, some AR LBD mutations appear to be more sensitive to ARV-110, which may allow for biomarkers to be used in patient selection for treatment. Additional AR PROTACs are under development in metastatic PCa, such as ARV-766 (NCT05067140).

ODM-208 is a novel, nonsteroidal selective inhibitor of CYP11A1, the first enzyme in steroid biosynthesis and upstream to CYP17A1, which is targeted by abiraterone. This allows for a more complete inhibition of steroid biosynthesis, including progesterone. Upregulation of progesterone after treatment with abiraterone may result in PCa progression in some patients because progesterone acts as an agonist of the AR T878A LBD mutant[94]. ODM-208 has demonstrated promising results in patients with mCRPC previously treated with abiraterone and/or enzalutamide, with 53% (24/45) of patients achieving a serum PSA reduction of at least 50% from the baseline concentration in a phase 2 trial[95]. Data also suggest that AR LBD mutants may be more sensitive to ODM-208. However, treatment with ODM-208 requires management for adrenal insufficiency[95].

In androgen-dependent PCa cells, the AR forms phase-separated condensates with transcriptional coactivators. These are recruited to specific genomic regions known as super-enhancers, which leads to high transcription levels of oncogenic genes[96]. Identifying compounds that interfere with the formation of phase-separated condensates may drive the development of novel agents to target the AR pathway that are independent of AR structure. One example is inobrodib (CCS1477), a novel small-molecule inhibitor of the p300/CBP conserved bromodomain that prevents the formation of phase-separate condensates and activation of super-enhancers. Despite promising results in preclinical studies, clinical trial experience suggests limited activity in mCRPC[97].

Another approach to indirectly target the AR structure is to target chaperones that help to stabilize and transport the AR from the cytoplasm to the nucleus. Heat shock protein 27 (HSP27) is a stress-activated chaperone important for AR stabilization and transportation. OGX-427 is an antisense inhibitor of HSP27 that disrupts AR signalling in mCRPC. In a phase 2 clinical trial, a PSA decline of ≥ 50% was observed in a higher proportion of patients receiving OGX-427 plus prednisone (47%) vs. prednisone alone (24%)[98].

Dr. Gleave noted that, while ADT in combination with novel ARPIs form the foundation of mHSPC treatment, improved understanding of mechanisms of treatment-acquired resistance has led to the identification of new targets and the development of new drugs. AR NTD and DBD inhibitors represent a potential new approach, but are currently stalled at early development due to challenges in chemistry, stoichiometry, and pharmacokinetics. AR-directed PROTACs and



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CYP11A1 inhibitors have shown encouraging activity in early clinical trials and are likely to continue to be investigated in phase 3 studies. Research on novel approaches to target the AR pathway is ongoing and its implications for clinical practice are highly anticipated.

Dr. Uğur Selek (Türkiye) provided an update on key clinical trials examining radiotherapy for PCa. Dr. Selek started by discussing outcomes of the phase 3 RTOG 0534-SPPORT trial, which randomized patients to salvage treatment with prostate bed radiotherapy (PBRT), PBRT plus short-term ADT, or PBRT plus pelvic lymph node radiotherapy (PLNRT) plus short-term ADT. The trial demonstrated that salvage PBRT and PLNRT combined with short-term ADT resulted in meaningful reduction in progression after prostatectomy in patients with PCa[99]. With advances in PSMA PET/CT imaging, lymph nodes that require treatment intensification can be identified, which may help to further improve outcomes with the treatment regimen identified in the trial.

The phase 3 PACE-A trial was the first to compare stereotactic body radiotherapy (SBRT) to laparoscopic or robotic radical prostatectomy in patients with low- or intermediate-risk localized PCa. MRI staging was performed prior to randomization. Co-primary endpoints were patient-reported outcomes of Expanded Prostate Cancer Index Composite (EPIC-26) questionnaire on the number of absorbent pads per day and the EPIC bowel subdomain score at 2 years. Compared to surgery, SBRT resulted in improved urinary continence, with fewer patients using any urinary pads at 2 years (4.5% vs. 46.8%, respectively)[100]. While SBRT caused more gastrointestinal (GI) side effects, most were minor at 2 years. Better sexual function was also achieved with SBRT vs. surgery (31.9% vs. 20.5%, respectively)[100].

PACE-B is another phase 3 trial that investigated the noninferiority of SBRT compared to conventional radiotherapy (CRT) for localized PCa. The primary endpoint was freedom from biochemical and/or clinical failure (BCF). With a median follow-up of 73.1 months, the 5-year BCF event-free rate was 95.8% with SBRT vs. 94.6% with CRT, demonstrating noninferiority[101]. At 5 years, GI and GU toxicities were similar with SBRT and CRT, despite more elevated GU toxicity with SBRT within the first 24 months of follow-up[101]. Given the noninferiority compared to CRT, as well as its convenience for patients and cost effectiveness to healthcare systems, SBRT should be discussed as a new SOC in low-risk and favourable intermediate–risk PCa.

The phase 3 CHHiP trial examined CRT vs. hypofractionated high-dose intensity-modulated radiotherapy for localized PCa. Patients were randomized to CRT (74 Gray [Gy] delivered in 37 fractions over 7.4 weeks) or one of two hypofractionated schedules (60 Gy in 20 fractions over 4 weeks or 57 Gy in 19 fractions over 3.8 weeks)[102]. The 10-year BCF-free rates were 76.0% with 74 Gy, 79.8% with 60 Gy, and 73.4% with 57 Gy, indicating noninferiority between the 74 Gy/37 fractions and the 60 Gy/20 fractions (HR_{60} = 0.84; 90% CI, 0.72 to 0.97)[103]. Time to distant metastases and OS were also similar across treatment arms. While QoL associated with more severe GI and GU bother was more prevalent in the 60 Gy and 57 Gy arms, the observed rates were overall low at 5 years[103].

PEACE-1 was an open-label phase 3 trial in mHSPC that compared SOC (ADT with or without docetaxel) to SOC plus radiotherapy, SOC plus abiraterone, or SOC plus radiotherapy and abiraterone[104]. The addition of radiotherapy to intensified systemic therapy with SOC plus abiraterone resulted in improved rPFS in the low-volume population. Furthermore, the addition of radiotherapy to SOC plus abiraterone reduced the rates of serious GU events in the overall population, irrespective of metastatic burden[105].

In the phase 2 EXTEND trial, the addition of metastasis-directed therapy (MDT) to intermittent hormone therapy was evaluated in oligometastatic PCa. Compared to hormone therapy alone, progression-free survival (PFS) was improved with the combination of MDT plus hormone therapy (HR = 0.25; 95% CI, 0.12 to 0.55; $P < 0.001$). Eugonadal PFS was also improved with the treatment combination[106], suggesting that when patients have normal testosterone levels, the time to progression is longer with the addition of MDT.

ARTO was a phase 2 trial that examined the benefit of adding SBRT to abiraterone and prednisone in patients with oligometastatic CRPC. The trial met its

primary endpoint, demonstrating an improved biochemical response rate, defined as a PSA decrease ≥ 50% from baseline, with SBRT plus abiraterone and prednisone. An improvement in PFS, but not OS, was also seen with the addition of SBRT to the treatment regimen[107].

Lastly, Dr. Selek presented the results of MIRAGE, a phase 3 trial that evaluated the potential advantages of MRI vs. CT guidance for reducing acute grade ≥ 2 GU toxicity. The trial demonstrated that MRI-guided SBRT reduced the incidence of acute grade ≥ 2 GU toxic effects and was associated with lower impact on patient-reported QoL[108].

During a Q&A, Dr. Selek discussed the high rate of urinary incontinence associated with surgery in PACE-A. He explained that the trial defined incontinence as the use of even one urinary pad per day, which differs from other trials. Dr. Selek noted that nocturia and urgency are the main acute toxicities observed during radiotherapy, which need to be kept in mind to guide treatment selection. If a patient has difficulty urinating before treatment, it may worsen after the patient starts radiotherapy. This may guide treatment selection between SBRT and hypofractionated radiotherapy. In the MIRAGE trial, the use of MRI guidance decreased the area treated with SBRT, which also reduced GU toxicity.

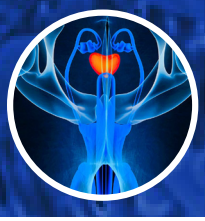
The last presentation was by Dr. Tian Zhang (United States), who provided an overview of CAR-T therapy in GU cancers. The adaptive immune system is key for providing a long-lasting response to foreign antigens. Early in childhood, T cells learn how to discriminate self from nonself proteins to activate an immune response. As cancer cells develop, they express neoantigens on their surface that can be recognized by T cells and trigger cytotoxic mechanisms with the goal of eradicating or inhibiting proliferation of cancer cells. The T-cell receptor complex (TCR) is critical for antigen recognition. It only recognizes antigens presented by the major histocompatibility complex (MHC) class I and requires a costimulatory signal through the cluster of differentiation (CD) 3 zeta chain. Compared to TCR, antibodies recognize any antigen, do not require antigen presentation through MHC, and show generally stronger interaction than the TCR-antigen-MHC interaction.

CAR-Ts are T cells that have been engineered to express specific T-cell receptors to recognize particular antigens on tumour cells, enabling T-cell specificity and cytotoxicity. There have been several generations of CAR-Ts. The first generation comprised only a CD3 zeta domain and was unable to prime resting T cells or drive sustained cytokine release, resulting in very limited tumour cell death even in vitro. The second generation included a second costimulatory domain (CD28 or 4-1BB), which was combined in the same T-cell receptor in the third-generation CAR-Ts. The fourth generation is called T cells redirected for universal cytokine-mediated killing (TRUCKs). These are enhanced with transgenes to secrete cytokines (e.g., interleukin 12 [IL-12]) or express additional costimulatory ligands that allow tumour infiltration[109].

The manufacturing and delivery of CAR-Ts is a complex and individualized process. Manufacturing requires the collection of autologous T cells from each patient. In vitro, the T cells are activated, expanded, and genetically engineered to express the chimeric antigen receptor (CAR). The CAR-T cells are then delivered to the patient via infusion[110].

The first engineered T cells were developed at the Whitehead Institute in 1992. During the 1990s, the first and the second generation of CAR-Ts were developed. In 2002, preclinical data from the Memorial Sloan Kettering Cancer Center (MSKCC) demonstrated activity of CD19-directed T cells against B-cell lymphoma cells[111]. Subsequently, CD19-directed CAR-Ts resulted in positive outcomes in clinical trials in B-cell acute lymphoblastic leukemia (ALL)[112], leading to the first CAR-T approval in the United States for B-cell ALL in 2017[109]. Many CAR-T therapies have since been approved by the FDA, including CD19-directed CAR-Ts for hematologic malignancies and B-cell maturation antigen (BCMA)-directed CAR-Ts for multiple myeloma.

Conversely, the development of CAR-T therapies in solid tumours has been challenging due to several constraints. Unlike hematologic malignancies, CAR-Ts



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require trafficking into solid tumours. Additionally, the tumour microenvironment may cause immunosuppression of CAR-Ts through the upregulation of checkpoint ligands as well as the presence of regulatory T cells and M2 immunosuppressive macrophages. It is also difficult to identify a cell surface target in solid tumours that is not expressed in normal tissue. Lastly, the cost of treatment and treatment-related toxicities poses an additional challenge to the development of CAR-T therapy in solid tumours[113].

Despite these challenges, there have been recent developments in CAR-T therapy for GU cancers. CD70 is a cell surface target expressed in the majority of clear cell renal cell carcinoma (ccRCC). While CD70 acts as a T-cell costimulatory ligand that induces T-cell activation, the expression of CD70 on tumour cells results in immunosuppression[114]. This has led to the development of allogeneic CD70-directed CAR-Ts, which are also termed "off-the-shelf" CAR-Ts. The manufacturing of allogeneic CAR-Ts involves the collection and storage of T cells from a healthy donor. Prior to genetic engineering, these T cells are silenced through deactivation of TCR and CD52 to prevent graft vs. host disease upon delivery to a patient. This "off-the-shelf" process has been implemented in the development of 2 allogeneic CD70-targeted CAR-Ts, CTX130 and ALLO-316, which have been evaluated in renal cell carcinoma (RCC) cohorts of phase 1 trials.

CTX130 was investigated in patients with unresectable or metastatic ccRCC in the COBALT-RCC trial[115]. The primary endpoint was dose escalation and safety. Patients enrolled in the trial had a median time from diagnosis of 4.9 years and 6 patients had documented refractory disease at the beginning of the study. Notably, no events of cytokine-release syndrome (CRS) that were grade ≥ 3 were observed. The disease control rate (DCR) was 77%, including 1 patient who achieved partial response[115].

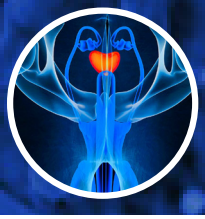
ALLO-316 was evaluated in patients with metastatic ccRCC in the TRAVERSE trial[116]. In all patients, irrespective of CD70 expression, the objective response rate (ORR) was 17% and the DCR was 89%. In patients who were CD70-positive, the ORR was 30% and the DCR reached 100%. Only 1 patient experienced CRS grade ≥ 3 and no graft vs. host disease was observed. Grade ≥ 3 neurotoxicity, infection, and prolonged cytopenia were more frequently observed. Overall, both trials demonstrated encouraging results.

In PCa, developments in PSMA as a biomarker for treatment have also driven advances in CAR-T therapy. Particularly, a PSMA-directed CAR-T has been armored with a tumour growth factor beta (TGF-β) sink that prevents TGF-β-driven immunosuppression in the tumour microenvironment. This CAR-T was evaluated in a phase 1 trial in patients with PSMA-positive mCRPC[117]. Patients had primarily bone and/or lymph node metastases, PSA at entry ranged from 5 to 1683 ng/mL, and time from mHSPC to mCRPC ranged from 1 to 12 years. Overall, 4/13 (31%) patients achieved a PSA decline > 30% from baseline. CAR-T infusion without lymphodepletion resulted in negligible PSA response, despite the CAR-T dose (1 to $3 \times 10^7\ m^{-2}$ or 1 to $3 \times 10^8\ m^{-2}$). One patient received 1 to $3 \times 10^8\ m^{-2}$ CAR-T following lymphodepletion and achieved almost complete PSA response. However, this patient died from CRS and multiorgan failure. All patients who received $3 \times 10^7\ m^{-2}$ after lymphodepletion also had some level of PSA response, which may warrant further investigation.

Two other phase 1 trials in PCa have reported results[118,119]. The most recently reported trial evaluated a PSCA-directed CAR-T in 12 patients with CRPC. Of those, 7 patients achieved stable disease and 1 had a PSA decline > 90%[119]. This is an emerging field in PCa that may be promising, especially for patients with refractory disease.

CAR-T therapy has also been investigated in a trial that included 21 patients, of whom 13 (62%) had testicular cancer[120]. The trial examined the efficacy and safety of a claudin-6 (CLDN6)-directed CAR-T (BNT211) in combination with a CAR vaccine. In patients with testicular cancer, the ORR was 45% and the DCR was 54%. Notably, 1 patient achieved complete response despite 6 prior lines of chemotherapy. Grade ≥ 3 adverse events related to CAR-T were seen in 60% of patients and dose-limiting toxicities occurred in 13% of patients.

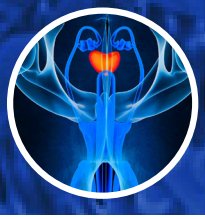
Ongoing and future CAR-T technology is exploring different approaches for therapy development. These



include developing a universal CAR without TCR or MHC; self-driving CAR-T guided to surface chemokine receptors; armored CAR-Ts that can resist the immunosuppressive tumour microenvironment; self-destruct CAR-Ts, able to stop cytotoxicity with external signals; as well as conditional CAR-Ts, which start cytotoxicity upon an external signal. Additional CAR natural killer cells and CAR macrophages are also making their way into the clinical pipeline.

Overall, engineered T cells have improved outcomes in hematologic malignancies and are now part of SOC in cellular therapies. Early work in GU cancers shows small efficacy signal but high toxicities. Many challenges remain in the development of CAR-T therapies in solid tumours, including cell surface antigen selection, T-cell trafficking into the tumour, and resistance in the tumour microenvironment. More developments in the clinical pipeline are expected as cellular therapies are refined.

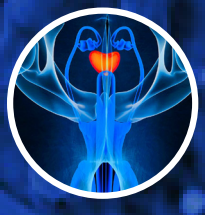
During a Q&A, Dr. Zhang discussed the limitations of CAR-T therapy in GU cancers. She noted that patients in good health may be better candidates for investigation with CAR-T, as the treatment regimen includes a conditioning phase with high-dose chemotherapy. Therefore, heavily pretreated patients are less likely to tolerate treatment. However, if there are positive signals and selection markers, it may be possible to identify patients who are more likely to respond to CAR-T and group them into a cohort to further investigate CAR-T therapy in GU cancers. Dr. Zhang also pointed out that CAR-Ts are expensive and not scalable with the current manufacturing model, but she hopes that this will be improved over time.



B2B: Prostate Cancer Summary

Abbreviations Used in the Text

ADT	androgen deprivation therapy
ALL	acute lymphoblastic leukemia
AR	androgen receptor
ARPI	androgen receptor pathway inhibitor
AUC	area under the curve
BCF	biochemical and/or clinical failure
BCR	biochemical recurrence
CAR	chimeric antigen receptor
CAR-T	chimeric antigen receptor T cell
ccRCC	clear cell renal cell carcinoma
CD	cluster of differentiation
CHIP	clonal hematopoiesis of indeterminate potential
CI	confidence interval
CRPC	castration-resistant prostate cancer
CRS	cytokine-release syndrome
CRT	conventional radiotherapy
ctDNA	circulating tumour DNA
DBD	DNA-binding domain
DCR	disease control rate
DRE	digital rectal examination
ECE	extracapsular extension
EPIC-26	Expanded Prostate Cancer Index Composite
ePLND	extended pelvic lymph node dissection
FDA	US Food and Drug Administration
FDG	fluorodeoxyglucose
GI	gastrointestinal
GU	genitourinary
Gy	Gray
HR	hazard ratio
HRR	homologous recombination repair
HRRm	homologous recombination repair mutation
HSP27	heat shock protein 27
ICG	indocyanine green
ITT	intent-to-treat
LBD	ligand-binding domain
LuPSMA-617	lutetium-PSMA-617
mCRPC	metastatic castration-resistant prostate cancer
MDT	metastasis-directed therapy
MHC	major histocompatibility complex
mHSPC	metastatic hormone-sensitive prostate cancer
mpMRI	multiparametric magnetic resonance imaging
MRI	magnetic resonance imaging
MSI	microsatellite instability
Neuro-SAFE	neurovascular structure-adjacent frozen-section examination
NTD	N-terminal domain
NVB	neurovascular bundle
ORR	objective response rate
OS	overall survival
PARP	poly(ADP-ribose) polymerase
PBRT	prostate bed radiotherapy
PCa	prostate cancer
PET	positron emission tomography
PFS	progression-free survival
PROTAC	proteolysis targeting chimera
PSA	prostate-specific antigen
PSCA	prostate stem cell antigen
PSM	positive surgical margins
PSMA	prostate-specific membrane antigen
QoL	quality of life
RARP	robotic-assisted radical prostatectomy
rPFS	radiographic progression-free survival
RPLND	retroperitoneal lymph node dissection
SBRT	stereotactic body radiotherapy
SOC	standard of care
SUV	standardized uptake value
TCR	T-cell receptor complex
TGF-β	tumour growth factor beta



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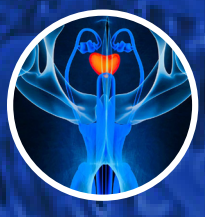

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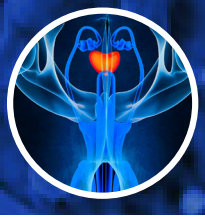

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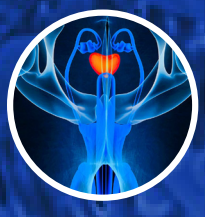

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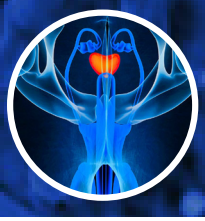

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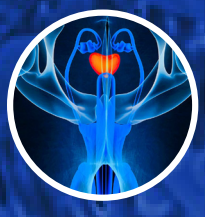

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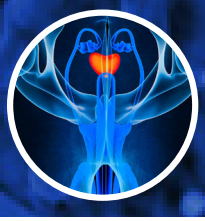

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