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Five Practice-Changing Advances on the Horizon Summary

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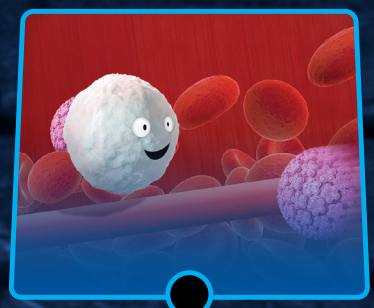

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B2B: Five Practice-Changing Advances on the Horizon Summary

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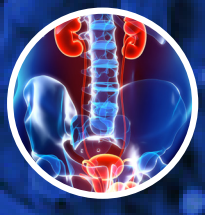
The 5th Bench-to-Bedside Uro-Oncology GU Cancers Triad Meeting, organized in conjunction with the 43rd Annual Congress of the Société Internationale d'Urologie, was held on October 13th, 2023, at the Istanbul Lutfi Kirdar International Convention and Exhibition Centre in Istanbul, Türkiye, and transmitted live on the *SIU@U* virtual platform. The programme concluded with a special session dedicated to the five practice-changing advances on the horizon for bladder, kidney, and prostate cancers, which was chaired by Drs. Simon Tanguay and Peter C. Black (Canada).

Dr. Carmen Mir (Spain) discussed key advances within the continuum of bladder cancer (BCa) management. The first advance is the use of magnetic resonance imaging (MRI), which is a promising tool for local staging, differentiating non–muscle-invasive BCa (NMIBC) from muscle-invasive BCa (MIBC). First results of the phase 2/3 BladderPath trial became available in 2022. This trial aims to evaluate whether MRI and biopsy can replace transurethral resection of bladder tumour (TURBT) in BCa staging[1]. Patients with suspected BCa were identified in the hematuria clinic, assessed for MIBC on a Likert scale at flexible cystoscopy, and randomized to either standard TURBT (Pathway 1) or MRI-based assessment (Pathway 2) with tumour biopsy. The median time to correct treatment for MIBC was significantly shortened in Pathway 2 compared to Pathway 1 (53 vs. 98 days; $P = 0.0046$). Additionally, no detrimental effect on the time to treatment for NMIBC was observed[1].

MRI data are also being evaluated to predict response to treatment. In a cohort analysis from the phase 2 PURE-01 trial, the ability of the Vesical Imaging–Reporting and Data System (VI-RADS) to predict response to neoadjuvant treatment with pembrolizumab was assessed[2]. VI-RADS uses multiparametric MRI (mpMRI) parameters to predict the probability of MIBC. Using multivariable analysis, the authors demonstrated that VI-RADS 0 to 3 scores were significantly associated with pT ≤ 1 N0 response. The pre-pembrolizumab model performed with an area under the curve (AUC) of 0.80. The AUC post-pembrolizumab was 0.90[2].

The second advance is developments in en bloc resection technique to improve the quality of TURBT. The quality of technique when performing TURBT is critical for improving outcomes. Implementation of a surgical checklist during TURBT can impact recurrence rates[3], and the presence of detrusor muscle on initial TURBT is a marker of resection quality that has prognostic value for early recurrence[4]. A recent prospective, noninferiority trial randomized patients with tumours ≤ 3 cm to undergo en bloc TURBT or conventional TURBT[5]. The rate of detrusor muscle presence for en bloc TURBT was noninferior to that of conventional TURBT, and pT1 substaging was improved with the en bloc approach. No increased risk of bladder perforation was observed[5]. In another open-label phase 3 trial, en bloc TURBT was superior in retrieving detrusor muscle specimen compared to conventional TURBT (80.7% vs. 71.1%; mixed-model $P = 0.01$) for tumours 1 to 3 cm in size. Bladder perforation was less common with en bloc TURBT. At a median follow-up of 13 months, recurrence rates were similar between both approaches[6]. These results highlight how the technique for performing TURBT may change in coming years.



The third advance focused on combination therapies for bacillus Calmette-Guérin (BCG)–unresponsive NMIBC. For patients with high-grade NMIBC (intermediate/high-risk papillary tumours or carcinoma in situ [CIS]), intravesical BCG after TURBT is an established and effective therapy to help prevent recurrence. Nonetheless, recurrence does occur, creating a pressing need for alternative treatments. Such therapies also could benefit patients who cannot access BCG due to the ongoing global shortage.

The open-label phase 2/3 QUILT 3.032 trial evaluated BCG in combination with intravesical N-803, an interleukin (IL)-15 immunostimulatory fusion protein complex. In cohort A, treatment resulted in a complete response (CR) of 71% in patients with CIS. In cohort B, which included patients with papillary tumours, the combination led to disease-free survival (DFS) of 48%[7]. Adverse events were primarily low grade and no serious adverse events were considered treatment related. Quality of life (QoL) assessments were also positive with the treatment combination[8].

Other treatment combinations are also under investigation. In the single-arm phase 2 CORE1 trial, the oncolytic adenovirus cretostimogene grenadenorepvec (CG0070) is being examined in combination with pembrolizumab in patients with CIS. CG0070 is a serotype 5 adenovirus engineered to express granulocyte-macrophage colony stimulating factor (GM-CSF) and replicate in cells with mutated or deficient *RB* gene. At 12 months, CG0070 plus pembrolizumab resulted in a CR of 68%[9]. Additional studies of CG0070 alone (BOND-003, NCT04452591) or in combination with immune checkpoint inhibitor therapy (PIVOT-001, planned study) will help elucidate the potential role of CG00070 for the treatment of BCG-unresponsive NMIBC.

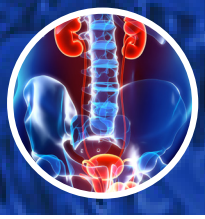
Also on the horizon is EG-70, a nonviral gene therapy comprising a nanoparticle formulation of plasmids that encode IL-12. EG-70 is administered intravesically and produced encouraging results in a phase 1 trial[10]. A phase 2 trial is planned to continue in 2023.

Despite advances, there are several issues regarding new agents and treatment combinations for BCG-unresponsive NMIBC. Most trials are single arm and lack comparative data. Study populations, outcomes definitions, and study designs differ considerably across studies. Furthermore, data are limited by the lack of long-term follow-up.

The fourth advance regards the extent of pelvic lymph node dissection during radical cystectomy, which has critical implications for urologists. Results of the phase 3 SWOG S1011 trial were recently reported[11]. This trial was conducted over the course of 10 years and tested the hypothesis that extended lymphadenectomy (ELND) is associated with improved DFS and overall survival (OS) compared to standard lymphadenectomy (SLND). Patients with T2 to T4a BCa who were scheduled to undergo radical cystectomy were randomized to either SLND or ELND. Up to 71% of patients in both arms were stage T2 and 57% received neoadjuvant chemotherapy. The median number of total lymph nodes removed with SLND was 24 (range, 6 to 61) and with ELND was 39 (range, 15 to 94). No differences in DFS (hazard ratio [HR] = 1.10; 95% confidence interval [CI], 0.87 to 1.42; 1-sided $P = 0.40$) or OS (HR = 1.15; 95% CI, 0.89 to 1.48; 1-sided $P = 0.87$) were observed between the SLND and ELND arms. A trend towards potential DFS benefit with ELND in more locally advanced BCa (pT3 to pT4a) was observed. ELND was also associated with increased morbidity and perioperative mortality.

The role of ELND vs. SLND was also examined in the LEA trial. Patients with cT1 to cT4a cNx cM0 BCa were included. The trial excluded patients who received neoadjuvant chemotherapy and lymph nodes > 1 cm above the aortic bifurcation. After a median follow-up of 58.4 months, there was no benefit of ELND over SLND in the time to progression and OS. However, long-term cancer-specific survival was significantly improved with ELND vs. SLND (76% vs. 65%; HR = 0.65; 95% CI, 0.43 to 0.96; log-rank $P = 0.03$)[12].

The final advance was improvements in patient selection for bladder preservation strategies. Two retrospective studies published in 2023 demonstrated that radical cystectomy offers no benefit over bladder-sparing trimodal therapy (TMT) for either DFS[13] or metastasis-free survival (MFS)[14] in adequately selected patients with MIBC. In another retrospective study, the role of TMT with radical dose radiotherapy was compared to radical cystectomy in patients with



Five Practice-Changing Advances on the Horizon Summary

clinically node-positive MIBC. No difference in OS was observed between TMT and radical cystectomy. While outcomes for this patient population are poor, receiving a form of radical treatment provided substantial benefit over palliative care[15].

There is a strong rationale for offering bladder preservation to select patients. However, key prospective clinical trials differ considerably in which primary endpoints are being assessed. Results of the RETAIN trial were reported in 2023[16]. This single-arm, noninferiority phase 2 trial examined a risk-adapted approach for MIBC based on TURBT staging after neoadjuvant chemotherapy. However, the trial did not meet the predefined cut-off for significance for MFS to declare the risk-adapted approach noninferior[16]. Alternatively, results from the phase 2 HCRN GU 16-257 trial were more encouraging. This trial reported a clinical CR of 43% with gemcitabine, cisplatin, and nivolumab therapy after TURBT. Patients with a clinical CR also had significantly better MFS and OS[17]. Phase 3 trials are presently recruiting to examine the role of adding an immune checkpoint inhibitor to bladder-sparing strategies. These include SWOG S1806 (TMT plus atezolizumab, NCT03775265) and KEYNOTE-992 (TMT plus pembrolizumab, NCT04241185).

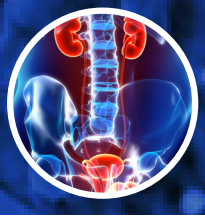
During the Q&A, Dr. Mir noted that, while results of the BladderPath trial are encouraging, it is still early to foresee the future implications for clinical practice of the alternative management pathway with MRI and biopsy evaluated in the trial.

The following presentation was by Dr. Patrick O. Richard (Canada), who examined the 5 practice-changing advances on the horizon for kidney cancer. First, Dr. Richard discussed advances in the role of active surveillance in the management of complex renal cysts. The Bosniak classification of cystic renal masses was updated in 2019, aiming to reduce inter-reader variability among radiologists[18]. Tse and collaborators[19] applied the updated system to retrospectively determine the prevalence of malignancy and histopathological features of Bosniak class III and IV masses. The prevalence of malignant Bosniak III masses ranged from 49% to 76% and of malignant Bosniak IV from 76% to 87%. This suggests that up to 51% of Bosniak III and up to 24% of Bosniak IV cysts are likely to be benign. It has been demonstrated that malignant cystic renal cell carcinoma (RCC) may have a cancer-specific survival of up to 100% after 10 years following excision[20]. Stage for stage, malignant renal cysts have better prognosis and are more indolent than solid RCC[21]. Malignant cysts appear to grow slowly, even on active surveillance[22], and have low metastatic potential[23–27]. Therefore, the current surgery-based management of malignant renal cysts leads to considerable overtreatment.

While active surveillance may provide an alternative to reduce overtreatment of renal cysts, it is also important to consider whether this approach is oncologically safe. Despite the limited evidence available, 4 retrospective studies of active surveillance with follow-up ranging from ~2 to 5.5 years have demonstrated metastatic rates ≤ 1.2% and ≤ 3.4% for Bosniak III and IV, respectively[24–27]. Treatment rates were 16% to 30% for Bosniak III and 14.2% to 62% for Bosniak IV across studies, suggesting that the majority of patients stayed on active surveillance. Therefore, this approach may be oncologically safe for some patients.

It is important, however, to carefully consider which patients are eligible for active surveillance, as well as how those patients should be followed and when to intervene. Because good quality data for renal cysts are scarce, in 2023 the Canadian Urological Association (CUA) proposed an update of the guidelines for the management of cystic renal lesions[28]. This update adopted intervention and follow-up criteria based on the literature available for small renal masses. In Canada, the observational SOCRATIC multicentre study (NCT04558593) is currently recruiting to compare active surveillance vs. surgery, with the goal to better inform the safety of active surveillance in the management of complex renal cysts.

Second, Dr. Richard discussed the role of cytoreductive nephrectomy in 2023. CARMENA was a phase 3 trial that compared upfront cytoreductive nephrectomy with the tyrosine kinase inhibitor (TKI) sunitinib vs. sunitinib alone[29]. The trial demonstrated that sunitinib alone was not inferior to cytoreductive nephrectomy followed by sunitinib in patients with metastatic clear cell RCC (ccRCC) with intermediate- or poor-risk disease.



Despite these results, cytoreductive nephrectomy still has a role in the management of metastatic ccRCC. In a retrospective study of newly diagnosed patients, deferred cytoreductive nephrectomy after sunitinib was shown to improve progression-free survival (PFS) and OS compared to sunitinib alone or upfront surgery followed by sunitinib[30]. In the prospective, randomized SURTIME trial, deferred cytoreductive nephrectomy vs. upfront surgery showed significant OS improvement in the intent-to-treat population (HR = 0.57; 95% CI, 0.34 to 0.95; *P* = 0.03); however, statistical significance was not seen in per-protocol analysis[31]. In the era of immunotherapy for metastatic ccRCC, retrospective data suggest that cytoreductive nephrectomy may even improve OS outcomes when combined with immunotherapy-based regimens compared to immunotherapy alone[32].

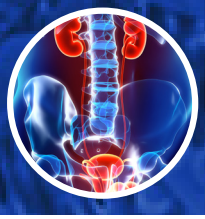
Understanding which patients may benefit from upfront cytoreductive nephrectomy is still challenging. Recently, the SCREEN score was proposed to improve surgical risk stratification by integrating common radiologic features with known prognostic factors associated with mortality within the first year after surgery[33]. The score incorporates 7 criteria for risk stratification: presence of systemic symptoms, number of metastases ≥ 3, total metastatic tumour burden ≥ 5 cm, presence of bone metastases, presence of anemia, low albumin, and neutrophil to lymphocyte ratio > 4. The SCREEN score was shown to predict 1-year mortality better than the International mRCC Database Consortium (IMDC) criteria[33].

Dr. Richard highlighted that randomized controlled trials are needed to examine the role of cytoreductive nephrectomy in the era of immunotherapy. Trials are ongoing. He noted that cytoreductive nephrectomy should be considered for palliation in patients with symptomatic primary tumours and those with intermediate-risk IMDC, based on individualized decision-making through a multidisciplinary team. Deferred cytoreductive nephrectomy may be considered for patients with partial response or CR after systemic therapy, although determining the ideal time for surgery is challenging.

Third, Dr. Richard examined treatment advances for non-ccRCC. The phase 2 PAPMET trial compared sunitinib with the MET-directed inhibitors cabozantinib, crizotinib, and savolitinib in patients with metastatic papillary RCC. While the crizotinib and savolitinib arms were closed early due to futility, cabozantinib resulted in longer PFS compared to sunitinib (9.0 vs. 5.6 months; HR = 0.60; 95% CI, 0.37 to 0.97; 1-sided *P* = 0.019)[34]. The objective response rate (ORR) was higher with cabozantinib than sunitinib (23% vs. 4%; 2-sided *P* = 0.010). Two small studies reported results earlier in 2023. In cohort 10 of COSMIC-021, the combination of cabozantinib plus atezolizumab was evaluated in metastatic non-ccRCC, resulting in an ORR of 31%[35]. Another phase 2 trial that examined treatment with cabozantinib plus nivolumab in a similar patient population demonstrated an ORR of 54% with the combination, as well an ORR of 47% in papillary tumours[36]. Importantly, the phase 2 KEYNOTE-B61, which evaluated treatment with pembrolizumab plus lenvatinib in 158 patients with non-ccRCC, recently demonstrated an ORR of 49% in the overall cohort, 54% in the papillary RCC cohort, and 28% in chromophobe RCC cohort[37]. Based on these results, Dr. Richard noted that pembrolizumab plus lenvatinib may be considered a new standard-of-care option in non-ccRCC until higher quality evidence becomes available.

Fourth were advances in sequencing of checkpoint inhibitor therapy for metastatic RCC. The phase 1b/2 KEYNOTE-146 trial examined the role of pembrolizumab plus lenvatinib in treatment-naïve or previously treated patients with metastatic RCC[38]. A median PFS of 12.2 months (95% CI, 9.5 to 7.7) was observed. In patients previously treated with an immune checkpoint inhibitor, treatment with pembrolizumab plus lenvatinib resulted in an ORR of 58%, which suggests that immunotherapy rechallenge may have activity in some patients. Interestingly, up to 20% of patients in the United States have received a second-line immune checkpoint inhibitor rechallenge for metastatic RCC, based on real-world data[39].

Results of the open-label, phase 3 CONTACT-03 trial were recently published[40]. The trial investigated the combination of atezolizumab plus cabozantinib vs. cabozantinib alone in patients with metastatic RCC who progressed with previous immune checkpoint inhibitor treatment. No improvements in PFS or OS



Five Practice-Changing Advances on the Horizon Summary

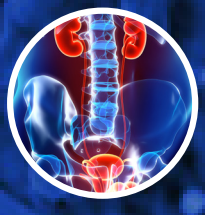
were seen with the combination. Additionally, grade ≥ 3 and serious adverse events were more frequent with atezolizumab plus cabozantinib vs. cabozantinib alone[40]. These results do not support the addition of atezolizumab to targeted therapy after progression on previous immune checkpoint inhibitor. Importantly, these results highlight the need for phase 3 trials, even in the presence of encouraging phase 2 data. Further prospective trials are required to better understand if immunotherapy with an alternative mechanism of action might be of benefit for rechallenge.

CONTACT-03 did not address 2 important questions: (1) if rechallenge is feasible after a delayed period since previous immunotherapy and (2) if rechallenge is feasible post adjuvant treatment with pembrolizumab. In 2023, participants at the Canadian Kidney Cancer Forum developed consensus statements regarding management of ccRCC after adjuvant therapy[41]. Patients who experience recurrence ≥ 6 months after completion of adjuvant therapy should be offered standard-of-care first-line treatment for metastatic ccRCC. However, those who recur during treatment or within 6 months of completing adjuvant therapy should be treated similarly to patients who have progressed on first-line immunotherapy for metastatic ccRCC.

Lastly, Dr. Richard presented advances in radioligand therapy for RCC. Results of the phase 3 ZIRCON trial demonstrated encouraging performance of zirconium-89 (^{89}Zr)-girentuximab in the diagnosis of renal masses[42]. Girentuximab is a tracer that targets carbonic anhydrase IX (CAIX), a cell surface glycoprotein that is overexpressed in ccRCC[43]. Similar to advances in targeting the prostate-specific membrane antigen (PSMA) with the radioligand lutetium-177 (^{177}Lu)-PSMA, girentuximab may be linked to ^{177}Lu to target CAIX-expressing RCC cells. This approach is currently under investigation in 2 clinical trials in metastatic ccRCC: in STARLITE 2 (NCT05239533), which is examining ^{177}Lu-girentuximab in combination with nivolumab, and in a study from the MD Anderson Cancer Center (NCT05663710), which is evaluating ^{177}Lu-girentuximab in combination with cabozantinib and nivolumab. Results of these phase 2 trials are eagerly awaited.

During the Q&A, Dr. Richard noted that metastatic burden as well as histological subtype are important in guiding patient selection for upfront cytoreductive nephrectomy. For instance, a patient with chromophobe RCC may not respond well to systemic therapy. However, if a patient has diffuse metastatic disease, that patient is unlikely to derive any benefit from upfront cytoreductive nephrectomy, regardless of the histology. Dr. Richard also commented that cabozantinib and pembrolizumab plus lenvatinib are currently the best supported treatments for non-ccRCC, based on phase 2 prospective trials. No other treatment combinations are supported, according to the current evidence. Lastly, Dr. Richard explained that the SOCRATIC study is enrolling patient with lesions up to 7 cm. It is believed that the solid component might be more important than the cystic component, but currently there is no evidence to support this hypothesis. He mentioned that the current CUA guidelines do not discriminate between Bosniak III and IV due to the lack of strong evidence to support greater risk of metastases and aggressiveness in Bosniak IV vs. Bosniak III. The guidelines recommend active surveillance as the preferred approach in lesions < 2 cm and propose active surveillance or surgery as the preferred approaches in lesions 2 to 4 cm. These recommendations are mainly based on indirect evidence from the small renal masses literature.

Concluding this session was a presentation by Dr. Kirsten L. Greene (United States) on the 5 practice-changing advances on the horizon for prostate cancer (PCa). Dr. Greene first focused on the use of PSMA positron emission tomography (PET)/computed tomography (CT) for PCa detection prior to biopsy. While the availability of PSMA PET/CT is still limited, the possibility of implementing this imaging approach to support PCa diagnosis has been explored. In a prospective study, 60 patients with median prostate-specific antigen (PSA) of 30 ng/mL underwent PSMA PET/CT prior to biopsy[44]. The positive predictive value (PPV) of PSMA PET/CT was 86.7%. Lesions suspicious for PCa were observed in all scans. PSMA-guided biopsies detected PCa in 56/60 (93.3%) of patients. In another prospective study, PSMA PET/CT was



performed in 81 patients with suspected PCa with either an elevated PSA 4 to 12 ng/mL or abnormal digital rectal examination (DRE)[45]. PSMA PET/CT performed with an accuracy of 85% and AUC of 0.876. Biopsy was positive in 31/81 (38.3%) patients.

The addition of MRI to PSMA PET/CT can help improve the diagnostic performance of imaging for clinically significant PCa. This was seen in the prospective PRIMARY study, in which the combination of PSMA PET/CT plus mpMRI improved the negative predictive value (NPV) and sensitivity for diagnosing PCa, suggesting the potential of this approach to reduce unnecessary biopsies[46]. Dr. Greene noted that this is particularly important in countries where other biomarkers are limited, as MRI and PET/CT appear to be more widely available.

Taking a step forward, a prospective cohort study examined the role of preoperative mpMRI and PSMA PET/CT, in addition to clinical criteria, to guide radical prostatectomy without a prostate biopsy. All patients had PCa at the time of radical prostatectomy and many were high risk[47].

The second advance is on imaging equipment with long axial field of view PET scanners, also known as Quadra. This equipment is manufactured in limited quantities (~10 per year) and has a feature called ultra-high sensitivity mode[48,49]. Quadra has the potential for improved sensitivity, such as detecting 1 mm lesions compared to the threshold of 5 mm lesions with current PSMA PET scans; lower radiation dose; and improved image quality. However, these PET scanners have limitations, such as the cost and the required training to operate the equipment and interpret scans. In an initial evaluation of clinical performance, the long axial field of view PET scanner demonstrated improved imaging sensitivity but different timing for reading the PET scan compared to standard PET scan[50].

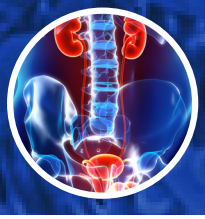
The third advance is the intraoperative visualization of lesions with PSMA-linked fluorescence. In a first-in-human evaluation, a novel near-infrared PSMA-targeted fluorescence imaging agent was evaluated in patients with high-risk PCa undergoing robotic-assisted radical prostatectomy[51]. A dose of 25 µg/kg was administered 24 hours prior to surgery. A higher dose incurred in higher rate of false positives in lymph nodes. The areas with agent uptake were visualized with commercially available Firefly fluorescence imaging. In lymph nodes, the fluorescent PSMA agent performed with a PPV of 97% and NPV of 45%. On residual disease, the PPV was 100% and the NPV was 80%, highlighting the utility of this approach on surgical margins. Notably, 29% of patients had disease seen only on sensitive Firefly fluorescence. Concordance with pathology was 63%[51].

A phase 2a feasibility trial investigated the intraoperative imaging performance of OTL78, another PSMA-targeted fluorescent tracer[52], and identified the optimal dosing of 0.03 mg/kg 24 hours before surgery. The sensitivity for positive margins was 82%. Similarly, this study also showed dose-dependent false positive rates for lymph nodes.

The fourth advance is in developments in PCa theranostics. Beta emitters, such as ^{177}Lu, have a depth of penetration ranging from 0.7 to 2.1 mm. On the other hand, alpha emitters, such as actinium-225 (^{225}Ac), have a much narrower depth of penetration of 47 to 85 µm, which may make them more attractive for PCa radioligand therapy[53]. Currently, ^{177}Lu-PSMA-617 is the only radioligand available for the treatment of metastatic castration-resistant PCa (mCRPC). Several alpha and beta isotopes are under investigation for PCa theranostics, which may open the possibility of rechallenging a patient with a different radioligand in the future.

Theranostics are also under investigation in earlier PCa settings. In the phase 1/2 LuTectomy trial, the efficacy of upfront ^{177}Lu-PSMA was investigated in 20 patients with high-risk localized PCa[54]. ^{177}Lu-PSMA resulted in partial responses in 55% of patients, and 45% achieved a PSA decline > 50% from baseline. Ultimately, all patients underwent robotic radical prostatectomy. While these results are encouraging, ^{177}Lu-PSMA did not eradicate PCa completely.

The combination of ^{177}Lu-PSMA with other systemic agents is also under investigation. In the phase 1 PRINCE trial, ^{177}Lu-PSMA combined with pembrolizumab resulted in a median radiographic PFS (rPFS) of 11.2 months. The 12-month rPFS and OS were 38%



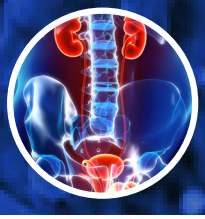
and 83%, respectively[55]. In the currently recruiting phase 2 EVOLUTION trial (NCT05150236), ^{177}Lu-PSMA in combination with ipilimumab and nivolumab will be evaluated in patients with mCRPC. In metastatic hormone-sensitive PCa (mHSPC), ^{177}Lu-PSMA in combination with standard of care (androgen receptor pathway inhibitor [ARPI] and androgen deprivation therapy [ADT]) is being examined in the phase 3 PSMAddition trial (NCT04720157).

The fifth advance presented by Dr. Greene was the solidification of focal therapy's place as a well-studied initial treatment for PCa. A prospective, multicentre analysis of 1379 patients treated with focal high-intensity focused ultrasound (HIFU) in the United Kingdom demonstrated a failure-free survival (FFS) of 69% at 7 years[56]. For patients with intermediate- and high-risk PCa, 7-year FFS rates were 68% and 65%, respectively. At 7 years, MFS and PCa-specific survival rates were 100% and OS was 97%.

A trial of 106 patients randomized to either focal or extended irreversible electroporation (IRE) resulted in a treatment failure rate between 22.6% and 25% with either approach at 6-month biopsy[57]. Another study examined MRI-guided HIFU in 101 patients with intermediate-risk PCa. At 24 months, 78/89 (78%) of patients had no evidence of grade group ≥ 2 PCa in the treated area[58].

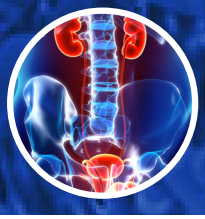
It is important to note that focal therapy is seen as an attractive treatment option by many patients, partly because of its lower impact on QoL, including sexual function. Good quality evidence exists and more trials are underway to evaluate various focal therapy options, which may lead to important revisions in clinical practice guidelines[59,60]. Therefore, focal therapy should be accepted as a conventional treatment in adequately selected patients.

During the Q&A, Dr. Greene discussed whether there is a role for prophylactic prostatectomy in men who have prognostic *BRCA* alterations but no evidence of PCa. In her opinion, there is not currently a role for prophylactic prostatectomy as it has such a tremendous impact on QoL. Dr. Greene also addressed the potential of PSMA PET/CT prior to biopsy to improve outcomes of focal therapy. There are some trials and case series that have investigated this approach and showed encouraging results. While one of the studies that she presented used only imaging to support radical prostatectomy, Dr. Greene noted that the current standard of care required to guide decision-making in nearly all practices is a diagnosis of clinically significant PCa using biopsy. In the future, it might be possible to identify a maximum standard uptake value (SUVmax) for PSMA PET to omit a biopsy in clinical practice. In this context, PSMA PET/MRI may be an important approach to guide these procedures. Lastly, Dr. Greene addressed potential differences between positive surgical margins with neurovascular structure-adjacent frozen-section examination (NeuroSAFE) and intraoperative fluorescence. She believes that intraoperative fluorescence offers the advantage of directly seeing the fluorescent tissue during resection and definitively resecting that tissue, as opposed to NeuroSAFE, which does not actually visualize the tissue of concern at the time of resection.



Abbreviations Used in the Text

^{177}Lu	lutetium-177
AUC	area under the curve
BCa	bladder cancer
BCG	bacillus Calmette-Guérin
CAIX	carbonic anhydrase IX
ccRCC	clear cell renal cell carcinoma
CG0070	cretostimogene grenadenorepvec
CI	confidence interval
CIS	carcinoma in situ
CR	complete response
CT	computed tomography
CUA	Canadian Urological Association
DFS	disease-free survival
FFS	failure-free survival
HR	hazard ratio
IL	interleukin
IMDC	International mRCC Database Consortium
mCRPC	metastatic castration-resistant prostate cancer
MFS	metastasis-free survival
MIBC	muscle-invasive bladder cancer
mpMRI	multiparametric magnetic resonance imaging
MRI	magnetic resonance imaging
NeuroSAFE	neurovascular structure-adjacent frozen-section examination
NMIBC	non–muscle-invasive bladder cancer
NPV	negative predictive value
ORR	objective response rate
OS	overall survival
PCa	prostate cancer
PET	positron emission tomography
PFS	progression-free survival
PPV	positive predictive value
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
QoL	quality of life
RCC	renal cell carcinoma
rPFS	radiographic progression-free survival
SLND	standard lymphadenectomy
TMT	trimodal therapy
TURBT	transurethral resection of bladder tumour
VI-RADS	Vesical Imaging–Reporting and Data System



Five Practice-Changing Advances on the Horizon Summary

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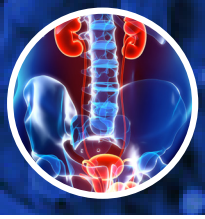

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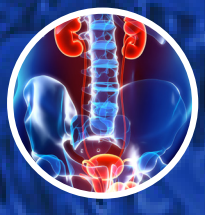

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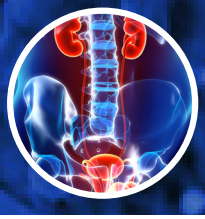

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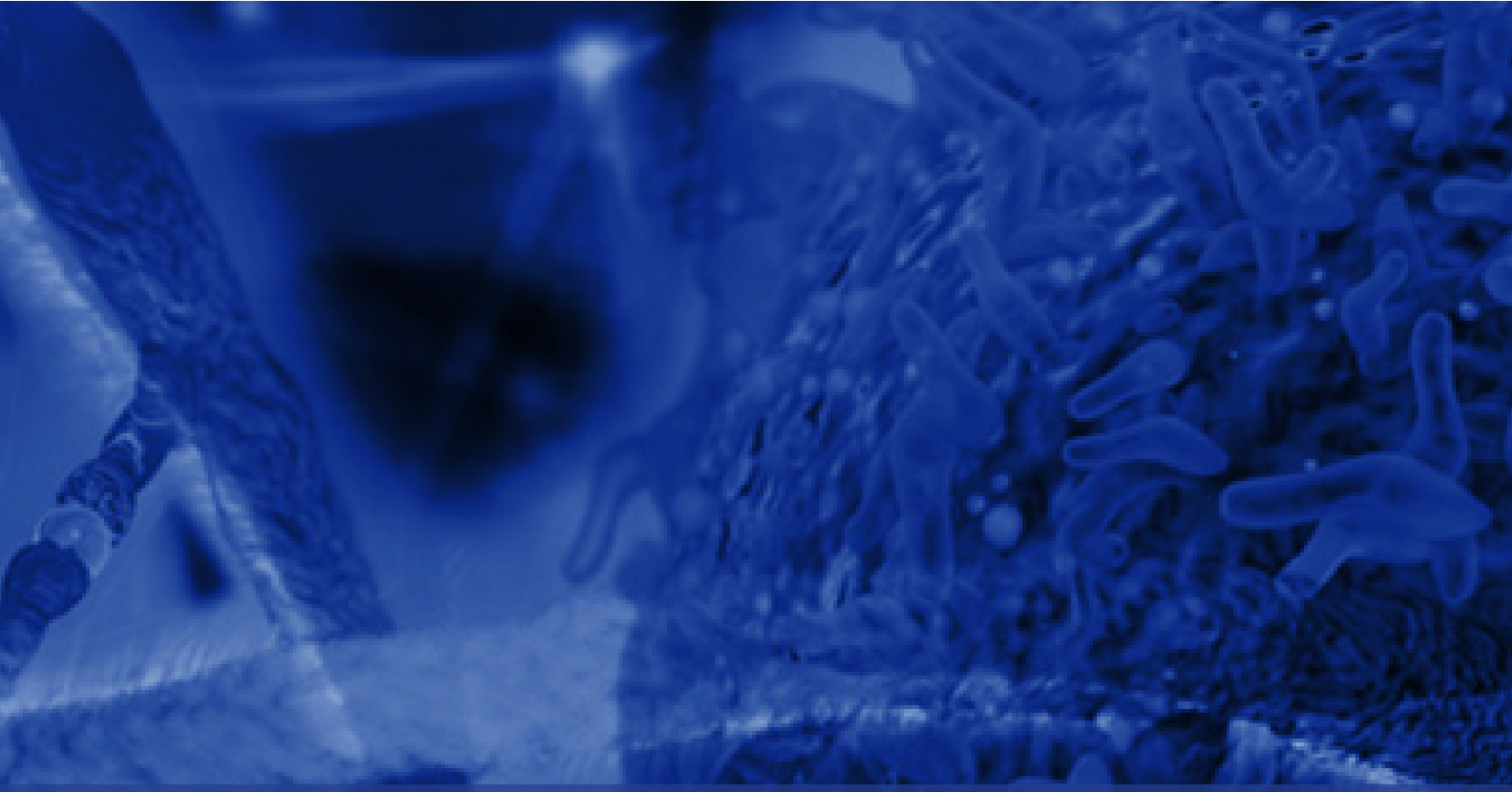

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