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Conference Report

B2B: Kidney Cancer Summary

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The 6th Bench-to-Bedside Uro-Oncology: GU Cancers Triad Meeting, organized in conjunction with the 44th Annual Congress of the Société Internationale d'Urologie, was held on 25 October 2024, in New Delhi, India, and transmitted live on the *SIU@U* Congress platform. The second session, on kidney cancer (KCa), took place in the afternoon and was moderated by Dr. Simon Tanguay (Canada) and Dr. Maxine Tran (United Kingdom). This session began with a presentation on whether partial/radical nephrectomy (PN/RN) will be obsolete by 2030, and was followed by two debates, the first on use of stereotactic body radiation therapy (SBRT) vs. percutaneous ablation for small renal masses, and the second on use of enucleation in PN. The next presentation was about adjuvant therapy for KCa, and the final session was on systemic therapy in non–clear cell renal cell carcinoma (nccRCC).

First, Dr. Tran discussed the contemporary utility of diagnostic PN/RN. She explained the disadvantages of current diagnostic practices, particularly with respect to patient exposure to what may result in unnecessary surgical interventions. For instance, a study of more than 15 million Medicare patients in the United States, aged 65 to 85, found that receiving a thoracoabdominal computed tomography (CT) scan was associated with an increased likelihood of intervention to the kidneys. In fact, increased risk of CT use was correlated with increased risk of undergoing nephrectomy (r = 0.47, 95% confidence interval [CI] 0.31–0.16) [1].

Not all kidney tumours are cancers. In a study of 18,060 patients who received PN, 30.9% had benign findings [2]. Importantly, surgery for a benign tumour carries the same risks as surgery for a cancerous tumour. A 2012 British Association of Urological Surgeons (BAUS) audit revealed that, among 1044 PNs performed in the United Kingdom, the rate of Clavien-Dindo (CD) classification ≥ 3 complication was 5%, and 4% of procedures were converted to an RN. The benign pathology rate was 18% overall and as high as 36% among those under the age of 40 [3].

There is a need for better diagnostic tools, particularly in the setting of small renal masses. Current diagnostic tools are limited to cross-sectional images, usually derived from triple-phase CT, which can indicate whether a tumour is enhancing (solid) or not, but does not definitively indicate whether it is cancerous. An analysis of the BAUS audit data from

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2013 to 2017 revealed that, among 32,130 PN/RNs, there were 1202 renal oncocytomas. The rate of CD $\geq$ 3 complications was 4%, and there were 5 deaths within 60 days of surgery [4]. In addition, in patient forums, patients report that they feel considerable anxiety and guilt when undergoing resection of what turns out to be a benign mass.

Currently available presurgical diagnostic tools for renal tumours include percutaneous renal tumour biopsy (RTB). A systematic review and meta-analysis revealed that it is safe and accurate, with a diagnostic rate of 92%, core biopsy sensitivity of 99.1%, and specificity of 93.2% [5]. Nevertheless, uptake of RTB remains very low, although its use is increasing. The primary concern is the risk of tumour seeding, according to several single-centre studies [6–8]. Dr. Tran noted the oddity that concern about seeding is much greater for KCa than for many other solid tumour cancers. The clinical significance of this risk is yet to be determined.

Percutaneous RTB presents with several limitations. It remains an invasive procedure, requires a temporary halt of anticoagulants, does not address tumour heterogeneity, is unsuitable for cystic tumours, and may not be feasible depending on the tumour size and location. Nevertheless, European Association of Urology (EAU) guidelines recommend renal mass biopsies prior to active surveillance or ablative therapy [9].

Another diagnostic tool is ^{99m}technetium sestamibi (MIBI) single photon emission CT (SPECT)/CT. MIBI is lipophilic and cationic, so cells with a high mitochondrial content appear very bright on the scans [10]. In a systematic review and meta- analysis of 489 patients with 501 renal masses who underwent this modality, MIBI SPECT/CT demonstrated a sensitivity for oncocytoma and hybrid oncocytic/chromophobe tumours (HOCT) (vs. all other renal lesions) of 89% (95% CI = 70–97%) and a specificity of 98% (95% CI = 91–100%). Nevertheless, there was a high risk of bias and heterogeneity amongst the studies, so the level of evidence remains low [11]. Another limitation is the inability to distinguish among chromophobe renal cell carcinoma (chRCC), HOCT, and low-grade oncocytic tumours. Fortunately, these are all indolent tumours with a good prognosis. It also remains unclear how cystic tumours present under MIBI SPECT/CT. Tran and colleagues will soon report on the results of the Multi-MIBI study, a prospective multicentre feasibility study exploring whether MIBI SPECT/CT can be introduced into the diagnostic KCa pathway, using histology as the reference standard [12]. This trial has completed recruitment at 6 sites in the United Kingdom.

Yet another available tool is ^{89}zircon-DFO-girentuximab for positron emission tomography (PET)/CT. Girentuximab is a monoclonal antibody for carbonic anhydrase IX (CAIX), which is highly expressed (90%) in clear cell renal cell carcinoma (ccRCC). In the multicentre, international, open-label ZIRCON trial, the sensitivity for detecting ccRCC was 85.5% (95% CI = 81.5–89.6%), and the specificity was 87% (95% CI = 81–93.1%) [13]. While this modality certainly has utility, said Dr. Tran, it is limited by the fact that uptake is not specific to ccRCC. Papillary tumours and benign oncocytomas can also have uptake of CAIX because it is a nonspecific marker of hypoxia. In addition, approximately 10% of ccRCC tumours do not express CAIX. Finally, the practicalities of this scan may limit its use. Dosing of the radioactive tracer and the scan itself must be performed several days apart. Some of its greatest potential promise is in the detection of occult metastases, according to a phase 1 study [14].

The liquid biopsy is the holy grail of diagnostic tools, as it is totally noninvasive, said Dr. Tran. The ultimate goal is to identify a biomarker relevant to KCa. Ones that have been tested include circulating tumour cells, cell-free DNA, and extracellular vesicles (EVs), but to date no trials have confirmed their clinical utility. The greatest promise appears to be for EVs because they are more abundant in the circulation and secreted fluids [15].

In conclusion, to answer the question as to whether diagnostic PN/RN will be obsolete in 2030, Dr. Tran does not believe it will be. Nevertheless, she hopes that diagnostic PN/RN will be used less frequently and that the final diagnosis will not be as much of a surprise to as many patients following surgery. Hopefully, new diagnostic techniques will allow for more accurate distinction between benign and cancerous tumours prior to surgery.

During a Q&A, an attendee asked why National Comprehensive Cancer Network guidelines recommend biopsy for cystic lesions if biopsy is unsuitable for these types of tumours. Dr. Tran replied that biopsy is still used in cystic lesions in cases of a Bosniak 3 or 4 solid nodule > 15 mm. Dr. Tran added that she offers biopsy to all patients with a small renal mass if they are candidates for active treatment, and about 60% of patients agree to undergo biopsy.

Next was a debate moderated by Dr. Tanguay on nonsurgical management of the small renal mass: SBRT vs. percutaneous ablation. Dr. Vedang Murthy (India) presented the case for SBRT. He started by pointing out that there is a large body of evidence supporting SBRT in this setting, including at least a dozen prospective trials and randomized controlled trials (RCTs) [16–19], as opposed to none for thermal ablation in this setting.

For instance, the 2022 International Radiosurgery Consortium of the Kidney individual patient meta-analysis of SBRT for primary renal cell carcinoma (RCC) revealed 92.0% cancer-specific survival, 5.5% local failure, and 10.8% distant failure at 5 years [18]. More recently, the nonrandomized phase 2 FASTRACK II trial of SBRT for RCC yielded a 5-year local control rate of 100% [19].

This high control rate can be achieved with a low risk of complications, with grade 3 to 4 complication rates ranging from 1% to 4% [20]. A meta-analysis of 42 studies conducted from 2013 to 2023, which evaluated outcomes of treating RCC tumours with a median size of 3.4 cm, revealed that SBRT was associated with a 0.2% risk of grade 3 to 5 toxicity, which was lower than the risk associated with ablation (4.3%) and PN (4.7%) [21].

Importantly, tumours of any size can be treated with SBRT. Small renal masses can be treated with one fraction, while larger masses can be treated with up to 3 or even 5 fractions, all with very high rates of local control [16,17,19]. In contrast, for thermal and percutaneous ablation, increasing tumour size is associated with poorer outcomes [22]. In fact, 2022 EAU guidelines do not recommend these techniques for renal masses > 3 cm [9].

Tumour location is not an impediment for SBRT. In the FASTRACK II trial, as many as 43% of patients had high R.E.N.A.L. Nephrometry Score, and this did not limit use of SBRT. Involvement of the pelvicalyceal system and vessels does not represent a problem. The only challenge is bowel involvement, but this presents issues for most percutaneous techniques [19]. By contrast, for radiofrequency ablation (RFA) and cryoablation of lesions close to the renal pelvis, the phenomenon of heat/cool sink reduces efficacy. That can be countered with multiple probes or longer duration of treatment, but this is time- and cost-inefficient, as well as being associated with a higher risk of complications [23]. For "safe" tumours, microwave ablation works well, but for any tumours near the bowel or renal pelvis, local progression has been shown to be up to tenfold higher [24].

SBRT can be used for RCC tumours regardless of histology. On the other hand, there is evidence that thermal ablation does not perform as well with ccRCC as with papillary RCC (pRCC) or nccRCC [25,26], possibly due to the high vascularity of these tumours, which could result in loss of heat during ablation.

An important benefit of SBRT is access. Interventional radiologists, who perform ablation, are generally located in large centres, at least in India, but are less likely to be present in secondary or tertiary centres. On the other hand, SBRT requires a simple setup with a standard linear accelerator that has good image guidance. Such setups are more widely available than those required for ablation. In addition, SBRT is a noninvasive

procedure that does not require sedation or anesthesia. It takes only about 5 to 7 min to perform. In contrast, cryoablation requires 2 to 3 h of anesthesia, which can be especially challenging in patients with multiple comorbidities.

In the RADSTER trial, RFA was compared with SBRT among 24 patients with biopsy-confirmed RCC. It demonstrated that RFA had significantly higher rates of negative biopsy at 1 year (100% vs. 31%) and loss of enhancement (83% vs. 23%) [27]. What the study failed to take into account, however, is that repeat biopsy should not be performed after SBRT because the masses decrease over several years [28]. In addition, CT scans are not indicated because lesion enhancement is not correlated with progression [29].

Dr. Murthy concluded that SBRT is a superior choice because it has the most evidence, results in high rates of disease control, has a low risk of complications, can be used in a wide range of tumours, is easy to access, and is noninvasive. He also emphasized that there is an overall lack of data regarding selection of surgery, SBRT, or ablation in this setting.

During a Q&A, Dr. Tanguay asked Dr. Murthy how he follows up his patients, given that the tumours remain hypervascular and shrink slowly over time. Dr. Murthy replied that they perform magnetic resonance imaging every 6 months to evaluate the size. They also measure glomerular filtration rate (GFR) and conduct regular clinical follow-up.

Next, Dr. Hazel Warburton (United Kingdom) debated in favour of cryoablation over SBRT for nonsurgical management of small renal masses. Cryoablation, she said, is delivered in a single session, is minimally invasive, demonstrably eliminates all viable tumour, and provides cure as opposed to just failure to progress. As with surgery, it offers the ability to manipulate bowel and minimize ipsilateral parenchymal injury. In contrast, stereotactic ablative radiotherapy (SABR) has a biological effect, rather than an ablative effect.

A cryoablation setup is less expensive than an SBRT setup, particularly if the facility already has a CT scanner in which patients can undergo general anesthesia or heavy sedation. It remains necessary to use argon, but Dr. Warburton now defrosts her needles with electricity, eliminating the need for helium.

Cryoablation does require the expertise of an interventional radiologist, as CT allows for a high degree of accuracy for guiding the needles. Dr. Warburton, herself a urologist working with a team of interventional radiologists, performs the procedure. She presented her data from Manchester University NHS Foundation Trust covering the period from 2013 to 2022. She typically treats all-comers, including patients on whom surgical colleagues do not want to operate or who have a growing positive surgical margin. The age of cryoablation patients ranges from 49 to 87 years, with a mean age of 76. The tumour size has ranged from 8 to 54 mm, with a mean of 28.3 mm. Outcomes from cryoablation are similar to those of patients treated with surgery, with a disease-free survival (DFS) of 97% (excluding the metastatic group), a primary treatment efficacy of 93% (94% with second treatment), overall survival (OS) of 85%, and grade 1 complication rate of 13% (0.9% for grade 2, and no grade 3–5 complications). One death occurred prior to induction due to cardiac arrest in a patient with a low ejection fraction following an anaphylactic reaction to antibiotics. Another patient with an inoperable central 55-mm tumour received 7 needles and experienced a postoperative hemorrhage but ultimately recovered.

In the medical literature, reported 5-year local recurrence-free survival (RFS) using cryoablation for RCC tumours with a median size of 33 mm was 93.9% [30]. In a 10-year prospective study of cryoablation for stage 1 RCC, 10-year DFS was 94%, with an OS that was superior to RN or PN, especially in higher-risk patients (Charlson/Deyo Combined Comorbidity score $\geq$ 2) [31]. Dr. Warburton treats RFA failures with cryoablation, and microwave ablation is available within her institution. Regardless of the type of ablation used, she said, outcomes are good, and morbidity is low [32].

Regarding the FASTRACK II trial mentioned by Dr. Murthy, the endpoint of local control and no progression at 1 year was achieved in all patients, but Dr. Warburton argued that similar outcomes could be achieved with surveillance alone [19]. Patients did experience a drop in GFR. Nevertheless, SBRT can be considered a safe modality in the short term. What remains unclear is what will happen in the long run. A systematic review and meta-analysis suggests a local recurrence rate of 70% to 100% [33]. While these outcomes could indeed be due to inappropriate biopsy and scanning, the issue remains that there is no way to know if the cancer is appropriately treated other than waiting for the occurrence of secondary disease.

Comparing the pros and cons of cryoablation vs. SBRT side-by-side reveals the benefits of cryoablation. In terms of tumour size, guidelines recommend treating tumours up to 40 mm with cryoablation, but Dr. Warburton said that tumours up to 60 mm can be treated with this modality. In contrast, there are no data to guide decision-making about what tumour size is appropriate for SBRT treatment. Cryotherapy is appropriate for all patients who want a definitive treatment for their cancer and is especially appropriate for patients with a low GFR. The only challenge in this setting is that those patients can be difficult to follow up due to limited ability to use contrast agent. SBRT, on the other hand, lowers GFR, so this can be a limiting factor for patient selection. Cryoablation is also appropriate for patients with a toxic abdomen, comorbid conditions, postsurgical recurrence, metastatic disease when there is a new primary tumour, and multiple tumours. There are also data on its efficacy in multiple cell types. Conversely, SBRT is appropriate only among patients for whom palliative care is the only other option, and it can irradiate only one area at a time. The worst complication from cryoablation is the need for a top-up treatment. With SBRT, on the other hand, the biggest risk is that the disease continues to progress unchecked. Cryoablation patients are followed up using tight scrutiny with CT, similar to surgery, but SBRT patients cannot be followed up with either scanning or biopsy. A good outcome with cryotherapy is cure, while with SBRT it is only lack of progression.

Dr. Warburton concluded that cryoablation is curative, safer than surgery, inexpensive, associated with low toxicity, and is suitable for all indications. Thus, the only reasonable question is whether to choose cryoablation or surgery. SBRT, on the other hand, remains experimental and should be reserved for those without the option of surgery or cryoablation. In fact, guidelines consider SBRT an experimental option to use when no other curative therapy is feasible [9,34,35].

During a Q&A, an attendee asked Dr. Warburton if, given that she treats all-comers with cryoablation, there is any indication for PN. She replied that she operates according to guidelines, but data are lacking to confirm their claims that PN should be the gold standard. Some PNs can be quite challenging, such as for central or upper posterior tumours. These can be very successfully treated with cryoablation. Such tumours are at increased risk of complications with focal therapy, however. Sometimes surgery is required following cryoablation, if there are multiple tumours, but it would be difficult to perform a PN following unsuccessful cryoablation.

A second debate followed, moderated by Dr. Tran, about whether enucleation is appropriate during PN. Dr. Gagan Gautam (India) started the debate by arguing the pro side. PN, he said, is the standard of care for small renal masses because it has similar oncological efficacy to RN, with better preservation of renal function and decreased cardiovascular morbidity over the long term [36]. Enucleation is a nephron-sparing surgery in which the tumour is peeled away from the kidney, sparing the pseudocapsule, with a focus on preserving as much healthy tissue as possible. Key advantages of enucleation are better renal function preservation, decreased warm ischemia time, and reduced morbidity. Oncological outcomes are similar.

A 2017 study that compared standard PN with an enucleation technique revealed that preservation of parenchyma and GFR were both superior with enucleation, and these benefits were maintained over time [37]. On a multivariable analysis that took into account non-modifiable risk factors, including age and preoperative GFR, resection technique emerged as one of the greatest predictors of preserved renal function [37]. In a second study, this time comparing robot-assisted tumour enucleation with standard margin, PN revealed better outcomes out to 12 months with enucleation [38]. There is also evidence that robot-assisted enucleation is associated with shorter operative time, shorter warm ischemia time, and better achievement of trifecta, as compared with robot-assisted PN [39].

A recent systematic review and meta-analysis comparing enucleation with standard resection during PN revealed that the enucleation technique was associated with lower odds of complications (odds ratio [OR] = 0.55, 95% CI = 0.34–0.87) and major complications (OR = 0.39, 95% CI = 0.19–0.79), while the odds of positive surgical margins remained similar (OR = 1.89, 95% CI = 0.57–6.29) [40]. Importantly, these benefits are achieved without compromise, as OS and cancer- specific survival have been shown to be similar with enucleation vs. standard PN in follow-up that spanned up to 7 years [38].

There are some situations in which enucleation is the only viable option in order to preserve as much normal parenchyma as possible. These include hilar tumours, multiple (hereditary) tumours, chronic kidney disease, or the case of a solitary functioning kidney. Using 3D virtual modelling for planning an enucleation is an excellent tool for identifying the location of the tumour in relation to the vasculature and the pelvicalyceal system.

Dr. Gautam concluded that enucleation should be the standard of care when conducting a PN because it offers better renal function preservation, decreased warm ischemia time, and reduced morbidity, while still offering similar oncological outcomes.

Next, Dr. Faiz Mumtaz (United Kingdom) argued against use of enucleation. The procedure, he said, is defined as a sharp, anatomical excision technique that requires staying close to the capsule and being certain that there is no parenchymal tissue involved. A standard resection, on the other hand, also involves a sharp excision but is non-anatomical, is performed away from the pseudocapsule, and involves taking a deliberate margin of parenchymal rim. Determining whether a resection was truly an enucleation is based on the surface-intermediate-base (SIB) score. According to this objective scoring technique, complete enucleation requires no parenchymal involvement, resulting in a SIB score of 0. If any parenchyma is involved, it is classified as an enucleo-resection (SIB score 1–3) [41]. The problems with this approach, said Dr. Mumtaz, are that there are no set objective criteria for interpretation, it is difficult to communicate, and the SIB score is not widely used in the medical literature. A resulting lack of a clear definition of enucleation in the medical literature skews the data and introduces bias.

Successful performance of a pure enucleation is dependent on tumour features, surgeon skill level and preferences, as well as the intraoperative scenario of the pseudocapsule and peritumoural tissues, said Dr. Mumtaz. The same group that developed the SIB score also published a study demonstrating that 71% of surgeons use more than one resection technique (enucleation or enucleo-resection) during a PN [42]. A failed enucleation will likely lead to an enucleo-resection because a surgeon must be quite experienced to resect the tumour while sticking closely to the capsule. An inexperienced surgeon may dig slightly into the capsule, causing a positive surgical margin. In fact, achievement of trifecta was lower with enucleo- resection (55%) than either enucleation (70%) or standard resection (70%). Also, the rate of positive surgical margins was 10% with enucleo-resection, compared with 5% for enucleation and 2.2% for standard resection [42].

The feasibility of enucleation depends on the pseudocapsule and peritumoural plane. Certain histological tumour types have a less defined resection plane. For instance, ccRCC

and paragangliomas have the thickest pseudocapsules, while angiomyolipoma/epithelioid tumours have a poorly defined pseudocapsule. Chromophobe tumours have the highest extra pseudocapsule extension, with arteries extending into it, making PN more difficult. Papillary tumours are low enhancing, with a very thin capsule. It is important to be mindful of surgical technique in these situations.

Some situations are particularly challenging for enucleation, including cystic lesions (risk of rupture), when there is an irregular or undefined surface of a tumour bed, potential for infiltration of sinus fat, and when the tumour abuts or invades a segmental vein. Contraindications to enucleation include highly aggressive tumours (Fuhrman grade 4), hereditary leiomyomatosis and renal cell cancer (HLRCC), and collecting duct carcinoma [43]. To perform an enucleation safely, said Dr. Mumtaz, it is imperative to know the margins of the tumour. This requires robotic ultrasound.

High-quality evidence on outcomes of tumour enucleation in the medical literature is limited, he said. In a 2019 systematic review and meta-analysis, most of the included studies were retrospective in nature. The few prospective RCTs that were included have significant limitations related to blinding of participants and personnel, as well as outcome assessment [44]. In other meta-analyses, the level of evidence demonstrating that enucleation is superior to standard PN is usually low in almost all series, with a very high risk of bias in almost all domains [40,45]. A randomized noninferiority trial defined noninferiority for enucleation vs. standard PN as an upper 95% CI bound of <7.5% for the difference in the proportion of patients with a positive surgical margin and then reported that enucleation is superior [46]. This does not support the findings of previous systematic reviews and meta-analyses demonstrating that positive surgical margins are higher with enucleation [40,45].

In the systematic review and meta-analysis first discussed by Dr. Gautam, there was no difference between enucleation and standard PN with respect to operative time and warm ischemia time. While the rate of positive surgical margins was not statistically different, it was numerically higher in the enucleation group. The superior GFR with enucleation may be at least partially due to the fact that PN was often performed clampless [40].

Dr. Mumtaz concluded that while enucleation may be an emerging technique, it requires a high level of experience and specific surgical situations for it to be carried out successfully. Some situations definitely warrant standard PN to ensure the primary objectives of the surgery are met. A high level of experience is also required to identify when it might be necessary to switch from enucleation to standard PN. Finally, there is no conclusive evidence on short-term outcomes or long-term oncological data to advocate superiority of enucleation. RCTs are needed, but ethical issues are a major constraint.

In a Q&A, an attendee asked about the SIB score and how a pathologist can determine if a resection represents a complete enucleation, given that the tumour pseudocapsule is just compressed tissue and there is no sharp delineation between the pseudocapsule and parenchyma. Dr. Mumtaz responded that there is no standardized reporting system. Pathologists do not report whether it is an enucleation or an enucleo-resection. They report only negative or positive margins. This is a problem. Surgeons should inform pathologists about the technique used so it can be reported accordingly. Dr. Gautam added that the most important information is the surgical intraoperative findings and how the surgeon feels about the surgery, rather than the pathologist's report. There is a certain degree of subjectivity involved in determining whether a particular surgery is truly an enucleation but, as his experience has increased, he has crept closer and closer to the capsule.

Dr. Tanguay then asked if the panellists may be concerned about the short degree of follow-up regarding recurrence risk available in the medical literature for pure enucleation, given that patients are increasingly younger in age. Dr. Mumtaz acknowledged that this

remains a pitfall of the procedure. Nevertheless, there is no established surgical margin required for standard PN either. As long as the surgical margin is negative, then long-term outcomes will likely be good. Dr. Gautam agreed but added that the main issue is how the surgical procedure is reported as enucleation vs. enucleo-resection, because currently it is subjective and biased. Ultimately, performing a successful enucleation with negative margins requires an experienced surgeon, a reality that skews the data.

Lastly, an attendee pointed out that reported rates of capsular infiltration are between 20% and 33%, and enquired whether surgeons are missing pseudocapsular infiltration rates by relying on negative margins. Dr. Gautam replied that a negative margin report from the histopathologist means they are observing only parenchyma. When pseudocapsule is present, it will be reported as positive margin.

The next presentation was by Dr. Tanguay, who discussed adjuvant therapy for RCC. The goal of adjuvant therapy, he said, is to prevent recurrence and improve cure rate. Toxicity remains a limiting factor, however, and it is important not to overtreat the patient. Finally, adjuvant therapy ideally should not affect treatment options if the cancer later becomes metastatic.

Previous clinical trials revealed that the tyrosine kinase inhibitor (TKI) sunitinib in the adjuvant setting improves DFS but not OS and has a relatively high rate of toxicity [47]. Despite approval of adjuvant sunitinib, uptake was never high. The KEYNOTE-564 trial changed the RCC landscape. This trial compared adjuvant pembrolizumab with placebo in higher-risk RCC patients. Most of the patients (85%) in the trial were M0 intermediate-high risk, and only about 5% had metastatic disease, with resection of their metastasis in the first year following diagnosis. Another 10% had sarcomatoid features. The first reports demonstrated an improved DFS with pembrolizumab at 24.1 months (hazard ratio [HR] = 0.68, 95% CI = 0.53–0.87), which was maintained through to 30.1 months (HR = 0.63, 95% CI = 0.50–0.80) [48]. Subgroup analyses revealed that higher-risk disease was associated with greater benefit from pembrolizumab [48], but Dr. Tanguay warned that the highest risk patients were a very small group. Importantly, sarcomatoid tumours did have a DFS benefit with pembrolizumab (HR = 0.54, 95% CI = 0.29–1.00) [48].

Follow-up of 57 months is now available for KEYNOTE-564, and the impact on DFS remains the same (HR = 0.72, 95% CI = 0.59–0.87). In fact, the separation between the placebo and pembrolizumab curves remains about the same over time, and DFS benefits were observed in all evaluated subgroups [49]. This update also included a report of OS in an intent- to-treat (ITT) analysis, demonstrating an OS benefit in favour of pembrolizumab (HR = 0.62, 95% CI = 0.44–0.87) [49]. This is the first time a drug was shown to offer an OS benefit in the adjuvant setting in this patient population. Again, subgroup analyses favoured the use of pembrolizumab in all subgroups [49]. This trial led to the approval of pembrolizumab as adjuvant therapy in the United States, Canada, and Europe.

There is a concern that all other studies with immune checkpoint inhibitors in the adjuvant setting performed at the same time were negative, including IMmotion010 (atezolizumab vs. placebo) [50], PROSPER (nivolumab vs. observation in the perioperative setting) [51], and CheckMate 914 (Part A: nivolumab plus ipilimumab vs. placebo; Part B: nivolumab monotherapy vs. placebo) [52,53]. Importantly, the patient populations were all slightly different in these studies. For instance, in PROSPER, because patient selection was made before surgery, many of the included patients were pT1 or pT2, which is associated with a low risk of recurrence [51]. In CheckMate 914, M1 with no evidence of disease (NED) patients were not included, but the study included a fair number of patients with pT2 tumours, which also may have a lower risk of recurrence [52,53]. In addition, toxicity was a major issue in CheckMate 914, with 33% of patients discontinuing due to

toxicity [52,53]. This was about double the discontinuation rates due to toxicity seen in the other studies [49–51].

All the tools used today to predict progression in RCC are related to clinical and pathological evaluation [54]. What remains unclear is the degree to which individual tumour biology plays a role. Recent research explored the potential prognostic role of a genomic classifier in RCC [55]. Using this classifier, patients who qualified for adjuvant therapy in the KEYNOTE-564 trial had a worse prognosis than those who did not. Among patients who did quality for adjuvant treatment, the genomic classifier helped further stratify and predict DFS over 5 years [55]. There is potential, therefore, to use genomic classifiers such as this one to identify the highest-risk patients for adjuvant therapy and spare those patients with the best prognosis.

Current EAU guidelines have a weak recommendation to use adjuvant pembrolizumab in high-risk ccRCC [56], but Dr. Tanguay expects this will be updated soon because these recommendations were provided before the OS data in CheckMate 914 became available. The guidelines also strongly recommend discussing toxicity, negative results of other studies, and potential impact on long-term outcomes with patients [56].

A lingering question is how giving pembrolizumab in the adjuvant setting will affect treatment options in the metastatic setting. There is a paucity of available evidence to answer this question. In one retrospective study, investigators examined patients who progressed following adjuvant therapy. Many of the patients relapse within the first 3 months after completion of adjuvant immunotherapy (IO). If they received subsequent treatment with IO or a TKI, their response was very similar in both groups [57]. According to Dr. Tanguay, this suggests that first-line therapy consisting of a combination of IO-IO or IO- TKI may not provide the same level of benefit in that patient population. Two studies have reported recently on patients with metastatic disease who were treated with IO and rechallenged a second time with IO. Both of these were negative studies, suggesting that immune checkpoint inhibitors are not likely to be beneficial in these patients.

Regarding tolerability of pembrolizumab, a large study of patients who received IO with pembrolizumab in the adjuvant setting for melanoma, lung cancer, or RCC showed similar side effect rates in each setting. Overall, this is a well-tolerated treatment [58]. A study of patient-reported outcomes in KEYNOTE-564 revealed only a small drop in quality of life [59].

Dr. Tanguay concluded that adjuvant pembrolizumab offers significant improvements in DFS and OS. It is well tolerated, with manageable toxicity. Patient selection for this therapy can be improved with better risk stratification. Questions remain regarding how best to select therapy among patients who will demonstrate disease progression and if these patients will have similar benefit with standard first-line therapy. Nevertheless, for patients, prevention of recurrence is paramount.

During a Q&A, an attendee asked about the potential to recommend SBRT to patients who progress on IO. Dr. Tanguay replied that, when the extent of metastasis is limited, there may be an important role for surgery or SBRT.

The final presentation was by Dr. Shilpa Gupta (United States), who discussed systemic therapy in nccRCC. She explained that ccRCC makes up about 75% of all RCC, pRCC types 1 and 2 make up about 16%, and chRCC about 7%. The final 2% comprises medullary type, translocation type, and collecting duct type RCC [60]. Importantly, nccRCCs are all very different from each other from histopathological, molecular, and genomics points of view, and thus require different treatments. In 2024, the European Society for Medical Oncology (ESMO) updated their guidelines to include molecularly defined nccRCC [61].

For pRCC and chRCC, TKIs targeting vascular endothelial growth factor (VEGF) are effective, as are mammalian target of rapamycin (mTOR) and *MET* inhibitors. For MiT

family translocation tumours, VEGF and mTOR inhibitors have been shown to be effective. Collecting duct RCC responds to VEGF inhibitors, but medullary type RCC has a DNA repair mechanism that makes it inherently resistant to TKIs.

Compared with ccRCC, metastatic nccRCC has a worse prognosis, with OS durations that are about 10 months shorter. The rarity of these entities has contributed to lack of large RCTs and uncertainties for optimal treatment recommendations. There is an unmet need to do more dedicated clinical trials in nccRCC [62]. Traditionally, treatments for nccRCC have been adopted from trials in ccRCC.

The small ESPN trial compared everolimus with sunitinib in nccRCC, showing poor results with both [63]. The PAPMET trial was slightly larger, examining a variety of TKIs in pRCC. It revealed that cabozantinib was more effective than sunitinib in these patients in terms of progression-free survival (PFS) and OS, probably because cabozantinib also inhibits the *MET* and *AXL* pathways [64].

Single-agent IO has been shown to be effective in nccRCC, particularly pRCC. For instance, cohort B of the KEYNOTE-427 trial demonstrated a median PFS of 4.2 months with use of pembrolizumab [65]. Doublet IO-IO therapy has also been shown to be effective, such as in the CheckMate 920 trial, in which ipilimumab plus nivolumab offered a median PFS of 3.7 months and a median OS of 21.2 months [66]. Dr. Gupta noted that while responses were not that high, the tail end of the PFS and OS curves were maintained for a long period of time.

The phase 2 SUNNIFORECAST trial compared ipilimumab plus nivolumab vs. sunitinib among patients with metastatic or locally advanced nccRCC. This is the first prospective RCT of IO-IO vs. a standard of care therapy in this setting. The 12-month OS was 87% with IO-IO therapy vs. 77% with sunitinib ($p = 0.01$), and median OS was 42 vs. 34 months ($p = 0.292$) [67]. Subgroup analysis revealed good activity for IO-IO therapy across histological subtypes [67].

For pRCC, TKIs targeting VEGF and IO have successfully been used in combination in single-arm trials. For instance, cabozantinib plus nivolumab has demonstrated an overall response rate (ORR) of 47% [68]. The ORR was 50% in unclassified tumours without papillary histology as well as in translocation type tumours. Regardless of the histology, the ORR in the first-line setting was 54%, dropping to a still substantial 36% in the second-line setting [68]. In another single-arm trial, lenvatinib plus pembrolizumab had an ORR of 54%, again with efficacy across histological subtypes [69]. The latter finding reflects the experience with lenvatinib plus pembrolizumab in ccRCC as well.

Single-arm trials have also shown efficacy in pRCC with cabozantinib plus atezolizumab (ORR = 47%) [70], but the combination of bevacizumab with atezolizumab was less successful (ORR = 25%) [71] and was not pursued further. Currently, atezolizumab is not being investigated in phase 3 trials in nccRCC.

Savolitinib, an important *MET* inhibitor, has demonstrated preclinical activity and some clinical activity as a single agent in nccRCC [72]. When combined with the IO durvalumab, the ORR was 53% [73]. Dr. Gupta warned, however, that this study comprised only 17 patients. Notably, when the *MET* inhibitor savolitinib was studied alone, the ORR was only 18% [72], so combining *MET* inhibitors with IO appears to be a more promising approach.

Based on the success of SUNNIFORECAST, an ongoing phase 3 RCT is currently comparing ipilimumab plus nivolumab with sunitinib as first-line therapy in advanced pRCC. In another phase 3 RCT, zanzalintinib (a newer generation TKI that also targets MET) plus nivolumab is being compared with sunitinib in a similar patient population. In the PAPMET2 trial, cabozantinib plus atezolizumab is being compared with cabozantinib alone in patients with metastatic pRCC [74].

The phase 3 SAVOIR trial, comparing savolitinib with sunitinib in MET-driven pRCC, was closed early because efficacy was not much improved in the experimental arm and because of difficulty with accrual [75]. Since savolitinib was more effective when combined with durvalumab [73], the phase 3 SAMETA trial will be comparing savolitinib plus durvalumab with each agent used as monotherapy in advanced *MET*-driven pRCC [76].

Examining the evidence together suggests that, for nccRCC, anti-VEGF TKIs stand out, and combination therapy, particularly lenvatinib plus pembrolizumab, is most effective. Guidelines still recommend enrolment in clinical trials and cabozantinib for nccRCC, but they have added the regimens that showed promise in single-arm trials to the "other recommended regimens" and "useful in certain circumstances" sections [35].

Dr. Gupta concluded by noting that it is promising to see dedicated trials in nccRCC. Both IO-TKI and IO-IO are valid options. There is a need to broaden the scope and outreach of trials in nccRCC to advance the field further, given the rarity of these entities and challenges with trial enrolment.

In a Q&A session, an attendee asked if there are any head-to-head trials between everolimus plus lenvatinib vs. cabozantinib. The everolimus plus lenvatinib combination covers the spectrum of molecular pathways that cabozantinib does, and cabozantinib has a low compliance rate due to toxicity. In India, the attendee has difficulty even starting patients at a dose of only 40 mg because of toxicity. Dr. Gupta said that, in the Western population, cabozantinib is the most well-tolerated TKI. She recommended trying to lengthen the treatment duration with dose reduction. To date, everolimus plus lenvatinib vs. cabozantinib has not been compared head-to-head. It is unclear if everolimus plus lenvatinib would be equally effective.

Dr. Tanguay asked how Dr. Gupta treats metastatic chRCC tumours. She replied that she uses a TKI plus everolimus combination because IO is not effective in these tumours. In HLRCC pRCC tumours, she would use erlotinib with bevacizumab.

Dr. Tran asked whether Dr. Gupta has come across epithelioid angiomyolipomas, which keep recurring with surgery and have a poor prognosis. Dr. Gupta has not seen one of these patients and does not know what the long-term data with TKIs or IOs are in that setting. Dr. Tanguay noted that he has had one patient with epithelioid angiomyolipomas. He treated the patient with everolimus, and the tumour regressed.

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Abbreviations

BAUS	British Association of Urological Surgeons
CAIX	carbonic anhydrase IX
ccRCC	clear cell renal cell carcinoma
CD	Clavien-Dindo
chRCC	chromophobe renal cell carcinoma
CI	confidence interval
CT	computed tomography
DFS	disease-free survival
EAU	European Association of Urology
EV	extracellular vesicle
GFR	glomerular filtration rate
HOCT	hybrid oncocytic/chromophobe tumour
HLRCC	hereditary leiomyomatosis and renal cell cancer
HR	hazard ratio
IO	immunotherapy
KCa	kidney cancer
MIBI	^{99m}technetium sestamibi
mTOR	mammalian target of rapamycin
nccRCC	non–clear cell renal cell carcinoma
ORR	overall response rate
OS	overall survival
PET	positron emission tomography
PFS	progression-free survival
PN	partial nephrectomy
pRCC	papillary renal cell carcinoma
RCC	renal cell carcinoma
RCT	randomized controlled trial
RFA	radiofrequency ablation
RN	radical nephrectomy
RTB	renal tumour biopsy
SBRT	stereotactic body radiation therapy
SIB	surface-intermediate-base
SPECT	single photon emission computed tomography
TKI	tyrosine kinase inhibitor
VEGF	vascular endothelial growth factor

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