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Conference Report

B2B: Prostate Cancer Summary

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The 7th Bench-to-Bedside Uro-Oncology: GU Cancers Triad Meeting, organized in conjunction with the 45th Annual Congress of the Société Internationale d'Urologie, was held on 31 October 2025, in Edinburgh, Scotland, and transmitted live on the *SIU@U* Congress app. The third session, on prostate cancer (PCa), took place in the afternoon and was moderated by Prof. Caroline M. Moore (United Kingdom). This session began with a panel discussion on assessing different energy sources for focal therapy in localized PCa. This was followed by a balloon debate on various approaches to robotic prostatectomy, examining whether the data are sufficient for widespread implementation. The session concluded with 2 presentations: the first on the role of metformin plus androgen deprivation therapy (ADT) in metastatic hormone-sensitive PCa (mHSPC), and the second on the role of theranostics in locally advanced PCa.

Prof. Moore introduced the panel of experts discussing the use of different energy sources for focal treatment of localized PCa. To begin, Mr. Alistair Grey (United Kingdom) presented on the use of irreversible electroporation (IRE). He explained that this relatively new intervention is an ablative therapy that differs from other ablative treatments in that it does not have a thermal component. Instead, short pulses of high-intensity direct current are applied to the target area using electrodes via a brachy grid. This causes the cell membranes to depolarize, making the cells permeable to water, which causes cell apoptosis (as opposed to cell necrosis). This approach may have mechanistic advantages compared with other focal therapies [1].

In recent years, studies undertaken in Australia [2], the United States [3], Spain [4], and France [5] have provided increasing evidence of the efficacy of IRE for PCa. Collectively, these studies demonstrate failure rates of about 15% over 5 years, and a low risk of incontinence and erectile dysfunction (about 20–30%). According to Mr. Grey, the technique is quick (usually <60 min) and relatively straightforward to learn, although there is a degree of skill with ultrasound required, and it is more difficult at the extreme apex. Fusion can be used, if required. The procedure is contraindicated in patients with pacemakers. A patient

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registry has been implemented (NCT02255890) to support the development of practice guidelines for use of IRE.

Next, Dr. Kara Watts (United States) presented on TULSA-PRO transurethral high-intensity focused ultrasound (HIFU). TULSA-PRO, she explained, is similar to transrectal HIFU in that it induces thermal coagulative necrosis, but some key differences are that the TULSA-PRO device contains 10 thermal applicators, any number of which can be activated depending on the length of the prostate. Each thermal applicator has a 3-cm focal point, yielding a total potential maximum ablation volume of 140 mL. In comparison with the transrectal HIFU, the transurethral approach can treat a larger volume of tissue in a shorter amount of time. Also, because it treats circumferentially around the urethra, there are very few areas in the prostate that the ablative technology cannot reach.

Importantly, TULSA-PRO HIFU must be performed in a magnetic resonance imaging (MRI) unit under general anaesthesia. The device's function is based on closed-loop temperature monitoring, a system designed to estimate temperature change in tissue based on proton resonance frequency shift. Briefly, the system compares a baseline (pre-treatment) phase map MRI image with live treatment MRI images (phase maps). The difference between the images for each region is then used to calculate an estimated temperature delivered to that treated tissue. Since temperature is a relative measurement, external temperature is needed to establish a baseline. Thermometry is accurate only in water-based tissue and is much less reliable in fat. In addition, temperature change cannot be distinguished from motion, so it is imperative the patient remain still.

Data comparing TULSA-PRO HIFU with transrectal HIFU or other ablative modalities are not fully mature. To date, the longest-term data on outcomes after transurethral HIFU come from the TACT trial, which evaluated outcomes after whole gland transurethral HIFU. At 1 year, the presence of Grade Group (GG) $\geq$ 2 on biopsy was 21%. Functional outcomes were favourable, with 92% of patients maintaining urinary continence and 75% maintaining erectile function [6]. In addition, 2 studies of partial-gland ablations showed similarly encouraging findings, with one showing 9% [7] and the other showing 7% [8] GG $\geq$ 2 on biopsy at 6 months, again with excellent functional outcomes [7,8].

Next, Dr. Rafael Sanchez-Salas (Canada) delivered a comprehensive overview of high-intensity focused ultrasound as an ablative modality for PCa. He highlighted that although HIFU was originally developed for the treatment of benign prostatic hyperplasia it has since evolved to become the most widely used energy source for focal therapy in localized PCa.

HIFU operates by concentrating ultrasound waves on a defined focal point within the prostate, generating rapid and localized hyperthermia. This abrupt temperature rise induces gas bubble formation, leading to cavitation, mechanical collapse of microcavities, and subsequent rupture of cell membranes. The immediate effect on the targeted tissue is coagulative necrosis, followed approximately 1 week later by an inflammatory phase and, subsequently, by fibrotic remodelling within 2 weeks.

Dr. Sanchez-Salas noted that the ideal anatomic targets for HIFU are posterolateral situated lesions, where energy delivery and lesion accessibility are most favourable. Conversely, treating apical lesions remains technically challenging because of the close proximity of the sphincter and urethra, which restricts ablative precision. HIFU platforms currently include transrectal and transurethral systems, with an MRI-guided transrectal platform (ExAblate) expected to expand capabilities in the near future.

When the currently available evidence is synthesized, it is apparent that use of HIFU balances between cancer control and preservation of quality of life. Reported clinical outcomes in localized PCa show 12- to 24-month clinically significant cancer relapse-free

survival of approximately 85%, with urinary incontinence rates close to 3% and new-onset erectile dysfunction in 10–20% of men [9–12].

Next, cryotherapy was described by Prof. Hashim Ahmed (United Kingdom). He pointed out that HIFU is usually the first approach in focal therapy, with cryotherapy reserved for treating anterior tumours. Importantly, cryotherapy has been performed for much longer than HIFU and is an excellent ablative approach. The technique is similar to brachytherapy or perineal biopsy, and it is used to treat medium-risk and some high-risk tumours. With an ultrasound probe in the rectum to guide treatment, needles of about 16 gauge inserted through the perineum are used to drive argon gas, which produces an ice ball that reaches temperatures below −40 °C. Usually, a couple of applications are required to treat the target volume. Notably, the ablative effect occurs 2–3 mm within the ice ball, so it is important to push the ice front below the desired area of ablation. This is why an anterior approach is preferable, as it spares the rectum.

Over time, the approach to cryotherapy for PCa has become more focal, and the ability to target specific areas has improved considerably. Cancer control outcomes are excellent, with a recent systemic review and meta-analysis that comprised 2778 patients demonstrating an overall survival (OS) rate of 98%, cancer-specific survival (CSS) of 99%, metastasis-free survival (MFS) of 99%, and a biochemical progression-free survival of 73%. The rate at which patients required a second focal session was 6%, and only 6% required radical prostatectomy (RP) [13].

Once the ablative treatment options were described, the panel went on to a case-based discussion, presented by Prof. Moore. The first case was that of a 73-year-old male with a prostate-specific antigen (PSA) of 10 ng/mL, and Gleason score (GS) of 3 + 4 for 2 mm at external biopsy. An MRI suggested the patient had more significant disease, and a second biopsy resulted in a diagnosis of adenocarcinoma, with a GS upgrade to 3 + 5 (10% Gleason pattern 5), with 2 foci measuring 3 mm and 5 mm. Neither perineurial nor lymphovascular invasion was observed.

Dr. Sanchez-Salas said that, given his pattern 5 disease, it would be important to confirm, in discussion with a tumour board, whether the patient is a good candidate for focal therapy. If he is deemed to be a good candidate, then he would use either IRE or cryotherapy, in both cases combined with fusion. Dr. Watts said TULSA could be used for an anterior lesion, but she nevertheless agreed with Dr. Sanchez-Salas that she would hesitate to use focal therapy in a patient with pattern 5 disease, as there is a lack of evidence for outcomes in this setting. Mr. Grey agreed that IRE and cryotherapy are both viable options but again shared concern regarding focal treatment in this patient. He suggested considering the maximum core length at biopsy in conjunction with the size of the lesion. If there is a significant mismatch, there may be undersampling, and it is possible that the proportion of the tumour that is pattern 5 may be higher than estimated. Prof. Ahmed added that while pattern 5 is a concern, it should not resist the low temperature of cryotherapy. Thus, the major concern is the risk of micrometastases. The challenge is to determine the appropriate diagnostic techniques for ruling that out.

The patient underwent IRE 4 years ago, and he is still doing well, with a PSA of 1.29 ng/mL. He continues to be monitored via MRI no more than once a year.

The second case was that of a male with a 7 mm peripheral zone GS 3 + 4 lesion that was 10% Gleason pattern 4. His PSA was 6 ng/mL. Imaging revealed a probable tumour in the right mid and apical peripheral zone and an indeterminate lesion in the right anterior gland. The prostate volume was 50 mL. Dr. Sanchez-Salas would treat the tumour with HIFU. For the indeterminate lesion, he would consider a hemiablation. Another option would be a sonoablation on the posterolateral right side of the prostate, including the apex. Dr. Watts said TULSA could also play a role here, with a theoretical benefit that it could be

used to treat both lesions at once. Conversely, Mr. Grey did not believe that IRE would be a good option in this patient because it is not as easy to visualize energy delivery as it is with cryotherapy or HIFU. In addition, the needles are fixed during delivery of cryotherapy whereas they are moveable during delivery of IRE, which can be a problem if the patient is not perfectly still. Both these factors can make sphincter injury more likely with lesions at the extreme apex. He would probably use HIFU in this patient. He would also like to examine the apical margin from a sagittal or cranial view to determine how close the lesion is to the sphincter.

Prof. Ahmed would treat the indeterminate anterior lesion after a second biopsy, to clarify whether it was indeed cancerous. If it was not, he would use HIFU to treat the posterior lesion. He avoids cryotherapy with posterior lesions to prevent damaging the rectum. It is important to keep in mind, he noted, that the urethral warmer used during cryotherapy can protect the medial margin of the tumour, particularly at the apex. If both lesions were cancerous, it would be important to explain to the patient that this increases the possibility that a third will emerge in a short period of time.

This patient did undergo a biopsy of the indeterminate anterior lesion and was treated with HIFU. At 5 years, his PSA was 3.2 ng/mL, and imaging revealed a stable appearance, with no suspicious focal lesions.

The final case was that of a male in his mid-70 s with a 5 mm GS 3 + 4 midline posterior lesion and a PSA of 11 ng/mL. Prof. Ahmed pointed out that evidence shows that midline posterior lesions are not well managed through active surveillance. Thus, he would likely treat with HIFU, although it would almost certainly result in the patient maintaining his erections but losing the ability to ejaculate. He would not consider cryotherapy in this case. Mr. Grey would also use HIFU. While IRE is feasible in this case, it is more difficult to perform in midline posterior lesions, especially if they reach the apex. Dr. Watts said this patient would be difficult to treat with transperineal cryotherapy. TULSA would be a reasonable option, targeting the posterior plane only, but the logistics of incorporating TULSA for most centres is a consideration. Finally, Dr. Sanchez-Salas said he would use transrectal HIFU. This patient was treated with HIFU and continues to do well 5 years later.

The next session was a balloon debate on the best approach to robotic prostatectomy: NeuroSAFE, a Retzius-sparing robot-assisted radical prostatectomy (RARP), single-port RARP, or hood-sparing RARP. A poll taken at the outset of the session revealed that the majority of the audience (80%) uses a robotic multi-port approach, while the remaining 20% use the Retzius-sparing approach.

Presenting the NeuroSAFE approach was Dr. Derya Tilki (Germany). If the goal is to deliver the best possible surgery, then intraoperative frozen section should be widely implemented, she said. Advantages of NeuroSAFE include that the indication for a nerve-sparing procedure is individualized to the true extent of disease, and positive margins are recognized during surgery and can be dealt with immediately. This allows for broadening the indication for a nerve-sparing procedure. Thus, 2 goals are achieved with this technique: reduction of positive margins and the ability to use a nerve-sparing approach more often.

Alternatives to NeuroSAFE for determining whether nerve-sparing RP is appropriate are rife with uncertainty. For instance, nomograms [14,15] and MRI [16,17] do not always accurately predict extracapsular extension (ECE). For instance, one meta-analysis comprising 75 studies and 9796 patients revealed that the sensitivity for detecting ECE with MRI was only 0.57 (95% confidence interval [CI] 0.49–0.65) [18].

Dr. Tilki explained that with NeuroSAFE, almost the whole of the posterior section of the prostate is sent for frozen section during the surgery, with results used to guide the procedure. In her centre, this has led to a nerve-sparing rate > 99% in pT2 disease and 89%

in pT3b disease. The technique was initially developed for open RP but has been available for use with RARP for many years [19,20].

NeuroSAFE been adopted by many centres in many countries, resulting in a higher rate of nerve-sparing surgeries and a lower rate of positive surgical margins [21–25]. For the NeuroSAFE PROOF study, 407 patients were randomized to NeuroSAFE or standard RARP. Bilateral nerve-sparing was feasible in 82.1% of patients in the NeuroSAFE arm, compared with only 56.4% in the RARP arm. Surgical margins were not different between the 2 groups, with a 65% rate of negative surgical margins in the NeuroSAFE group vs. 72% in the standard RARP group. In addition, more of the positive margins in the NeuroSAFE arm were small, single margins (21% vs. 13%). The primary outcome of the trial was International Index of Erectile Function-5 at 12 months, and this was superior in the NeuroSAFE arm, with an adjusted mean difference of 3.18 ($p < 0.0001$) [26].

Dr. Tilki noted that the main limitation to NeuroSAFE is the need for complex infrastructure to perform it.

Next, Dr. Silvia Secco (Italy) presented on the Retzius-sparing approach to RARP. This technique, she explained, was developed about 15 years ago by Dr. Aldo Massimo Bocciardi and is now being increasingly used around the world. The procedure starts at the level of the seminal vesicles, moving laterally and then down at the level of the apex, finally moving onto the anterior surface of the prostate, reaching the apex. If oncologically safe, this approach allows for a total preservation of the neurovascular bundles, for sparing of the dorsal venous complex (DVC), the puboprostatic ligaments, and the endopelvic fascia. The Retzius-sparing approach can be performed using different platforms, including the DaVinci, Hugo-RAS, and Versius CMR.

There are several publications comparing standard RARP with the Retzius-sparing approach. While initial studies suggested an increased rate of positive margins with the Retzius-sparing approach, this reflected an early learning curve. More recent publications all demonstrate that while rates of positive margins and potency are similar to the standard anterior approach, patients are more likely to recover continence earlier with the Retzius-sparing approach [27–29]. This is because of the ability to preserve key structures with this approach. The Retzius-sparing approach also results in a lower risk of abdominal hernia and less likelihood of shortening of the penis, since vascularization is maintained [30].

Performing this procedure does not entail extra expenses relative to other robotic procedures; indeed, overall costs may decrease because patients use fewer incontinence pads or panty liners. There are also cost savings associated with the lower rate of complications and transfusion and avoiding the need for rehabilitation. Patients also achieve a higher QOL sooner. With regard to the learning curve, the outcomes are similar even during the learning stage, with just the duration of the procedure initially being longer [31–33]. Dr. Secco also emphasized that for any surgical procedure, the learning curve never really ends. There is always room for improvement [34].

Dr. John W. Davis (United States) next presented on single-port RARP. The single-port Da Vinci is the first purpose-built robot for single-access surgery. It is designed for small spaces and best suited for extraperitoneal, transvesical, and transperineal approaches [35]. It was developed by Intuitive Surgical in the United States, with limited release in the United States starting in 2018 and gradually expanding global approvals. Its main indications are urologic, transoral, colorectal, and thoracic. Key instrumentation characteristics include a finer bipolar, fresh disposable scissor tips for every case, a drivable camera, wide range of motion of boom, and less need for Trendelenburg. Challenges include less assistance access, instruments having a smaller range of motion, and reduced strength.

Currently, the strength of evidence for the single-port procedure is limited, with no known randomized controlled trials (RCTs) in development. A systematic review that

included 7 studies conducted by experts in high-volume centres involving 1239 patients found similar outcomes with the single-port approach vs. the standard approach with respect to time, blood loss, continence, potency, complications, surgical margin, and functional outcomes. The single-port approach, however, resulted in shorter hospital stay and catheterization time, as well as less need for pain medication, including opioids [36].

Cost is higher with the single-port approach, ranging from about $800 to $1000 US per case. The capital expenditure for the platform is also about $100,000 US more than other options. Some of that cost can be recouped with earlier hospital discharge.

A learning curve definitely exists for this procedure, with surgeons maximizing their outcomes after about 20–100 cases, said Dr. Davis. Some surgeons use the single-port device preferentially because their centres block out time for its exclusive use, which facilitates access to the operating room.

Dr. Davis concluded that single-port RARP is ready for implementation because it offers advantages in the case of a hostile abdomen, improves access in very small patients, is part of the evolution of minimally invasive/small space concept of surgery, and has multidisciplinary indications.

Lastly, Prof. Alan McNeill (United Kingdom) spoke about hood-sparing RARP. He explained that functional recovery following RP is highly dependent on surgeon experience. Thus, a technique that is easily learned and reproduced will deliver better outcomes in any single surgeon's hands. Key surgical skills include appropriate tissue handling to avoid hematoma and too much traction, and ensuring the sphincter complex remains stable.

The hood-sparing technique, described first by de Carvalho in 2020, is a technical modification to anterior RARP that preserves the neurovascular bundles right up onto the anterior surface of the prostate [37]. Prof. McNeill provided some tips on performing the surgery successfully. He starts by dissecting the vascular pedicle, then he divides the anterior fascia and DVC. Staying within the veins of the DVC protects against a positive margin. Using a Rocco stitch for posterior reconstruction prevents haematoma, which can negatively impact surgical results. He also uses continuous anastomosis, with the endopelvic fascia reconstructed anteriorly to ensure stability.

Although it takes some time to become proficient in the procedure, even early results can be superior to the standard approach to RARP. A single surgeon experience with 174 patients over 2 years revealed urinary incontinence domain scores on the Expanded Prostate Cancer Index Composite at 6–8 weeks of 66 with standard RARP vs. 79 with hood-sparing RARP; at 12 months, these scores were 83 vs. 88. Continence rates at 6–8 weeks were 43% with standard RARP vs. 76% with hood-sparing RARP, increasing to 82% vs. 97% at 12 months [38]. The rate of continence with hood-sparing is similar to that obtained with the Retzius-sparing approach, said Prof. McNeill.

Notably, there are no major challenges to the hood-sparing approach. Most robotic surgeons are already familiar with the anterior approach. Therefore, hood-sparing RARP is ready for widespread implementation, with uptake already on the rise. The learning curve is short, and as sphincter stability is provided with the anterior reconstruction, continence rates at 1 year are excellent. It is applicable in all cases, unlike Retzius-sparing RARP, without the extra resource required for NeuroSAFE.

During a Q&A session, the audience members voted on which RARP procedure they believed was ready for widespread adoption, based on cost, learning curve, and clinical outcomes. The results were 40% voting for Retzius-sparing RARP, 30% for NeuroSAFE, and 30% for the hood-sparing technique. Thus, Dr. Secco was given 2 min to further make the case for Retzius-sparing RARP while Dr. Tilki and Prof. McNeill each had 1 min to support the NeuroSAFE and hood-sparing techniques, respectively.

Dr. Secco emphasized the key advantages of Retzius-sparing RARP, notably high postoperative continence rates (92% immediately after catheter removal in her centre in patients <55 years of age with early-stage disease). These already high continence rates increase in the following weeks and months, especially in older patients. The learning curve is short, and this approach allows for the greatest potential to spare the greatest amount of healthy tissue and preserve those structures important for functioning while at the same time maintaining a level of positive margins similar to conventional RARP. NeuroSAFE, while a good alternative, requires too complex an infrastructure to perform. With Retzius-sparing RARP, there is the option to enlarge the dissection line intraoperatively to remove any additional tissue that appears malignant. The hood-sparing approach is essentially a more complicated form of Retzius-sparing RARP, performed by surgeons who do not want to move away from the familiarity of the anterior approach. While the main principle of the hood-sparing technique is to reconstruct, the main principle of Retzius-sparing RARP is not to damage the structures in the first place.

Dr. Tilki acknowledged that not every centre can offer the complex and expensive infrastructure needed for NeuroSAFE. She added that receiving the pathology results needed to direct surgery can take time.

Prof. McNeill said that he has explored using Retzius-sparing RARP instead of the hood-sparing approach, but he found it more difficult for himself and his assistant, as well as being more difficult to teach. He disagreed that it has a short learning curve and argued instead that it requires an experienced prostatectomist to perform it well. Because hood-sparing is easier to learn and teach, experience can be accrued more rapidly. That is what will deliver good functional outcomes in the long term, he argued, because surgeon experience remains the single best predictor of outcome.

In closing the session, Dr. Sanchez-Salas concluded that, while different surgeons have their own preferred technique, it is important to adapt to the individual needs of each patient. In a final vote, the hood-sparing approach received the highest proportion of votes.

The next presentation was on adding metformin to ADT for patients with metastatic HSPC, with a discussion of the OS and metabolic outcomes from STAMPEDE Arm K. This was presented by Prof. Nick James (United Kingdom). He pointed out that metabolic derangement is a hallmark of cancer and remains a neglected target. Another hallmark of cancer is chronic inflammation, and obesity is associated with a chronic inflammatory state [39]. It is thus concerning that ADT can cause patients to gain weight and increases the risk for developing type 2 diabetes. Some studies, although small, have suggested an anticancer effect for metformin in PCa [40,41]. This therapy is particularly attractive for use in combination with anticancer treatments, such as ADT, that have negative metabolic effects because, at the very least, they can mitigate those effects.

The hypothesis that metformin might improve OS among patients with HSPC being treated with ADT was tested in the STAMPEDE trial. This multi-arm, multistage trial has been running for 21 years, and it is scheduled to close in March of 2026. For Arm K of the trial, 1800 patients with metastatic HSPC and an HbA1C < 6.5% who were not on treatment for diabetes were randomized to standard of care (which included ADT plus an appropriate anticancer therapy, usually docetaxel) or standard of care plus metformin 850 mg once or twice daily (depending on tolerability). Patients could stay on metformin even if their cancer progressed. Only 1 patient received androgen receptor pathway inhibitors (ARPIs), as this therapy was not funded during most of the accrual period for the trial [42].

The primary outcome was OS, and a median OS of 54 months was projected, for a one-sided significance level of 2.5% and 92% power to detect a treatment difference hazard

ratio (HR) of 0.8. The prespecified targets were met in July of 2024, and 7 subgroups were prespecified for the final analysis (but not fully powered) [42].

Baseline characteristics were similar between the 2 groups. Prof. James pointed out that patients were in relatively good health, with most being non-smokers and taking aspirin and/or statins. Patients were divided by CHAARTED volume. Almost all patients (94% in each arm) had de novo disease, 12–14% had bone metastases, and 11–12% had visceral metastases, usually to the lungs. In both arms, ≥98% were World Health Organization performance status 0–1. In addition to ADT, the vast majority of patients (82–83%) also received docetaxel, which is an indicator of the high fitness level in this patient population. Age at randomization was 69, and median PSA was consistent with a metastatic population (80–87 ng/mL) [42].

After a median follow-up of 60 months, there was no significant improvement in OS with the addition of metformin (HR 0.91, 95% CI 0.80–1.03) [42]. Prof. James said that, frustratingly, the 60-month follow-up was the only analysis that was not significant. Subgroup analysis revealed fairly consistent results across subgroups with the exception of CHAARTED volume, where benefits of metformin were observed in those who were high CHAARTED volume (p for interaction = 0.0863). In the high-volume group, HR was 0.79 (95% CI 0.66–0.93), compared with an HR of 1.0 (95% CI 0.79–1.26) in the low-volume group [42]. This is consistent with metformin having a greater impact in patients who are more metabolically deranged. While the study was not powered to confirm this finding, it is worthy of further interrogation, said Prof. James. All metabolic parameters measured, including weight, serum glucose level, HbA1c, total cholesterol, and LDL cholesterol, were significantly improved with metformin despite none of the patients having diabetes and irrespective of disease volume [42]. Tolerability of metformin was as expected, with diarrhoea being the most common adverse event occurring more often in the metformin arm than the standard-of-care arm [42].

Patients from STAMPEDE will continue to be followed-up long-term by connecting the trial data with the United Kingdom's National Health Services digital databases. Data on bone outcomes in trial arms where patients were randomized to the addition of zoledronic acid or standard of care alone have already been published [43], and cardiovascular outcomes will be available soon. It would be interesting to see the effect of metformin in patients with high-volume disease treated with an ADT-ARPI doublet backbone, concluded Prof. James. As the lifespan of patients with PCa has increased in recent years, it is imperative to focus on improving QOL with interventions like these.

During a subsequent Q&A session, an audience member said that, despite this being a negative trial, the data presented were strong enough to recommend metformin routinely for PCa patients treated with ADT. Next, Dr. Peter Black (Canada) asked why the STAMPEDE trials are being closed down. Prof. James replied that it relates to United Kingdom's trial regulations that created a heavy administrative burden. As a result, the STAMPEDE trials will be stopped, and STAMPEDE II is starting up. Prof. Moore asked whether another metformin study will be conducted in this setting. Prof. James said they do not plan to do this, but he is hoping that longer follow-up will demonstrate an OS advantage, which will allow them to officially recommend it.

The final presentation was given by Dr. Jan Philipp Radtke (Germany) on theranostics in locally advanced PCa. Through an initiative by the European Prostate Cancer Centres of Excellence, Dr. Radtke and colleagues assessed the diagnostic performance of ^{18}F-prostate-specific membrane antigen-positron emission tomography/computed tomography (^{18}F-PSMA-PET/CT) in comparison with multiparametric MRI (mpMRI) among treatment-naïve patients with biopsy-proven unfavourable intermediate- or high-risk PCa before RP. All patients underwent both imaging modalities [44].

In 65 specimens obtained following RP, 22 had ECE and 349 PCa lesions were found, of which 324 were clinically significant (International Society of Urological Pathology [ISUP] GG $\geq$ 2). The pre-lesion accuracy for detecting clinically significant PCa was 75% with ^{18}F-PSMA-PET/CT and 80% with mpMRI ($p = 0.05$). The diagnostic accuracy of both modalities for detection of ECE did not significantly differ but was not high in either case (64% with ^{18}F-PSMA-PET/CT vs. 72% with mpMRI, $p = 0.22$). The use of ^{18}F-PSMA-PET/CT was superior, however, at predicting the presence of lower grade (ISUP GG 2–3) vs. higher grade (ISUP GG 4–5) cancers (Busshoff et al., in preparation).

In another study of 80 patients with intermediate- to high-risk PCa, the per-lesion sensitivity for staging of PCa was higher with PSMA-PET/CT (95%) than MRI (73%). Notably, however, the sensitivity for identifying ECE and seminal vesicle invasion was poor for both modalities (33–55%) [45]. In a meta-analysis of 29 studies on primary PCa detection, the ability to detect clinically significant cancer within the prostate gland was similar for both PSMA-PET/CT and MRI [46].

In a proof-of-concept study among 25 patients to assess the diagnostic accuracy of combined imaging, PSMA-PET/CT and MRI were performed upfront, followed by RP without prior biopsy. The authors found that a PET score of $\geq$4 with a maximum standardized uptake value (SUVmax) $\geq$ 4 (median SUVmax 9.5 [interquartile range 6.4–19.3]) was associated with a high likelihood that clinically significant PCa was present [47]. Nevertheless, improvement in the diagnostic accuracy of imaging is needed. The phase 3 PEDAL study, which randomized 236 patients to ^{18}F-DCFPyl-PSMA-PET/CT or mpMRI, revealed that the negative predictive value of PSMA-PET/CT is not high enough to rule out the likelihood of the presence of clinically significant cancer with confidence. In addition, the sensitivity is poor with both modalities [48].

Improvement in diagnostic accuracy can be obtained via the PRIMARY score, a validated scoring system for evaluating PSMA-PET/CT signals. Two recent studies have demonstrated that using the PRIMARY score does increase diagnostic accuracy, compared with the Prostate Imaging Reporting and Data System (PI-RADS) score [49,50].

With regard to detecting ECE, PSMA-PET and MRI are comparable, with a meta-analysis showing an area under the curve (AUC) of 0.77 and 0.78, respectively. Nevertheless, the diagnostic accuracy for ECE detection of both modalities requires further improvement [46]. Results were a little bit better for sensitivity and specificity to detect seminal vesicle infiltration with an AUC of 0.92 and 0.94, respectively [46]. In another meta-analysis of 49 studies, however, only 6 evaluated the ability to detect seminal vesicle infiltration, and the sensitivity was low, at 42%. Similarly, only 6 studies examined the ability to detect ECE, and the sensitivity was only 61% [51]. Thus, concluded Dr. Radtke, there remains no reliable way to detect seminal vesicle invasion or ECE using only imaging.

With respect to determining T stage, the study of 80 patients by Ma et al., among whom 54% were high-risk, provided no information about the definition of T3 disease [45]. Dr. Radtke pointed out that microperforation of the capsule, which is difficult to identify even on pathologic examination, is extremely difficult to detect on imaging. There is some evidence that PSMA-PET/CT is superior to MRI for determining T stage, but nevertheless there is a high degree of underestimation in both modalities. In one study, correct staging with PSMA-PET/CT was 45%, compared with 28% with MRI ($p < 0.003$), with underestimations occurring 41% of the time with PSMA-PET/CT and 64% of the time with MRI [52].

Going back more than 10 years, in the supplementary material from the first publications of the PI-RADS scoring, the authors provided valuable insight on how to identify ECE and seminal vesicle invasion on MRI [53–55]. More recently, a systematic review and meta-analysis of 46 studies suggested that tumour contact length (TCL) $\geq$ 15 mm and mean

apparent diffusion coefficient (ADC-mean) can be reasonable markers to more accurately predict microperforation of the capsule and ECE [56].

Another option for improving accuracy is to combine mpMRI with clinical parameters, such as clinical T stage and ISUP GG. A problem with risk modeling, however, is overfitting. Nevertheless, this limitation may be overcome with the support of expert MRI reading [57].

In the intraoperative setting, MRI can be used to guide frozen sectioning. In one study of 134 patients, this approach reduced the rate of positive surgical margins in 28% of patients [58]. Using intraoperative frozen sectioning in conjunction with 3D modeling in a proof-of-concept study also demonstrated good accuracy, with a positive surgical margin rate of only 15% [59].

For the proPSMA study, Australian researchers analyzed patients with high-risk PCa using PSMA-PET/CT, vs. standard CT imaging and bone scanning for the purposes of detection of lymph node staging. This was a crossover design, so all patients underwent all imaging. They found that PSMA-PET/CT was superior to standard CT imaging with respect to sensitivity, specificity, dose, and for directing treatment management [60].

There may also be a role for PSMA-PET/CT to guide neoadjuvant treatment. In the LuTectomy trial, 20 patients with high-risk PCa were treated with leutitium-177 PSMA-617 radionucleotide for 1 or 2 cycles. Therapy had an effect in 80% of patients, although no patients experienced a complete pathological response. One patient had minimal residual disease, and only 4 patients had biochemical recurrence after 24 months [61].

Dr. Radtke concluded that PSMA-PET/CT is the gold standard imaging modality in lymph node staging, and it might also aid in determining the role of neoadjuvant treatment in local advanced disease. While both mpMRI and PSMA-PET/CT can detect lesions within the prostate sufficiently, expert reading is necessary. Both imaging modalities need to be improved as standalone tests to determine ECE, but they are accurate in aiding intraoperative imaging or frozen sectioning.

During a Q&A session, an audience member said that in his practice, the accuracy of detecting T3 disease on MRI, when comparing with prostatectomy specimens, is about 50%. He asked whether radiologists ever ask for pathology results as a tool to improve their MRI readings. Several attendees responded that they always work in conjunction with pathologists. Another audience member noted that patients with high polygenic risk scores may have normal PSAs and an MRI invisible tumour. He asked whether these tumours may be visible on PSMA-PET/CT (or vice versa). Dr. Radtke replied that in screening trials, such as the PROBASE trial [62], this can occur among patients with low PSA levels. At the moment, PSA is the most robust screening tool, likely followed by MRI. The expertise needed for accurate reading is limited or lacking in many centres, presenting a barrier to the more widespread use of MRI for PCa screening. A final question was why there was a need to replace prostate biopsy with imaging, particularly if it requires RP (a far more invasive procedure than biopsy) for confirmation. Dr. Radtke emphasized that the studies exploring the role of imaging as a replacement for biopsy were only proof-of-concept studies, which required RP as a comparator. The ultimate goal is to reduce the number of biopsy sessions required without increasing rates of RP.

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Abbreviations

ADT	androgen deprivation therapy
AUC	area under the curve
CI	confidence interval
CT	computed tomography
DVC	dorsal venous complex
ECE	extracapsular extension
GG	Grade Group
GS	Gleason score
HIFU	high-intensity focused ultrasound
HR	hazard ratio
HSPC	hormone-sensitive prostate cancer
IRE	irreversible electroporation
ISUP	International Society of Urological Pathology
mpMRI	multiparametric MRI
MRI	magnetic resonance imaging
OS	overall survival
PCa	prostate cancer
PET	positron emission tomography
QOL	quality of life
PI-RADS	Prostate Imaging Reporting and Data Systems
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
RARP	robot-assisted radical prostatectomy
RP	radical prostatectomy
SUVmax	maximum standardized uptake value

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