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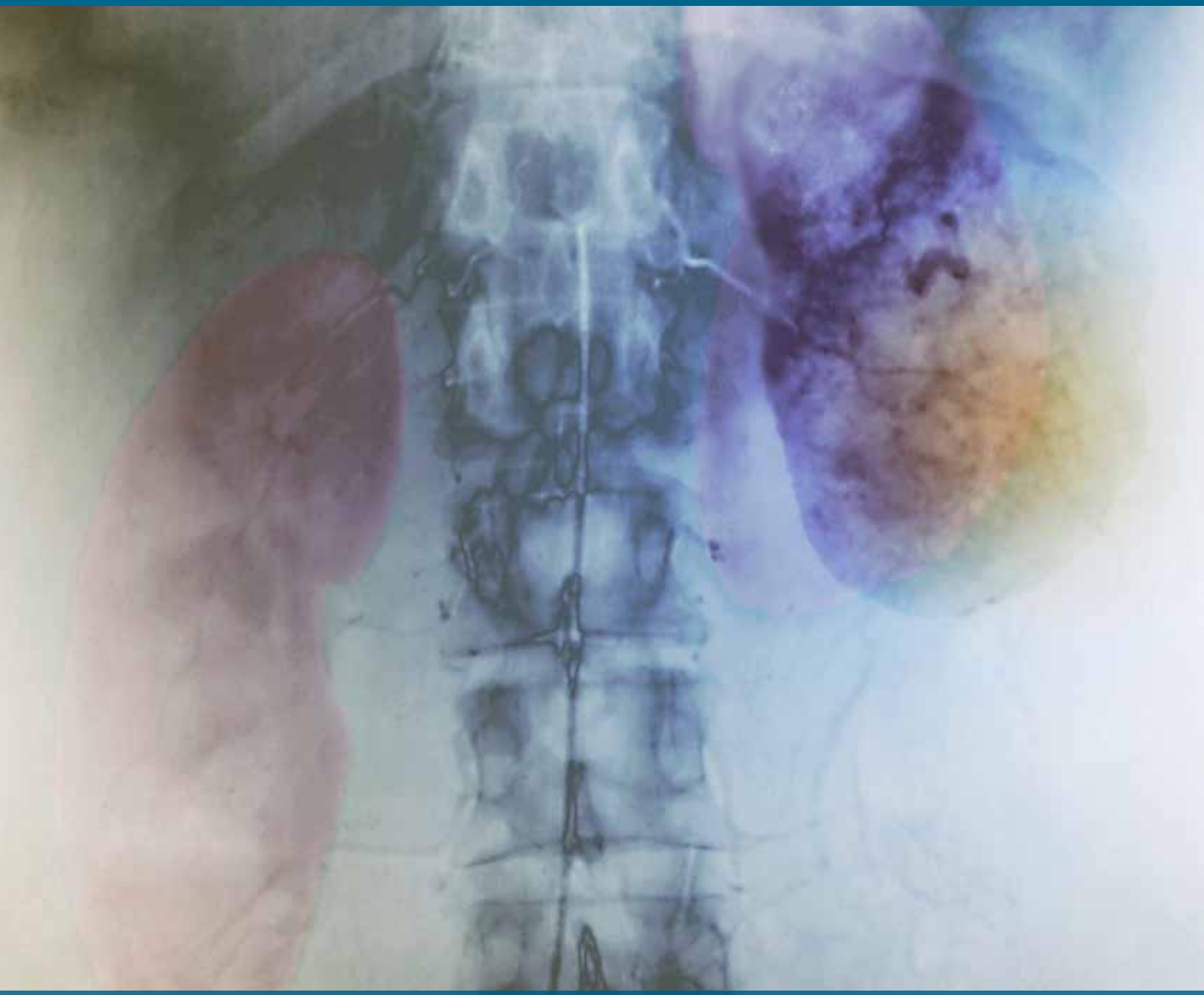

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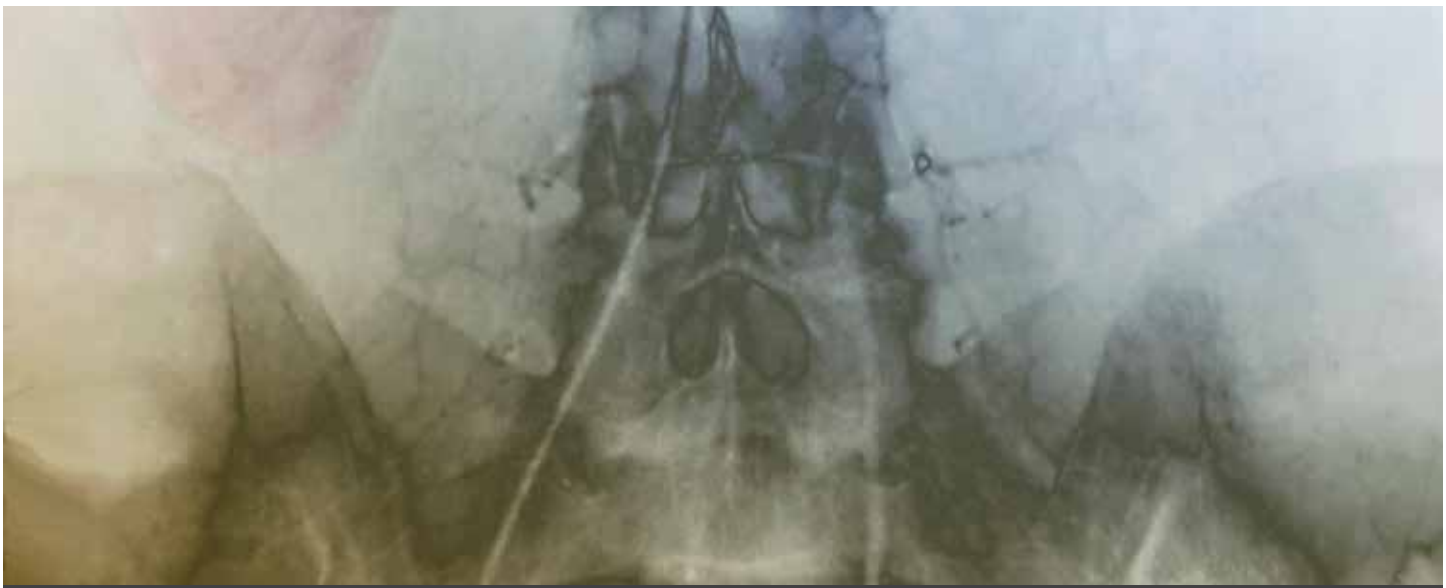

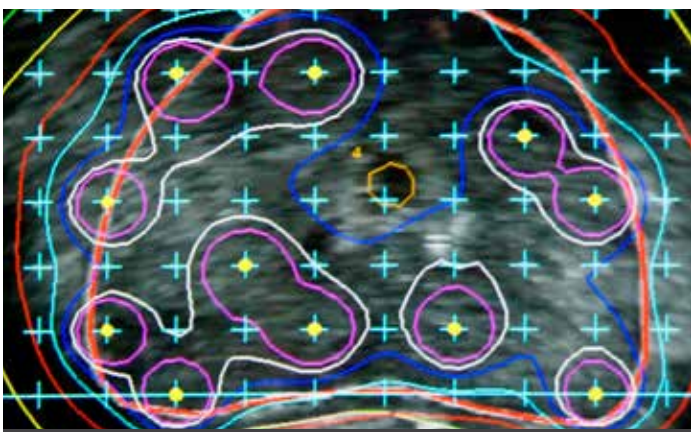

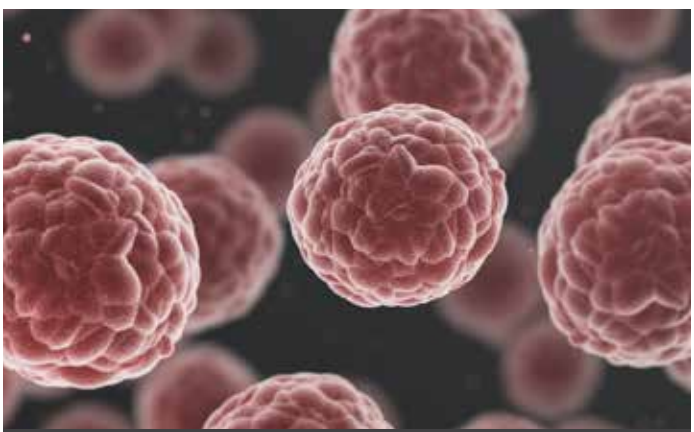

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FROM THE DESK OF THE EDITOR

Dear Colleagues:

Welcome to Volume 3, Third issue, of *Everyday Urology - Oncology Insights*.

In this issue, the applicability and utility of SpaceOAR® Hydrogel will be reviewed as well as the trials that led to its regulatory approval. SpaceOAR was designed as a means of diminishing rectal radiation toxicity. With a phase III trial reporting a decrease in acute and long-term rectal toxicity as well as enhanced patient reported quality of life outcomes, SpaceOAR is quickly being adapted as component of prostate cancer radiotherapy.

Daniel J. George, MD, and Robert G. Uzzo MD, FACS, review ''Nephrectomy in the era of targeted therapy,'' focusing on the significance of the CARMENA trial and the decision making involved regarding to proceed with a cytoreductive nephrectomy or not for patients with metastatic disease. Importantly, the clinical value and trial data of Sunitinib without cytoreductive nephrectomy is reviewed.

Ashish Kamat, MD, succinctly details within ''Blue light cystoscopy: insights on recurrence, progression, and clinical management,'' regarding the application of blue light cystoscopy, now recommended by both the American Urologic Association and Society of Urologic Oncology guidelines for cystoscopic evaluation for patients with non-muscle invasive bladder cancer. He analyzes the specific benefits of blue light cystoscopy for bladder cancer surveillance as well as during resection.

Over the spring and summer, leading urologists and oncologists have assembled at global meetings in order to share their research as well as to debate the merits of new data and diagnostics and their potential impact upon clinical decision making. These well-known international conferences enable collaboration across geographic boundaries, and thus this edition will further spotlight some timely developments in prostate, bladder and renal cancer research most recently presented.

From the 73rd annual Canadian Urological Association meeting was held in Halifax, Nova Scotia from June 23-24. Geoffrey Gotto, MD, discussion on the use of abiraterone acetate with prednisone in the treatment of metastatic castration resistant prostate cancer and Sumanta Pal, MD, overview of treatment updates in renal cell carcinoma, including results of CheckMate 214 and IMmotion 151 are both presented in this edition.

Also, highlights from July's 2018 Congress of the Mexican Association of Oncological Urology include a talk by Bernardo Gabilondo Pliego, MD on nephron sparing surgery, as well as a presentation by Daniel Olvera Posada, MD, on emerging biomarkers for prostate cancer detection are presented.

As always, thank you for reading *Everyday Urology - Oncology Insights*.

Sincerely,
Neal Shore, MD, FACS

Neal Shore, MD, FACS is an internationally recognized expert in systemic therapies for patients with advanced urologic cancers and innovative therapies to treat patients suffering from prostate enlargement symptoms. Dr. Shore was recently appointed President-Elect of the Large Urology Group Practice Association (LUGPA), which seeks to provide urologists with all the tools they need to effectively care for patients. Neal D. Shore, MD, FACS, is the Medical Director of the Carolina Urologic Research Center. He practices with Atlantic Urology Clinics in Myrtle Beach, South Carolina. Dr. Shore has conducted more than 100 clinical trials, focusing mainly on prostate and bladder disease.

PROSTATE-RECTUM SPACING DURING RADIATION THERAPY

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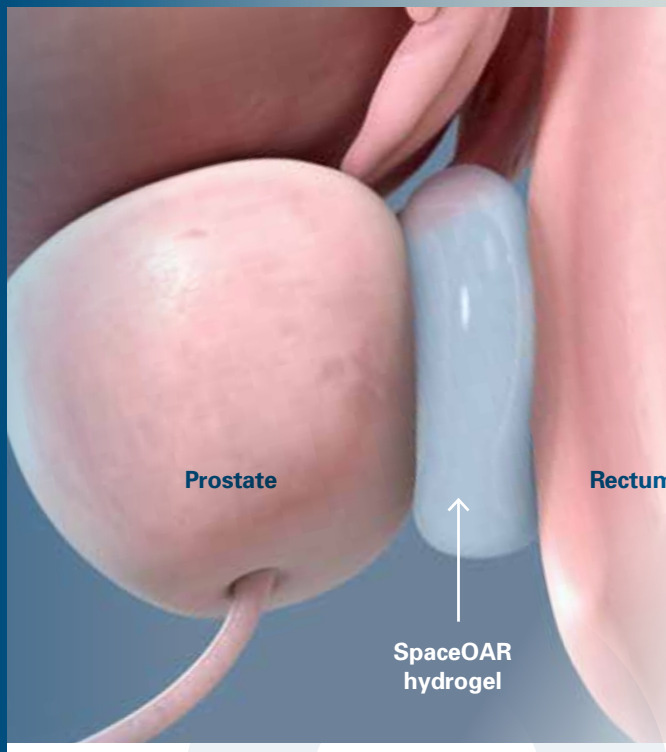

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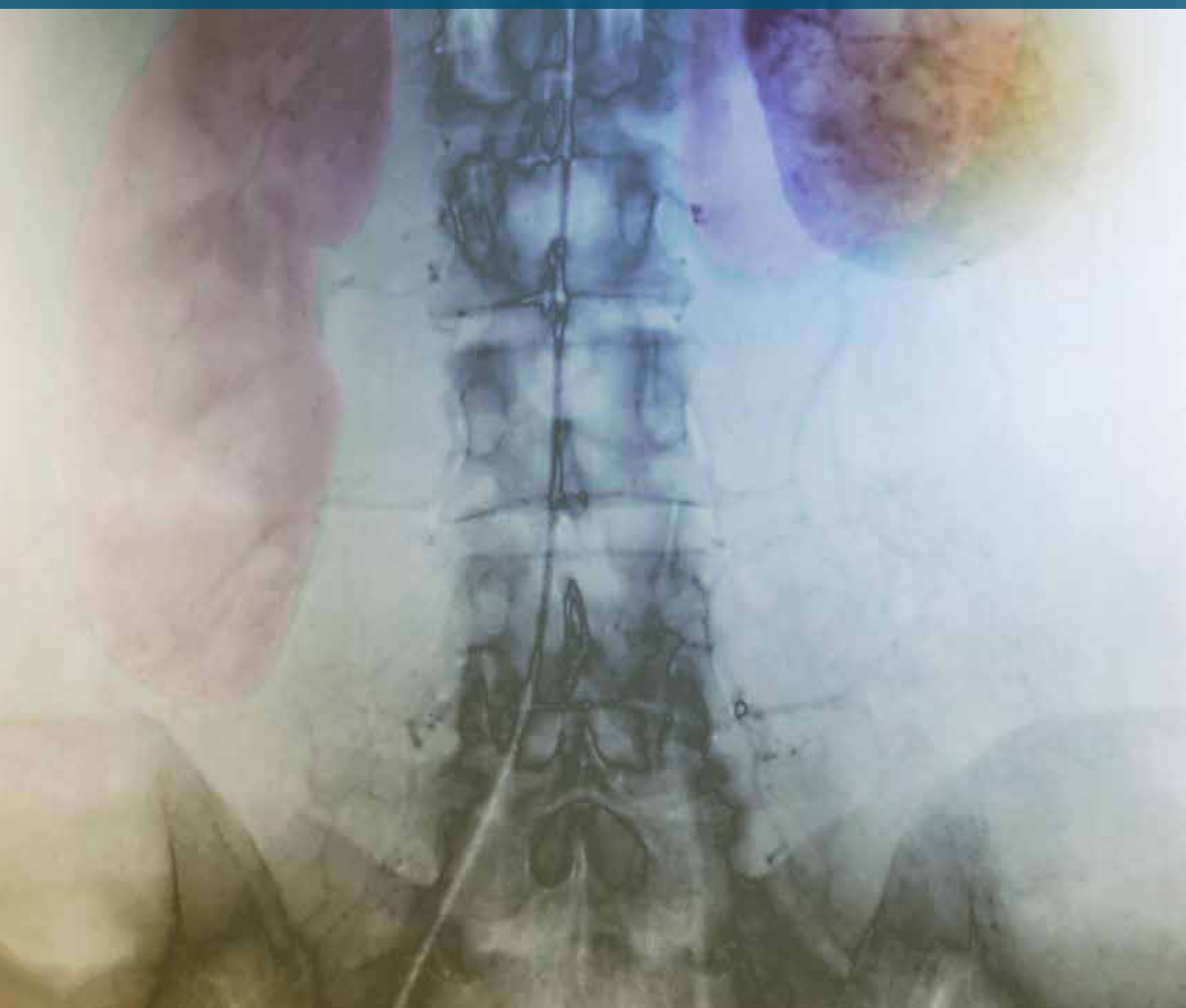
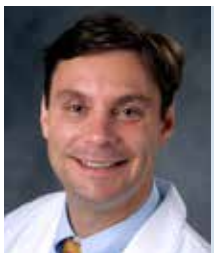
1. From 3 months onward post radiotherapy (data on file)
2. Hamstra, DA et al. Continued Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III Trial. Int J Radiat Oncol Biol Phys. 2017 Apr 1;97(5):976-985.

Nephrectomy in the Era of Targeted Therapy

TAKEAWAYS FROM THE CARMENA TRIAL

By Daniel J. George, MD and Robert G. Uzzo, MD, FACS





Daniel George, MD, is Professor of Medicine and Surgery, Divisions of Medical Oncology and Urology in the Duke University School of Medicine and leads the Duke Prostate and Urologic Cancer Center. He also has appointments in the Duke Clinical Research Institute and the Duke Cancer Institute where he is the Director of Genitourinary (GU) Oncology. Daniel George has led the Duke site for the Department of Defense (DOD) Prostate Cancer Clinical Trials Consortium since 2006.

Robert G. Uzzo, MD, is chair of the department of Surgical Oncology at Fox Chase , G. Willing "Wing" Pepper Chair in Cancer Research, Kidney, Bladder, and Prostate Cancer. Dr. Uzzo is a TRDG Member, senior vice president of the Physician Services, President of Fox Chase Cancer Center Medical Group, Inc., and professor of surgery at Temple University Health System.

A 62-year-old man presents with a one-week history of hematuria. Ultrasound and computed tomography identify a 7-cm exophytic anterior left renal tumor, adenopathy, and two small lung nodules. No bone or central nervous system lesions are detected. His Eastern Cooperative Oncology Group (ECOG) performance-status (PS) and Memorial Sloan-Kettering Cancer Center (MSKCC) scores are 1. The patient asks whether to undergo cytoreductive nephrectomy. What do you tell him?

This case highlights a common treatment dilemma. Along the clinical spectrum, cytoreductive nephrectomy remains appropriate for an otherwise healthy 41-year-old with renal cell carcinoma and oligometastases in the lung—while surgery does not make sense for an 80-year-old with competing risks and a high metastatic tumor burden. But most of our patients fall in the middle of these extremes. In our current era of effective targeted therapies for metastatic kidney cancer, how can we best manage decisions about cytoreductive surgery?

Two decades ago, no study had shown a definitive benefit for cytoreductive nephrectomy in patients with metastatic renal cell carcinoma. That changed in 2001, when two studies by the European Organization for Research and Treatment of Cancer (EORTC) and the Southwest Oncology Group (SWOG) demonstrated that surgery followed by interferon alfa-based immunotherapy significantly improved overall survival (OS) compared with interferon-alfa treatment alone. Median OS was 11.1 months in the nephrectomy-interferon arm versus 8.1 months in the interferon alone arm of the SWOG 8949 trial.[1] Similar results were seen in EORTC 30947, and these findings established the role of cytoreductive nephrectomy in the standard initial management of metastatic kidney cancer.[2]

Those findings and that clinical decision made sense at the time, particularly given the lack of effective systemic therapies. But in 2005, a sea change began when the FDA approved sorafenib (Nexavar), an orally available multikinase inhibitor of tumor cell proliferation and angiogenesis, as the first targeted treatment for kidney cancer (FIGURE).[3] In the pivotal trial, sorafenib therapy roughly doubled progression-free survival (PFS) compared with placebo in patients with metastatic cytokine-refractory clear-cell disease.[4] Shortly thereafter, the FDA approved sunitinib (Sutent), a vascular endothelial growth factor receptor tyrosine kinase inhibitor, based on promising objective response data.[5] These results were confirmed in a phase III front-line study in which sunitinib significantly improved PFS over interferon-alfa treatment (hazard ratio, O.54; 95% confidence interval [CI], 0.45 to 0.64; P<.001) and trended toward improved OS (HR, 0.82; 95% CI, 0.67 to 1.001; P=.051).[6]

More pivotal trials and approvals followed over subsequent years, raising questions about the role of cytoreductive nephrectomy in this new era of targeted systemic therapies.[7] Observational studies and big-data analyses sought to clarify this role,[8,9] most notably a large retrospective study by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC).[10] In this study of patients with synchronous metastases from renal cell carcinoma, initial cytoreductive nephrectomy led to a 40% reduction in the hazard of death compared with systemic therapy (usually sunitinib) without surgery.[10] However, uncontrolled, retrospective analyses are limited by selection bias. Furthermore, surgery only appeared to benefit patients who had three or fewer IMDC prognostic factors,[10] underscoring the need to refine surgical selection criteria.

Despite landmark improvements in the effectiveness of systemic therapy, a decade ago, cytoreductive nephrectomy was so entrenched in our practice that it was difficult to have equipoise regarding its benefit. Starting in 2009, the phase III CARMENA trial (NCT00930033) sought to bridge that gap by randomly assigning intermediate and poor-risk patients with metastatic kidney cancer to receive sunitinib only (50 mg daily on a 4:2 schedule) or upfront nephrectomy followed by sunitinib beginning 3 to 6 weeks after surgery.[11] The results, which were reported at the 2018 meeting of the American Society for Clinical Oncology (ASCO),[12] illustrate important tradeoffs between surgery and systemic therapy in our patients with metastatic kidney cancer. Understanding their implications can help us optimize patient care and promote thoughtful multidisciplinary management in the era of targeted therapy, immunotherapy, and increasingly effective combinations.

OVERVIEW OF CARMENA

CARMENA was a 79-center randomized clinical trial of 450 adults with metastatic clear-cell renal cell carcinoma and an ECOG-PS of 0 or 1.11 This was designed as a non-inferiority trial, which made sense—if sunitinib alone was just as effective as nephrectomy followed by sunitinib, then postponing nephrectomy could spare patients the perioperative risks of surgery and enable them to immediately begin systemic disease control.

Patients in CARMENA were naïve to systemic therapy, deemed amenable to cytoreductive nephrectomy by their surgeon, and eligible for treatment with sunitinib.[11] They had Memorial Sloan Kettering Cancer Center (MSKCC) intermediate-risk (one or two prognostic factors) or poor-risk disease (three or more prognostic factors).[13] Additionally, they either had no brain metastases or had received surgery or radiotherapy for brain metastases without corticosteroids and without progression for 6 weeks. The primary endpoint was OS.

The trial ran until 2017, for a median follow-up time of 50.9 months (95% confidence interval [CI], 44.0 to 56.9 months; range, 0.0 to 86.6 months).[11] At this time, an interim analysis of the intention-to-treat population, stratified by MSKCC risk score, produced a 0.89 hazard ratio for OS (95% CI, 0.71 to 1.10), upholding the study hypothesis of non-inferiority. Median OS times were 18.4 months in the sunitinib-only arm and 13.9 months in the surgery-sunitinib arm. Findings were similar in MSKCC risk-score subgroups (intermediate-risk: HR, 0.92; 95% CI, 0.6 to 1.24; poor-risk: HR, 0.86; 95% CI, 0.62 to 1.17). Based on these findings and the trial's slow accrual, the steering committee decided to close the study early.[11]

SUNITINIB WITHOUT SURGERY: TRULY NON-INFERIOR?

But was sunitinib alone truly non-inferior to cytoreductive nephrectomy followed by sunitinib? Non-inferiority comparisons usually focus on the upper limit of the 95% confidence interval. The CARMENA investigators determined that sunitinib without surgery would be clinically acceptable if the upper bound of the 95% confidence interval for the OS hazard ratio did not exceed 1.20.[11] In the intention-to-treat analysis, the upper limit of the 95% confidence interval for OS was 1.10, with a hazard ratio of 0.89 favoring sunitinib alone. Thus, sunitinib without surgery was found clinically acceptable in this patient population.

However, a per-protocol analysis told a different story. This analysis included only those patients who were actually treated as assigned (sunitinib alone or sunitinib with surgery). Here, the upper limit of the confidence interval crossed the 1.20 threshold. Median OS times were 20.5 and 18.3 months, respectively, with a hazard ratio of 0.98 (95% CI, 0.77 to 1.25).[11] Based on this result, it is harder to definitively conclude the non-inferiority of sunitinib without surgery when this patient population is treated as planned.

The wider confidence intervals of the per-protocol analysis reflect the fact that many CARMENA patients were not treated as planned. In the surgery-sunitinib arm, 7% of patients did not receive nephrectomy, and an additional 18% never received sunitinib.[11] In the sunitinib-only arm, 5% of patients did not receive sunitinib, and an additional 17% subsequently underwent cytoreductive nephrectomy, although this was allowed on study.[11]

These results show that none of us can predict with 100% accuracy which patients are fit enough to undergo cytoreductive nephrectomy and recover enough to receive systemic therapy. Likewise, some patients who are treated with sunitinib first might have such a robust, near-complete response in their metastases that a consolidative nephrectomy makes sense. This is why intention-to-treat analyses are so useful—they include all the unexpected outcomes of patients, from those who drop off a study after becoming too sick to those with extraordinary responses. This mirrors real-world practice.

Despite slight discrepancies between analyses, the results of CARMENA are practice-changing. They reflect a more contemporary practice pattern and the largest prospective study thus far in this setting. These findings support the practice of deferring nephrectomy in order to initiate systemic therapy in patients who are relatively poor-risk, with metastatic tumor burdens of at least 4 cm, even if their performance status is good. These patients were well represented in the intention-to-treat analysis of CARMENA, which showed non-inferiority with sunitinib alone.

RATIONALES FOR DEFERRING NEPHRECTOMY

Although relatively few large, controlled studies have evaluated deferred nephrectomy, their results largely reinforce this approach for carefully selected patients. For example, in the randomized multicenter SURTIME trial (NCT01099423) of 99 patients with synchronous, predominantly intermediate-risk metastatic renal cell carcinoma, three cycles of sunitinib prior to cytoreductive nephrectomy did not improve progression-free rate

(PFR) at 28 weeks compared with upfront nephrectomy followed by sunitinib.[14]

The SURTIME trial was underpowered due to slow accrual, but the intention-to-treat analysis of OS showed a signal in favor of deferred nephrectomy. While median OS was 32.4 months in patients who first received sunitinib versus 15.1 months in patients who first received nephrectomy (HR, 0.57; 95% CI, 0.34 to 0.95; P = .032), sample size precluded definitive conclusions.[14] Despite the small size of this study, SURTIME suggest that deferred nephrectomy is reasonable for some intermediate-risk patients with advanced kidney cancer in our current era of targeted therapy.

Secondary results from the phase III CheckMate 214 trial (NCT02231749) point the same way. The presence of a primary tumor did not influence the results of CheckMate214, in which ipilimumab-nivolumab showed a significant survival advantage over sunitinib among intermediate and poor-risk patients with treatment-naïve, advanced or metastatic renal cell carcinoma.[15]

The results of CheckMate 214 led to an FDA approval of ipilimumab-nivolumab for this patient population.[16] Since CARMENA began, the FDA has approved several other first-line treatments for metastatic kidney cancer, and the most recent management guidelines from the National Comprehensive Cancer Center (NCCN) give both pazopanib and sunitinib category 1 (preferred) recommendations for the first-line treatment of metastatic clear-cell disease in IMDC favorable-risk patients.[17] For intermediate and poor-risk patients, a phase II randomized controlled trial showed a significant PFS advantage for cabozantinib versus sunitinib.[18] We lack head-to-head comparisons of these agents with upfront nephrectomy, but it is reasonable to conclude that they might perform at least as well as sunitinib, given appropriate patient selection for surgical deferment. As even more efficacious systemic treatments for kidney cancer emerge, we will need to further refine our selection criteria for initial surgery.

Finally, there are at least two biological rationales for prioritizing initial systemic therapy over cytoreductive surgery. The first is that the primary tumor can be a rich source of neoantigens,[19] and treatments that stimulate even a modest or short-lived response in this tumor might prime the immune system for a stronger response to immuno-oncologic therapy. This is a key rationale for the perioperative design of the ECOG-ACRIN cooperative group's PROSPER RCC study (NCT03055013), which is evaluating the efficacy of neoadjuvant and adjuvant nivolumab in patients with localized kidney cancer undergoing nephrectomy.[20]

The second biological rationale is that delaying nephrectomy might avoid or slow metastasis. Studies of patients with breast cancer have identified a sharp peak in the risk of metastatic recurrence approximately 12 to 18 months after surgery.[21] In preclinical studies of mice, T-cells were found to keep breast cancer tumor cells in check.[21] Surgery and subsequent wound healing disrupted this balance, leading to distant metastasis.[21] Confirmatory studies are needed; an intriguing hypothesis is that under certain yet-to-be defined clinical circumstances, surgery might induce an inflammatory response that could potentially heighten the risk of metastases. Taken together with the results of CARMENA, these observations support a thoughtful and multidisciplinary approach to the timing of surgery in patients with metastatic kidney cancer.

BENEFITS OF UPFRONT NEPHRECTOMY

Conversely, several findings from CARMENA do support initial nephrectomy in certain patients with advanced kidney cancer.

First, patients undergoing cytoreductive nephrectomy had fewer related complications, particularly urinary tract infections and hematuria. Surgery also was fairly well tolerated; the rate of postoperative mortality at 1 month was only 2%, and although 39% of patients experienced postoperative morbidity, only 16% developed Clavien grade III or higher surgical complications.[11,22] These data suggest that cytoreduction in a well-selected, randomized setting is better tolerated than previously reported.

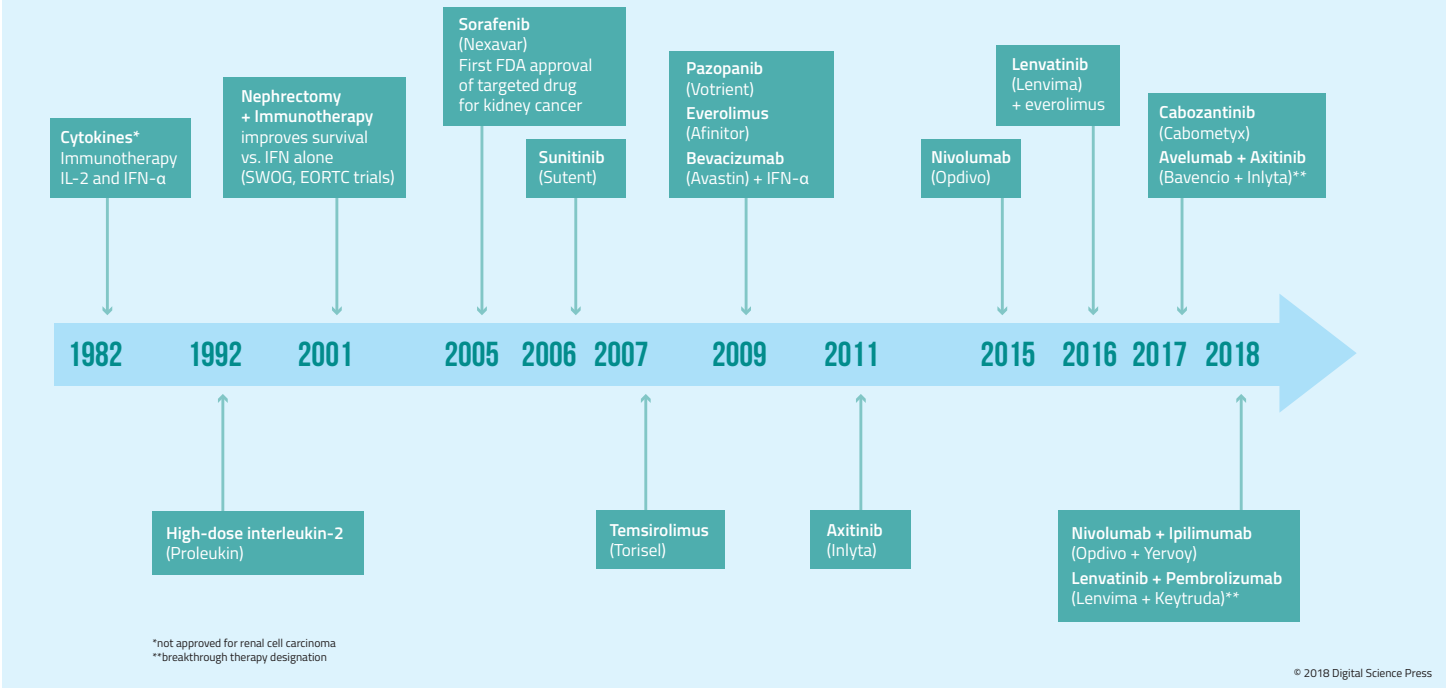
In contrast, patients in the sunitinib-only arm of CARMENA received an average of 2 months more sunitinib (8.5 vs. 6.7 months with nephrectomy-sunitinib; P=.04) and were more likely to develop grade 3-4 adverse events (43% vs. 38% for nephrectomy-sunitinib; P=.04). The most common grade 3-4 adverse events among patients who received sunitinib included asthenia, hand-foot syndrome, anemia, and neutropenia, all of which are documented side effects of sunitinib. Furthermore, nine patients in the sunitinib-only arm developed grade 3 renal or urinary disorders, compared with only one patient in the nephrectomy-sunitinib arm (P=.05).

Thus, CARMENA showed that initial nephrectomy in carefully selected patients can potentially shorten overall treatment duration, yielding fewer complications with a non-inferior outcome. The primary risk of this approach appeared to be undertreatment. Almost 48% of patients in the sunitinib-only arm achieved disease control beyond 12 weeks, compared with only 37% of patients assigned to nephrectomuy-sunitinib (P=.02). Importantly, nearly 23% of patients who underwent cytoreductive nephrectomy never recovered to an adequate degree to receive sunitinib.[11]

STUDY LIMITATIONS

Several limitations of CARMENA merit discussion. Firstly, the risk criteria used for enrollment may have biased the study population toward poor-risk patients. The investigators used the MSKCC model, which is used perhaps most often to risk-stratify patients with advanced kidney cancer. The original MSKCC model included five independent predictors of poor survival, one of which was lack of nephrectomy.[13] Because all CARMENA patients were considered candidates for nephrectomy, the 43% classified as MSKCC poor-risk had to have had at least three other negative prognostic factors. When the MSKCC model was

TREATMENT PROGRESS: ADVANCED KIDNEY CANCER



*not approved for renal cell carcinoma
**breakthrough therapy designation

developed, having just one poor prognostic factor reduced 1-year survival by almost 50%, and having three or more poor prognostic factors was nearly universally fatal at 1 year.[13]

Thus, CARMENA patients had additional negative prognostic indicators of poor outcomes even though they were amenable to nephrectomy.

This helps explain why median OS in CARMENA (18.4 months in the sunitinib-only group and 13.9 months in the nephrectomy-sunitinib group) was shorter than in other recent studies of metastatic kidney cancer. In CheckMate 214, median OS with sunitinib was 26.0 months although 38% of patients were classified as poor-risk based on IMDC criteria.[15] In the randomized phase II CABOSUN trial, median OS among sunitinib-treated patients was 21.8 months; 19% of patients were classified as IMDC poor-risk.[18]

In addition to poor-risk features, patients in CARMENA also had substantial metastatic tumor burdens. The median size of primary tumors exceeded 8 cm in greatest dimension and median overall tumor burden was at least 14 cm.[11] Thus, metastatic disease comprised at least 40% of overall tumor burden for most patients. Although the typical aim of surgical cytoreduction is to remove the vast majority of tumor burden, this would not have been possible for many CARMENA patients.

CARMENA excluded patients with low metastatic burden at the investigator's discretion;[11] patients with low metastatic burdens probably were not enrolled due to the prevailing belief that they would benefit from upfront removal of the primary tumor mass. Excluding these patients may have biased the results of this trial against surgery followed by sunitinib in those most likely to benefit from that strategy. Additionally, more patients in the nephrectomy-sunitinib arm had locally advanced stage T3 or T4 tumors (70%) than in the sunitinib-only arm (51%), which could have affected operative outcomes.

Finally, we note that CARMENA fell far behind in accrual. This may have been due to many unrelated factors. However, among many patients and physicians, surgery is reserved for those who are most motivated and subjectively believed to be most likely to benefit. This reflects not only a lack of truly coordinated multidisciplinary care for patients with advanced kidney cancer, but also, perhaps, a hope that surgery in some patients may be associated with disease regression or stabilization that might delay or, rarely, avoid the need for systemic therapy. It remains crucial to close this practice gap given our rapidly evolving treatment landscape.

SUMMARY AND TAKEAWAYS

The randomized phase III CARMENA trial compared sunitinib alone with nephrectomy followed by sunitinib in ECOG-PS 0 or 1 patients with intermediate or poor-risk metastatic clear-cell renal cell carcinoma. In the intention-to-treat analysis, sunitinib

without surgery was found to be non-inferior to initial nephrectomy followed by sunitinib. Overall, the results supported the use of sunitinib alone in lieu of nephrectomy, especially in poor-risk patients and patients with a high metastatic tumor burden. However, the trial suffered from slow accrual and excluded patients with metastatic favorable-risk disease, which somewhat limits the generalizability of the findings.

Despite its shortcomings, CARMENA provides the best data we are ever likely to have on postponing nephrectomy in the era of targeted therapy. This trial was approximately twice the size of the original SWOG study, and its survival findings reflect what we would expect for poor-risk patients with relatively high-volume disease treated between 2009 and 2017. The per-protocol analysis did not support the non-inferiority hypothesis, but as clinicians, we manage patients by intention to treat, and the intention-to-treat analysis demonstrated that for most patients with metastatic renal cancer, starting with sunitinib was just as effective as upfront nephrectomy for this patient population.

The results of CARMENA highlight the importance of identifying the correct therapies and sequence on a case-by-case basis. Treatment remains multimodal, and tradeoffs and patient preferences must be considered. For patients with high risk stage III renal cell carcinoma, options include adjuvant clinical trials and, in selected cases, adjuvant sunitinib therapy, which demonstrated a 24% reduction in risk of disease recurrence in the recent S-TRAC trial (NCT00375674).[23] While not all patients will choose this approach, appropriate patients should at least discuss it with a medical oncologist. For patients with newly diagnosed metastatic disease, we should consider prognostic risk scoring and metastatic tumor burden. Systemic therapy increasingly is a first choice, but palliative surgery should be an option for well-selected, good-risk patients or those who are symptomatic.

We lack prospective trials comparing nephrectomy with systemic targeted therapies in patients with very limited metastatic disease. Although many of these patients and their surgeons probably prefer surgery to remove a large primary tumor, data from CARMENA offer at least some support for initial sunitinib, followed by consolidative surgery to remove the primary tumor source if metastatic lesions show excellent partial responses or prolonged stable disease. As systemic therapies continue to improve, this approach may apply to other patient populations. For example, patients with substantial metastatic tumor burdens might receive initial systemic therapy and proceed to consolidative surgery, depending on their response.

Despite substantial recent progress in treating metastatic kidney cancer, most patients cannot be cured. The results of CARMENA indicate that cytoreductive nephrectomy continues to make sense for select patients. Rather than discarding nephrectomy, we will need to continue to refine patient selection as new data on systemic treatments emerge.

Such complexities demand a multidisciplinary approach for all patients with synchronous metastatic renal cell carcinoma and for any patient at significant risk of developing metastatic disease. We recommend multidisciplinary tumor boards over ad hoc consultations. Formal tumor boards help physician-specialists think more systematically and overcome our inherent biases. In doing so, we can assess cases more objectively and ultimately improve patient outcomes. ■

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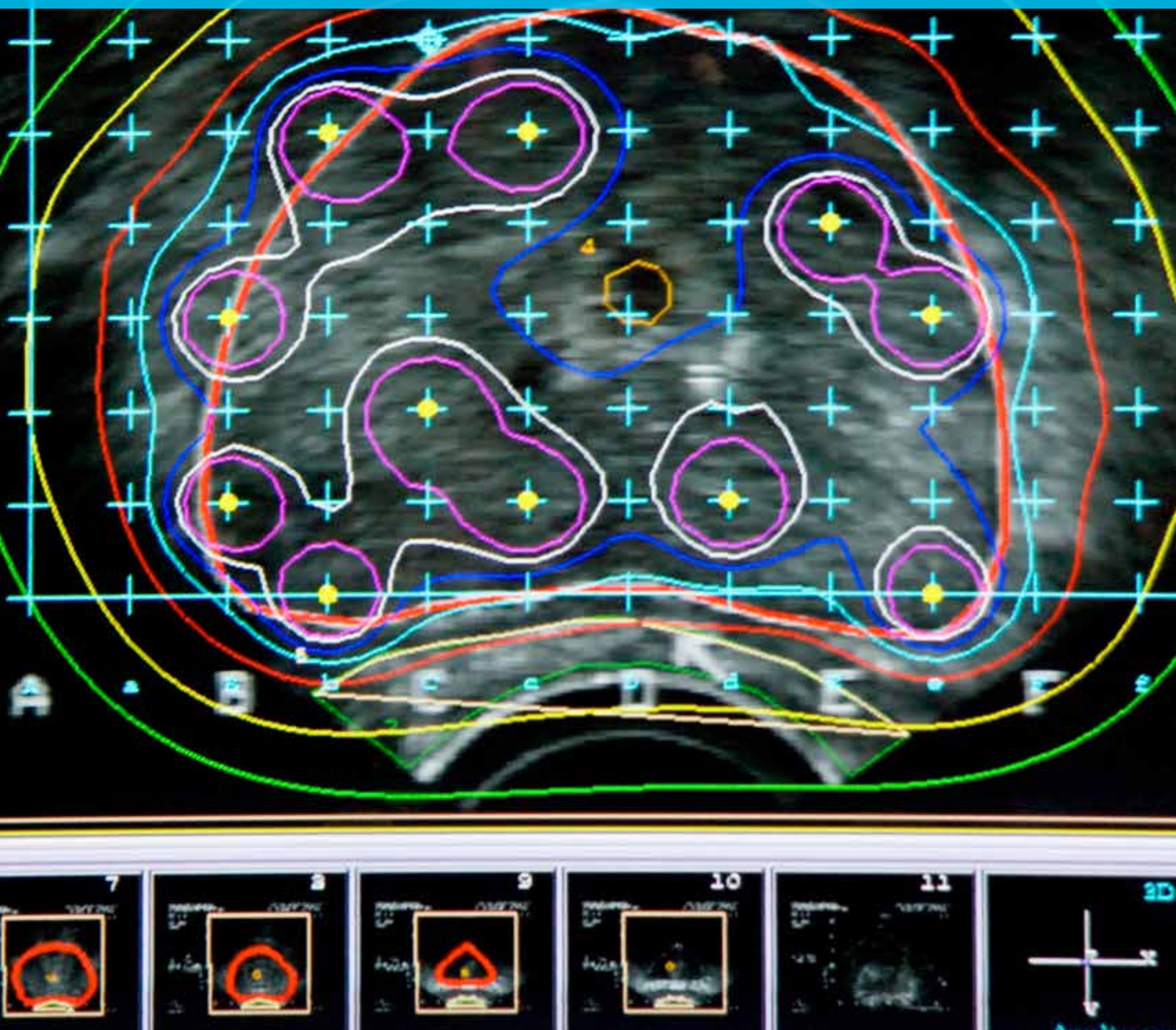
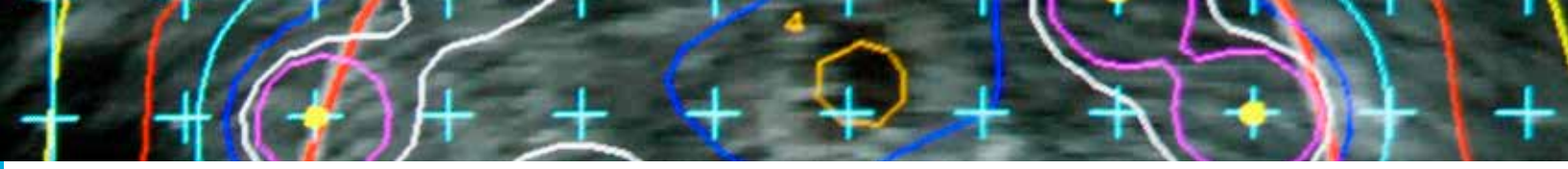
SPACERS AND PROSTATE RADIATION THERAPY: What Urologists Should Know

By Neal Shore, MD, FACS





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Radiation has been used to treat prostate cancer since the early 1900s.[1] In recent decades, advances in radiation delivery systems and the advent of computed tomography and magnetic resonance imaging have spurred the development of targeted, high-dose radiotherapy techniques such as intensity-modulated radiotherapy (IMRT), image-guided radiation therapy (IGRT), stereotactic radiation therapies, proton beam radiation therapy, and high-dose rate (HDR) brachytherapy.[2,3,4,5] These modalities have significantly improved biochemical disease-free survival in patients with localized prostate cancer and have added to the armamentarium of interventional localized prostate cancer options.[6]

Nonetheless, improved and extended long-term survival following prostate radiotherapy raises the concern of late-onset radiation-induced toxicity.[7] Sequelae such as chronic diarrhea, rectal stricture, tenesmus, rectal bleeding, urinary obstruction, urgency, incontinence, and sexual dysfunction may seriously undermine a patient's quality of life and also contribute substantially to healthcare costs.[8,9,10,11]

These toxicities are still encountered despite our ability to render more precise radiotherapies such as IMRT and IGRT.5 In a meta-analysis of five randomized trials, every 8 to 10-Gy increase in radiation dose to the prostate approximately doubled the odds of severe late-onset gastrointestinal or genitourinary toxicities and led to a 63% increase in the likelihood of more moderate toxicities.[7] In other recent trials of prostate radiotherapy, rates of late-onset grade 2 or worse toxicities were 14% to 25% for rectal sequelae and 12% to 46% for genitourinary sequelae.[4,12,13,14]

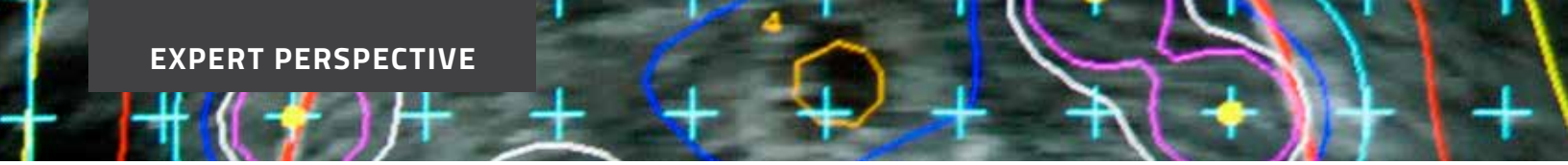
PROTECTING THE ORGAN AT RISK

The rectum is the radiation dose-limiting anatomical structure within the pelvis because of its fixed position immediately adjacent to the prostate.[5,6,15] Indeed, some studies suggest that as many as 75% of patients who undergo prostate radiotherapy develop acute proctitis, and some 20% develop chronic symptoms.[15] These risks further increase in the presence of conditions that predispose patients to vascular injury and ischemia, such as smoking, hypertension, diabetes, and atherosclerosis.[15] Studies using three-dimensional imaging show a strong correlation between rates of late rectal bleeding after prostate radiotherapy and the volume of rectal tissue receiving more than 70 Gy radiation.[6,16,17] More moderate radiation doses (40 to 50 Gy) also can lead to substantial late-onset gastrointestinal toxicities if a larger surface area of the rectum is exposed.[6]

Given these findings, investigators have tested various strategies for shielding the organ at risk (OAR), the rectum, during prostate radiotherapy. For example, endorectal balloons have been used to immobilize the prostate, and in some studies, they also appeared to reduce rectal irradiation during three-dimensional conformal radiotherapy (3DCRT).[6] However, endorectal balloons showed no significant dose-sparing effect during IMRT, which in many settings has replaced 3DCRT for prostate radiotherapy.[6,18] In addition, an improperly placed endorectal balloon can potentially decrease the efficacy of radiotherapy.[6,19] In one real-world study, researchers reported an average placement error of 0.5 cm, enough to partially shift the prostate outside the planned radiation effective treatment area.[19]

More recent work has focused on administering transperineal injections of various materials into Denonvilliers' space in order to shift the anterior rectal wall away from the prostate during radiotherapy.[20,21] Hyaluronic acid, blood patches, and collagen all have been tested; all were found to be well-tolerated, relatively easy to position under transrectal ultrasound guidance, and protective regarding rectal irradiation.[22,23,24,25] However, the deployment of these materials was not uniform. Untoward effects included the creation of too limited a perirectal space (buffer), material shift after placement, or too rapid biodegradation after deployment.[21,26]

In contrast, studies of off-label injections of DuraSeal



polyethylene glycol (PEG), a spinal sealant, showed excellent tolerability, ease of use, and significant rectal sparing during IMRT and low- and high-dose brachytherapy.[27,28]

DEVELOPMENT OF SPACEOAR

SpaceOAR (Augmenix, Bedford, MA, USA) was developed as an absorbable perirectal spacer made of biodegradable PEG-based hydrogel that is injected transperineally between the prostate capsule and the rectum under transrectal ultrasound guidance.[29]

In a multicenter single-arm phase II trial of 52 men with localized prostate cancer, CT simulation scans performed before and after placement of this spacer revealed decreases in rectal radiation that were consistent across investigative institutions.[30] Significant rectal sparing was observed across a radiation treatment range of 10 to 75 Gy.[30] The mean decrease in rV70 was 8.0% (standard deviation 4.2 %), and the median decrease was 7.8% (95% confidence interval, 0.3% to 19.5%).

In this phase II trial, initial and 12 month follow-up results demonstrated no grade 3-4 gastrointestinal toxicities and no grade 4 genitourinary toxicities, while only 2.1% of patients developed grade 3 genitourinary toxicities.[31] At 12 months, gastrointestinal toxicities were uncommon (4.3%) and were always grade 1, with no cases of gastrointestinal ulcer, stricture, or necrosis.[31] The incidence of late genitourinary toxicities was 17% for grade 1 events, 2.1% for grade 2 events, and 0% for grade 3 or worse events.[31]

PHASE III TRIAL

Based on the phase II results, researchers evaluated SpaceOAR in a 3-year, multicenter, randomized, controlled trial of 222 men with stage T1 or T2 prostate cancer (NCT01538628).[32] After undergoing CT and MRI-based radiation treatment planning and fiducial marker placement, participants were randomly assigned on a 2:1 basis to the spacer or control (no spacer) arm. Men in the spacer arm had the hydrogel spacer placed under intravenous anesthesia. Patients in both arms then received another set of planning scans followed by dose-escalated (79.2 Gy) IMRT of the prostate (with or without the seminal vesicles) in 44 fractions.[32]

The results of the phase III trial supported those from the phase II study. Spacer placement increased the perirectal space by a mean of 11.0 mm.[32] In the spacer arm, 97.3% of men had at least a 25% decrease in average projected volume of rectal tissue receiving at least 70 Gy (rV70).[32] Mean rectal v70 values were 3.3% after spacer placement versus 12.4% at baseline ($P < .0001$).[32] Rates of acute rectal toxicities generally were similar between groups, but men who received the spacer reported significantly less acute rectal pain compared with controls ($P = .02$).[32]

From 3 months onward, no patients in the spacer arm and 5.7% of controls developed grade 2 or worse rectal toxicities such as fecal incontinence, proctitis, or bleeding ($P = .012$).[33] Rates of late-onset grade 1 or worse rectal toxicities also favored the spacer arm (2% vs. 9.2% in the control group; $P = .028$). Men who received the spacer also had a significantly lower rate of grade 1 or worse urinary incontinence (4% versus 15%; $P = .046$), although rates of grade 2 or worse urinary toxicity were identical (7%) between arms.[33]

Secondary analyses of the phase III trial correlated SpaceOAR placement with significantly improved long-term patient-reported quality of life.[33] From 6 months onward, men who had received the spacer reported significantly better post-radiotherapy bowel quality of life compared with controls ($P = .002$), and the difference remained statistically significant at 3 years.[33] Additionally, 41% of controls reported long-term declines in bowel quality of life that met a predefined threshold for minimally important difference (MID), compared with only 14% of spacer recipients ($P = .002$). Men who received the spacer also reported significantly improved 3-year urinary quality of life versus controls ($P < .05$). Furthermore, 30% of controls reported declining urinary quality of life that met the MID threshold, versus only 17% of spacer recipients ($P = .04$).

Preliminary data also have correlated SpaceOAR placement with preserved sexual function after prostate radiotherapy.[5,34] In the phase III trial, the spacer reduced the average and maximum radiation doses to the penile bulb, as well as the volume of the penile bulb receiving 10 to 30 Gy (all $P < .05$).[34] Most (59%) men in this trial had low baseline sexual function, scoring below 60 on the Expanded Prostate Cancer Index Composite (EPIC).[34] However, among men with adequate baseline sexual quality of life, those who received the spacer reported better sexual function at 3-year follow-up versus controls (mean EPIC scores, 57.7 vs. 44.6, respectively; $P = .1$). Furthermore, among baseline-potent men, 66.7% of spacer recipients retained erections sufficient for intercourse at 3 years compared with only 37.5% of controls ($P = .046$).

SpaceOAR placement in the phase III trial also demonstrated similar safety and tolerability as that seen in the phase II trial. The rate of successful spacer deployment in the pivotal trial was 99%, and nearly all investigators reported that placing the spacer was easy or very easy.[32] There were no rectal perforations, serious bleeding events, or rectal infections in either study arm.

REAL-WORLD EXPERIENCE

In order to further characterize real-world experiences with SpaceOAR, a single-arm trial was prospectively conducted of 99 men with prostate cancer who received the spacer at 16 urology

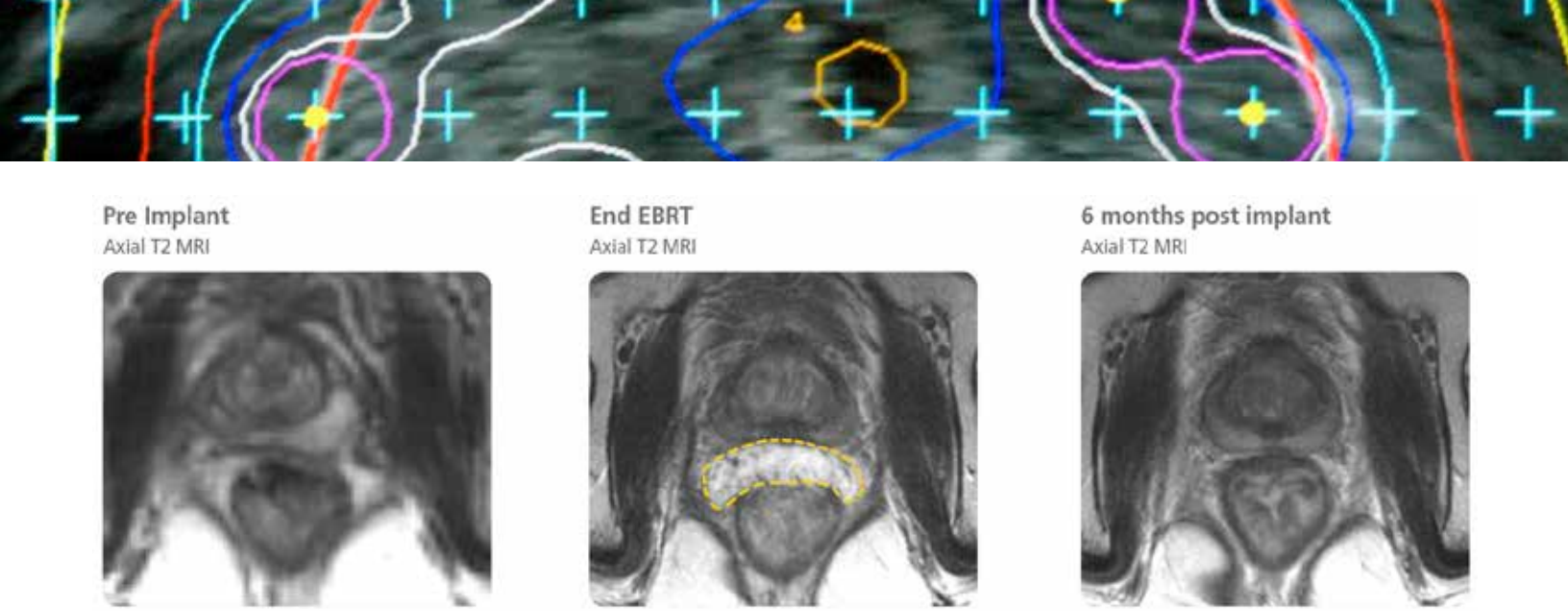


Figure 1. *SpaceOAR Clinical Trial Patient, MRI Images : Normal Anatomy, During Prostate RT and 6 months Following*

group practices.[35] A total of 95% of cases were performed within the office-clinic setting, while 5% were performed at ambulatory surgery centers. The average postprocedural perirectal space created was 10.7 mm, and 80% of urologists described the procedure as easy or very easy, while the rest described it as moderately easy. Fully 94% of patients said they would recommend the SpaceOAR procedure to other patients. Furthermore, 97% of patients said that they were less anxious about their pending radiation therapy knowing that they had SpaceOAR in place during treatment.

Placing SpaceOAR is technically straightforward for urologists who are familiar with ultrasound-guided transperineal injections. The spacer can be deployed at the same time that fiducial markers are placed.

Patients are placed in a lithotomy position and may receive either conscious sedation, local anesthesia with oral anesthesia or general anesthesia.[36] Under stepper-mounted side-fire transrectal ultrasound guidance, an 18-gauge needle is advanced through the perineal midline into the perirectal fat posterior to Denonvilliers' fascia and anterior to the rectal wall.[36]

Proper placement of the transperineal needle within the midline of Denonvilliers' space is key. It must be advanced at the prostate midline to prevent lateral injection of the hydrogel precursor and accelerator solutions.[36] If the needle enters the rectal lumen at any time during injection, the procedure should be abandoned to prevent infection.[36]

After confirming that the needle has been placed correctly, mid-gland hydrodissection with sterile saline solution is performed to expand the space between Denonvilliers' fascia and the anterior rectal wall. The needle is aspirated to confirm it is not intravascular. Then, without moving the needle, 10 mL of the PEG hydrogel precursor and accelerator solutions are injected into the expanded perirectal space.[31] These solutions polymerize within 10 seconds to form a soft hydrogel spacer approximately 1 cm in diameter.[36] The spacer persists for 3 months and is completely absorbed and cleared by renal filtration within 6 months.[30,36]

In the phase III trial, SpaceOAR was placed under intravenous sedation.[32] In my practice, I now use local anesthesia. I pre-medicate patients with an oral anxiolytic and wait 30 to 45 minutes before injecting any perineal local anesthetic. Next, I perform a perineal subcutaneous block, fan out the anesthetic along the skin, and then perform a diffuse block around the prostatic apex. I avoid injecting anesthetic along the right or left lateral aspects of the prostate to avoid creating any ultrasound artifact.

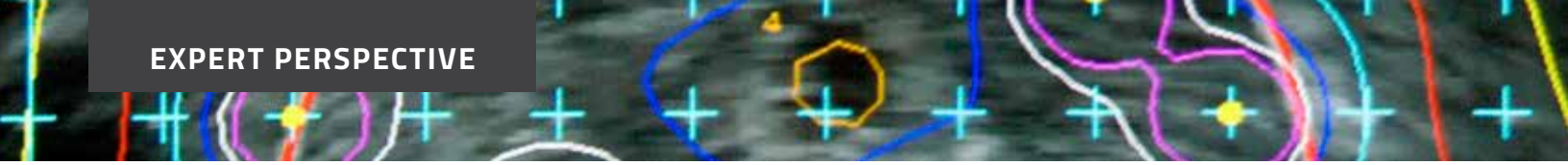
The learning curve for SpaceOAR is fairly rapid. Urologists who have experience with transperineal procedures and transrectal ultrasound should be very comfortable performing SpaceOAR insertions after just a few cases. Those who are comfortable with transrectal ultrasound, but not with transperineal needle placement, may consider using more anesthesia for their first few SpaceOAR cases in order to become comfortable with the technique.

SpaceOAR procedures require a side-fire transrectal ultrasound probe and a stepper. A floor-mounted stepper is more mobile and may be preferable to a table-mounted or bed-mounted stepper, but individual preferences will vary. Although a template grid often is useful for placing fiducial markers, it is not necessary and can impede proper angling of the needle when placing SpaceOAR.

REIMBURSEMENT AND TREATMENT PLANNING

Spacer placement can be performed in an outpatient setting or in a hospital surgery center. For patients with Medicare coverage, reimbursement is approved under CPT code 55874 (transperineal placement of biodegradable material, peri-prostatic single or multiple injections, including image guidance, when performed).[37]

Reimbursement in clinic settings is favorable. As of 2018, the national Medicare reimbursement averages were $3,797.24 for physician office-based spacer placement and $3,706.03 for hospital outpatient procedures.[38]



Based on this reimbursement rate, urologists whose practices purchased a side-fire transrectal ultrasound probe and stepper may achieve revenue neutrality after approximately 40 SpaceOAR cases.[35] Further efforts are underway to approve Medicare reimbursement of SpaceOAR placement in ambulatory surgery facilities.

Repeat imaging should occur about 5-10 days after placing the spacer to allow post-injection swelling to resolve.[39,40] This prevents overestimation of the prostate volume, which will presumably be coordinated by our radiation oncology colleague.

Some radiation oncologists elect to obtain a T2-weighted MRI and fuse to the repeat planning CT in order to better distinguish the hydrogel from the rectal wall.[39,40] The addition of MRI also helps confirm that the spacer was properly injected. It is not necessary to further monitor the spacer volume during radiotherapy in the pivotal multicenter trial, the spacer consistently retained a stable volume for 3 months after placement.[39]

TOXICITIES AND CAUTIONS

SpaceOAR has been well tolerated in studies to date. There have been no reports of local irritation or allergic reactions. However, several contraindications should be considered.

First, use of SpaceOAR is not recommended for locally advanced prostate cancer because it may not be possible to create an effective perirectal space, and also because a transperineal needle could potentially disseminate tumor cells within the pelvis.[39] Men who have previously undergone high-intensity focused ultrasound, cryotherapy, or radiotherapy of the prostate may have adhesions that could impede the injection of SpaceOAR.[39] SpaceOAR also is contraindicated for patients with clinically significant coagulopathies or active bleeding disorders. For other patients on anticoagulants, it may be possible to discontinue anticoagulants temporarily for the purpose of SpaceOAR placement.[39] Finally, SpaceOAR may not be appropriate for patients with prostatitis or anorectal inflammatory diseases for which there is increased risk of ulceration, fistula, or bleeding, such as ulcerative colitis or Crohn's disease.[39]

Although transient perineal discomfort has been reported, there have been no reports of rectal perforation, rectal infection, or serious rectal bleeding after placing SpaceOAR.[39] However, there has been a single report of a necrotic 1-cm rectal ulcer occurring 2 months after a patient underwent SpaceOAR placement prior to I-125 prostate brachytherapy.[41] This was the first case of rectal ulceration that the reporting physicians had observed in 55 SpaceOAR procedures.[41] The patient and physicians closely monitored the ulcer, and sigmoidoscopy showed complete resolution 3 months after the SpaceOAR procedure.[41]

After reviewing the case, the physicians reported that SpaceOAR had been placed under sterile conditions with routine antibiotic prophylaxis consisting of perioperative intravenous cephazolin plus 5 days of postprocedural norfloxacin (400 mg twice daily).[41] The only unusual aspect of this case was that the hydrogel had solidified prematurely within the SpaceOAR delivery system, requiring the system to be replaced mid-procedure.[41] The physicians concluded that mechanical injury might have been the cause of this ulcer. Since then, these physicians have begun tilting patient beds "head up" before inserting SpaceOAR to reduce downward angling of the needle and premature leaking of the precursor and accelerator solutions.[41] This is an appropriate precaution to consider. These physicians also remove the brachytherapy template to improve maneuverability of the SpaceOAR needle, advance the needle with the bevel away from the rectum to avoid perforation, take care to reduce pressure of the transrectal ultrasound probe against the anterior rectal wall, hydrodissect with normal saline to expand the perirectal space, inject no more than 10 mL of the precursor and accelerator solutions, and stop if they encounter resistance.[41]

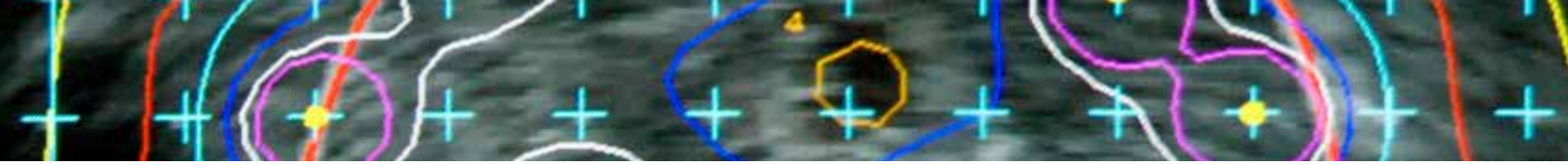
FUTURE DIRECTIONS

Research continues to evaluate the safety and efficacy of SpaceOAR across a range of prostate radiotherapies. One such modality is stereotactic ablative radiotherapy, an emerging external beam technique that delivers fewer but larger radiation fractions to the tumor target over an abbreviated treatment schedule.[42]

Earlier this year, oncologists in Ireland reported their experience with the first six participants in a clinical trial of SpaceOAR placement prior to stereotactic ablative radiotherapy.[43] All spacers were placed successfully, the only acute toxicity was grade 1 proctitis, spacer placement did not significantly alter clinical target volume dose coverage, and rectal irradiation dropped substantially: for example, by at least 42% for the volume of rectum receiving 36 Gy radiation.43 Furthermore, the probability of grade 2 or worse rectal bleeding fell from 4.9% to 0.8% (P = .03).[43]

Unfortunately, late-onset rectal ulceration is common after patients undergo stereotactic ablative radiotherapy. To understand whether placing a hydrogel spacer can meaningfully reduce this risk, a phase II trial (NCT02353832) at the University of Texas Southwestern Medical Center has enrolled 44 patients with low-risk prostate cancer. Planned follow-up time is 5 years, and secondary outcome measures include acute toxicities, at least a 50% reduction in the circumference of rectum receiving 24 and 39 Gy radiation, and the stability of the spacer during treatment.

Additionally, a post-marketing surveillance trial (NCT01999660) in Germany is recruiting an estimated 250 patients with T1 to T2, N0, M0 prostate cancer. The primary endpoint is late rectal complications for up to 5 years after IMRT, 3DCRT, or brachytherapy. The secondary outcome is quality of life based on the EPIC questionnaire in combination with the Short Form Health Survey (SF-12). The investigators also are evaluating the immediate feasibility and safety of hydrogel injection. Primary results are expected in January 2019. The results of this study will



help clarify the effects of SpaceOAR placement on late toxicities and quality of life across a range of radiotherapy modalities for prostate cancer.

SUMMARY

Injecting a transperineal spacer prior to radiotherapy can help prevent rectal adverse events by protecting the organ at risk (OAR) from radiation toxicity. Currently, the only FDA-approved prostate cancer spacing device available for use in the United States is SpaceOAR, a polyethylene glycol (PEG) hydrogel spacer. In clinical trials, SpaceOAR placement significantly reduced irradiation of the rectum and penis during prostate radiotherapy. Long-term follow-up of the pivotal phase III trial also showed significant reductions in late gastrointestinal and genitourinary toxicities, with corresponding improvements in bowel, urinary, and sexual quality of life.[5, 32, 33,34] The spacer is well tolerated, inserting it is straightforward, and the risk of postprocedural adverse events is low. It is becoming an important component of prostate radiotherapy. Additional studies of hydrogel spacers are ongoing. Urologists and radiation oncologists can work in tandem in order to further benefit prostate cancer patients who elect to proceed with radiation therapy. ■

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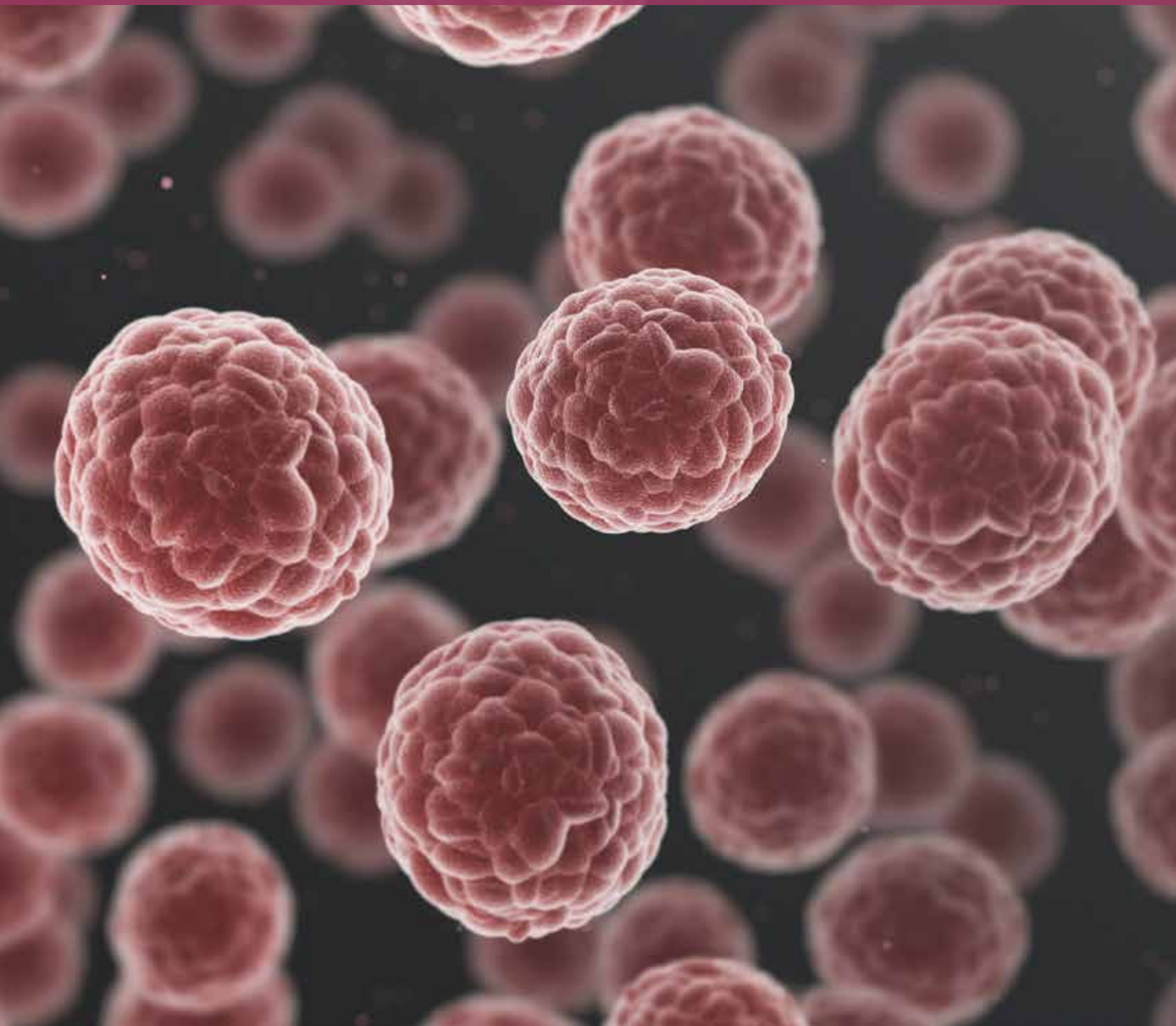
BLUE LIGHT CYSTOSCOPY: Insights on Recurrence, Progression, and Clinical Management

By Ashish M. Kamat, MD, MBBS



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More than 81,000 individuals are diagnosed with bladder cancer in the United States every year, of whom 75% have non-muscle invasive disease.[1,2] Unfortunately, half these cases recur despite transurethral resection of bladder tumor (TURBT), and from 5% to 25% of repeated recurrences progress to muscle-invasive disease.[3,4,5]

Reliable visualization of bladder tumors is crucial to the success of TURBT, but carcinoma in situ (CIS) and other low-grade flat lesions are difficult to detect under standard white light cystoscopy. 6,7,8 In a recent meta-analysis of raw data from six prospective studies, white light cystoscopy missed 24.9% of Ta and T1 tumors and 26.7% of CIS tumors. 9 Other studies have associated white light cystoscopy with miss rates of 10% to 45%, depending patient subgroups.[10]

Evidence consistently indicates that the addition of blue light cystoscopy to white light cystoscopy improves the detection and resection of non-muscle invasive bladder malignancies over white light cystoscopy alone.[11,12] Blue light cystoscopy is used in conjunction with a photoactive porphyrin, either 5-aminolevulinic acid (ALA) or hexaminolevulinate hydrochloride (HAL), which accrues preferentially in neoplastic tissue and fluoresces when exposed to blue light between 375 and 440 nm in wavelength.[13,14] In a large real-world study, HAL-assisted blue light cystoscopy detected bladder carcinoma in situ (CIS) with a sensitivity of 75%, compared with 52.8% for white light cystoscopy (P=.02).[12] In the previously cited meta-analysis of raw data, HAL-assisted blue light cystoscopy detected significantly more Ta tumors and CIS lesions compared with white light alone ($P < .001$ for each comparison).[9] Importantly, this result spanned subgroups of intermediate and high-risk patients and patients with both primary and recurrent tumors.[9]

Based on such findings, joint guidelines from the American Urological Association (AUA) and the Society of Urologic Oncology (SUO) now recommend offering blue light cystoscopy to all patients with non-muscle invasive bladder cancer and considering blue light cystoscopy for patients with a history of non-muscle invasive bladder cancer and positive cytology.[15]

It is important to emphasize that blue light cystoscopy should be used in conjunction with white light cystoscopy, not as a replacement. In a multicenter study of 311 patients with known or suspected bladder cancer, HAL-assisted blue light cystoscopy missed 9% of tumors visualized by white light cystoscopy, including 5% of T1 tumors.[16] In the same study, HAL-assisted blue light cystoscopy detected at least one additional tumor compared with white light cystoscopy in 29% of patients and detected at least one additional T1 tumor in 15% of patients.[16] Thus, both white light and blue light must be used in the same patient to obtain maximum benefit.

It is important to emphasize that blue light cystoscopy should be used in conjunction with white light cystoscopy and is not a replacement.

Hexaminolevulinate was approved by the U.S. Food and Drug Administration (FDA) in 2010 for the cystoscopic detection of non-muscle invasive bladder cancer in patients with known or suspected lesions based on prior cystoscopy.[17] Because the procedure has required a rigid cystoscope, it generally has been performed under anesthesia.

However, in February 2018, the FDA approved a supplemental new drug application for the use of a HAL in conjunction with

a flexible cystoscope, the Karl Storz D-Light C Photodynamic Diagnostic system.[17,18] This approval effectively expanded the use of blue light cystoscopy into outpatient settings. Understanding the advantages and caveats of blue light cystoscopy can help us better care for our hospitalized patients and outpatients with suspected or confirmed bladder cancer.

BLUE LIGHT CYSTOSCOPY REDUCES RISK OF RECURRENCE

Blue light cystoscopy has been used for approximately 20 years in Europe, and multiple studies there have associated this enhanced technique with significantly prolonged recurrence-free survival that is potentially maintained for years following TURBT.

In one such randomized study, 115 patients with non-muscle invasive bladder cancer underwent TURBT with either conventional white light cystoscopy or ALA-assisted blue light cystoscopy.[19] Cancer recurred after a median of 5 months in the white-light group compared with 12 months in the ALA blue light group.[19] After 36 months, rates of recurrence were 73% in the white-light group versus 59% in the blue-light group.[19] Centers elsewhere in Europe reported similar results. In a single-center randomized trial in Romania, blue light cystoscopy identified 25.8% more non-muscle invasive bladder tumors than did white light cystoscopy, leading to a 27% reduction in the rate of 12-month recurrence.[20]

Particularly compelling are the results of a phase III, randomized, prospective study of 814 patients in Germany with suspected bladder cancer at increased risk for recurrence.[6] All patients underwent white light cystoscopy and TURBT with or without intravesical HAL-assisted blue light cystoscopy before and after resection. 6 Among 286 patients with at least one Ta or T1 bladder tumor detected, blue light cystoscopy was associated with a 16% decrease in recurrence at 9 months.[6] This effect persisted at a median of 54 months of follow-up, when 38% of patients in the blue light group remained tumor-free versus 31.8% of the white light group (median time to recurrence, 16.4 months vs. 9.6 months, respectively; P = .04).[21] Furthermore, there was a trend toward a decreased risk of cystectomy in the blue light group.

Blue light cystoscopy has been used for approximately 20 years in Europe, and multiple studies there have associated this enhanced technique with significantly prolonged recurrence-free survival that is potentially maintained for years following TURBT.

The meta-analysis of raw data also linked HAL-assisted blue light cystoscopy and resection with a 24% lower risk of recurrence at 12 months compared with white light cystoscopy alone (risk ratio, 0.76; 95% confidence interval [CI], 0.63 to 0.92; P = .006).[9] In a separate single-center prospective study, researchers in the United Kingdom evaluated the effects of switching from standard white light cystoscopy to white light plus HAL-assisted blue light cystoscopy.[22] A total of 345 patients with non-muscle invasive bladder cancer underwent one of these modalities in conjunction with high-quality TURBT, followed by intravesical mitomycin C administered within 24 hours post-surgery.[22] One-year rates of recurrence were 38.9% when the hospital used only white light cystoscopy versus 21.5% after the addition of blue light cystoscopy (P < .001). This finding spanned risk-based subgroups and patients matched by age, multifocality, length of follow-up, and tumor grade, stage, and size. Furthermore, the reduction in risk of recurrence remained statistically significant at 3-year follow-up (39.0% vs. 53.3%, respectively; P=.02) (P < .001).[22]

Several other studies have compared longer-term rates of recurrence between blue light and white light cystoscopy. In a single-center medical database analysis of 159 cases of recurrent non-muscle invasive bladder cancer treated by a single surgeon performing TURBT, 44 cases involved HAL-assisted blue light cystoscopy and 115 cases were performed with white light cystoscopy alone.[23] In the multivariate analysis, blue light cystoscopy was associated with a significant reduction in 3-year risk of recurrence (adjusted hazard ratio, 0.42; 95% CI, 0.25 to 0.70; P = .001).[23] Three years after TURBT, 53.7% of blue light patients remained recurrence-free versus 27.4% of white light patients.[23]

Looking beyond TURBT, blue light cystoscopy also is useful for the surveillance of patients who are considered at high risk for bladder cancer recurrence. In a multicenter phase III study, 304 such patients received intravesical HAL (Hexvix® or Cysview®) and white light flexible cystoscopy, after which they were randomly assigned to undergo either blue light flexible cystoscopy or no additional evaluation.[8] Among 63 patients with confirmed recurrent malignancies, 20.6% (95% CI, 11.5% to 32.7%) were detected only by blue light cystoscopy (P<.0001). Strikingly, blue light cystoscopy detected additional lesions in 46% of patients.[8] Furthermore, among 26 CIS lesions, 34.6% (95% CI, 17.2% to 55.7%) were only detected by blue light cystoscopy.

BLUE LIGHT CYSTOSCOPY AND PROGRESSION

Disease progression is one of the most important clinical sequelae of non-muscle invasive bladder cancer, as it signifies worsening of disease and is an independent predictor of cancer-related mortality. 24,25,26,27 The effects of blue light cystoscopy on progression are less clear; early studies documented reductions in recurrence that did not appear to translate to an impact progression. 28,29

For example, in a prospective, randomized, double-blind

study, 370 patients with non-muscle invasive bladder cancer received either intravesical 5-ALA or placebo before undergoing cystoscopy under white and blue light.[29] Twelve months after tumor resection, rates of progression-free survival were identical (89%) between study arms.

In another 12-month, randomized, multicenter trial, 5-ALA-assisted blue light cystoscopy detected more lesions than white light cystoscopy alone, but did not confer significant improvements in progression-free survival.[30]

These results reflect at least two shortcomings in research on cystoscopy and progression. The first is the indolent nature of some early-stage bladder tumors; they may recur and progress over years, rather than months. We need longer-term prospective studies to assess the effects of enhanced tumor detection on progression of non-muscle invasive bladder cancer.

The second limitation is that older studies tended to define progression inconsistently, imprecisely, and often too strictly to detect clinically important events. It has been only four years since the International Bladder Cancer Group (IBCG) called for a uniform, more sensitive definition of progression in order to facilitate earlier-stage diagnosis as well as cross-study comparisons.[31] In this paper, the IBCG suggested defining progression as any one of the following: an increase in T stage leading to invasion of the lamina propria (T1 disease), the development of muscle-invasive disease (stage T2 or greater), progression to lymph node (N+) or distant metastasis (M1), or an increase in grade from low to high.[31]

Based on this new definition, does the addition of blue light cystoscopy to standard white light cystoscopy appear to affect progression? In the phase III study in Germany, which was published prior to the proposed IBCG definition, researchers defined progression as non-muscle-invasive tumors becoming muscle-invasive. Based on this definition, the researchers reported a non-significant trend toward lower risk of progression among patients who underwent HAL-assisted blue light cystoscopy instead of white light cystoscopy only.[6] After 9 months, progression to muscle-invasive disease had occurred among nine patients in the white light group and seven patients in the blue light group. After a median of 4.5 years, eight and 16 patients, respectively, had progressed to stage T2-T4 disease.[21]

Recently, my colleagues and I re-analyzed the German data based on the IBCG definition. 24 We identified more progressors in both groups: 31 (12.2%) patients in the blue-light group and 46 (17.6%) patients in the white-light group. Progression from Ta to CIS tumors occurred in four (1.6%) blue-light patients and 11 (4.2%) white-light patients.[24] The difference in rates of progression trended toward statistical significance, favoring the blue-light group (P = .085).[24] Median time to progression also was longer in the blue light group (P = .05), possibly because of better detection and resection of earlier-stage disease.[24] Furthermore, blue light cystoscopy was associated with a trend toward improved progression-free survival (P=.05).[24]

The authors of a recent systematic review and meta-analysis also concluded that the use of HAL-assisted blue light cystoscopy in combination with white light cystoscopy reduced the likelihood of progression following TURBT.[32] This meta-analysis, which specifically focused on progression, included four randomized studies and one retrospective study published between 2000 and 2016. Among 1,301 patients who underwent TURBT, approximately half received blue light cystoscopy in addition to white light cystoscopy while the rest were evaluated with white light alone.[32] After a median follow-up period of approximately 38 months, 10.7% of white-light patients had progressed, compared with only 6.8% of blue-light patients. As a result, the odds of progression were 64% higher among patients who underwent TURBT without blue light cystoscopy (median odds ratio, 1.64, 95% CI, 1.10 to 2.45; P=.01).[32]

Disease progression is one of the most important clinical sequelae of non-muscle invasive bladder cancer, as it signifies worsening of disease and is an independent predictor of cancer-related mortality.

In summary, while more research is needed, we have limited data suggesting that blue light cystoscopy can delay progression by facilitating earlier detection and resection of bladder tumors.

IMPACT ON PATIENT MANAGEMENT

Several studies also indicate that improved detection of bladder tumors with blue light cystoscopy leads to important improvements in management, including the use of intravesical therapy, earlier cystectomy, and closer surveillance.

In one prospective, randomized study of 362 patients with suspected non-muscle invasive bladder cancer, the use of HAL-assisted blue light cystoscopy detected more tumors in 35% of patients compared with white light cystoscopy alone.[33] Respective rates of recurrence were 7.2% versus 15.8% at 3 months, 21.6% versus 32.5% at 1 year, and 31.2% versus 45.6% at 2 years.[33] Although progression rates at 1 and 2 years did not significantly differ (2.4% vs. 4.4%; P=.2, and 4% vs. 7%, respectively; P=.12), the study authors reported that by detecting additional lesions, blue light cystoscopy led to meaningful changes in treatment, such as the use of intravesical BCG or chemotherapy instead of forgoing postoperative therapy.[33]

In another randomized study of 146 patients, an independent blinded urologist reviewed two sets of records, one of which only described the results of white light cystoscopy and the other of which also included the results of HAL-assisted blue light cystoscopy.[11] The addition of blue light cystoscopy findings improved

YEAR AUTHOR	MODALITIES	PATIENTS	OUTCOME
2018 Daneshmand	WLC +/- BLC + biopsy or TURBT	304 patients at high risk of recurrence	34.6% of recurrent CIS were detected only by BLC
2014 Gkritsios	WLC +/- BLC + TURBT	130 patients with NMIBC	29.6% recurrences detected only by BLC. Recurrence rates did not differ significantly after up to 40 months follow-up.
2013 O'Brian	HAL-PDD vs. WLC + TURBT + intravesical mitomycin C	249 patients with de novo NMIBC	Rates of secondary CIS detected: 26% for HAL-PDD vs. 14% for WLC (P = .04). No significant differences in recurrence between arms at 3 or 12 months.
2010 Stenzl 2012 Grossman 2016 Kamat	WLC +/- BLC + TURBT	814 patients suspected to have BC at increased risk for recurrence	At 9-month follow-up, recurrence rates: 47% for WLC-BLC vs. 56% for WLC-only. BLC: 16% lower recurrence at 9 months. Grossman: 551 patients followed >52 months; tumor-free rates 31.8% for WLC vs. 38% for WLC-BLC. Median rates of recurrence-free survival: 9.6 vs. 16.4 months, respectively (P=.04). Kamat: Based on updated IBCG definition of progression, time to progression was longer w/ HAL-BLC vs. WLC (P = .05)
2012 Geavlete	WLC +/- HAL-BLC + TURBT + mitomycin C +/- intravesical chemotherapy or BCG	362 patients with suspected NMIBC	HAL-BLC detected additional tumors in 35% of patients. 3-month recurrence: 7.2% for HAL-BLCàlower recurrence at 3 months (7.2% vs. 15.8% for WLC), 1 year (21.6% vs. 32.5%), 2 years (31.2% vs. 45.6%).
2011 Stenzl	WLC +/- BLC + TURBT	370 patients with NMIBC	Blue light with 5-aminolevulinic acid detected more tumors but did not did not improve 12-month recurrence-free or progression-free survival
2011 Drăgoescu	HAL-PDD vs. WLC	44 patients with NMIBC	HAL-PDD detected 25.8% more tumors than WLC (P=.004) and led to significantly lower recurrence rates through 12 months (HR=0.33, 95% CI 0.11-0.98).
2010 Geavlete	WLC or BLC + TURBT	446 patients with high-risk NMIBC (CIS, pTaG3, pT1)	Recurrence rates at Re-TURBT: 11.1% for blue light vs. 31.2% for white light. Recurrence rates by tumor type all favored blue light.
2007 Grossman	HAL-BLC and WLC	311 patients with known or suspected BC	HAL-BLC detected >1 more tumor than WLC in 29% of patients, and >1 more T1 tumor in 15%. WLC detected >1 more tumor than HAL-BLC in 9% of patients, and >1 more T1 tumor in 5%.

Table 1. *Blue light cystoscopy: Randomized controlled trials*

BC: bladder cancer
CIS: carcinoma in situ
HAL-BLC: hexaminolevulinate blue light cystoscopy
IBCG: International Bladder Cancer Group
NMIBC: non-muscle invasive bladder cancer
PDD: photodynamic diagnosis
WLC: white light cystoscopy

the management of 21.7% patients, including more extensive resections in 10 patients and additional postoperative procedures in 15 patients. 11 In a third small study of 39 patients, 38% had additional papillary and flat lesions detected by HAL-assisted blue light cystoscopy.[34] The use of blue light cystoscopy led to changes in management, including the use of BCG instead of mitomycin C, in 13% of patients.[34]

Blue light cystoscopy also is useful after TURBT to confirm treatment efficacy. By improving the accuracy of post-TURBT assessments, blue light cystoscopy can spare patients the pain, risks, and cost of unnecessary treatment.[35] This is because residual tumor that persists after TURBT and instillation therapy can be misinterpreted as treatment failure, leading to more radical treatment.[35]

SAFETY AND QUALITY OF LIFE

Blue light cystoscopy generally is well tolerated.[17,36] The main cause of adverse events is catheterization. In randomized trials of fluorescence cystoscopy and TURBT with up to 2 years of follow-up, the most common adverse events were hematuria, dysuria, and bladder spasm, which were equally likely with blue and white light cystoscopy and were concluded to be related to resection.[36] In another study of post-marketing data from more than 200,000 patients, there were no serious adverse events definitively attributed to HAL-assisted blue light cystoscopy and its repeated use did not appear to increase the risk of toxicities.[37]

Earlier and more accurate detection of non-muscle invasive disease can reduce and delay the need for more invasive procedures, such as repeat TURBT and cystectomy. As a result, several studies have found that the use of blue light cystoscopy led to significant reductions in health care costs and improvements in patient quality of life.[38,39,40]

Perhaps the most robust of these studies was a prospective, multicenter, phase III trial published in July 2018.[41] For the study, researchers used HAL-assisted blue light flexible cystoscopy for the office-based surveillance of non-muscle invasive bladder cancer in patients at high risk of recurrence.[41]

Among 304 enrolled patients, 103 individuals were referred for surgical examination, and 63 had histologically confirmed malignancies.[41] After patients underwent blue light cystoscopy, their scores on the anxiety instrument of the Patient-Reported Outcomes Measurement Information System (PROMIS) decreased by 2.6 points, an effect that was independent of patient gender, test performance, or cystoscopy result.[41] Furthermore, 94% of patients reported that blue light cystoscopy was worthwhile and that they would undergo it again, while 91% stated that they would recommend blue light cystoscopy to other patients.[41] Finally, three-quarters of patients said that they would be willing to pay for blue light cystoscopy out-of-pocket.[41] These findings suggest that blue light cystoscopy is acceptable to and valued by high-risk patients in outpatient settings.

ALTERNATIVES TO BLUE LIGHT CYSTOSCOPY

Fluorescence is not our only available option for enhanced cystoscopy. An alternative is narrow band imaging (NBI), a technology that excludes the red spectrum of light in order to increase contrast between mucosal vasculature and superficial tissue structures of the bladder.[42] Narrow band imaging does not require instillation of agents into the bladder, and the technology is already present on many cystoscopes used in clinics and hospitals.

Several studies have found that narrow band imaging detected CIS and other non-muscle invasive bladder tumors with greater sensitivity than white light cystoscopy alone.[42,43] In a randomized prospective trial, rates of 1-year post-TURBT recurrence rates were approximately 33% with narrow band imaging versus 51% with white light cystoscopy alone (P = .01).[44]

In another recent meta-analysis of 25 studies, narrow band imaging detected lesions in 10% more patients (95% CI, 5% to 14%) than white light cystoscopy and detected 19% more lesions per patient (95% CI, 15% to 25%).[43] Narrow band imaging also was associated with a significantly reduced rate of recurrence compared with white light cystoscopy. Pooled risk ratios were 0.43 (95% CI, 0.23 to 0.79) at 3 months and 0.81 (95% CI, 0.69 to 0.95) at 12 months.[43]

In another network meta-analysis of 15 randomized controlled trials, narrow band imaging and blue light cystoscopy were associated with a statistically similar risk of recurrence after TURBT (OR = 1.11, 95% CI, 0.55 to 2.1), and both modalities significantly outperformed white light cystoscopy alone.[42] To date, however, we have no randomized head-to-head studies of blue light cystoscopy versus narrow band imaging in the setting of either resection or surveillance.

Several studies have found that narrow band imaging detected CIS and other non-muscle invasive bladder tumors with greater sensitivity than white light cystoscopy alone.

SUMMARY

Enhanced cystoscopy techniques are an essential addition to our armamentarium for the detection and treatment of bladder cancer. Two recently developed technologies are currently in clinical use – narrow band imaging (NBI) and blue light cystoscopy. Among the two, blue light cystoscopy has been studied more extensively and has been shown to significantly improve the detection of initial and recurrent non-muscle invasive bladder tumors, particularly CIS and other low-grade flat lesions that are difficult to detect with white light cystoscopy alone. Results from

multiple studies indicate that blue light cystoscopy significantly improves recurrence-free survival and also is useful to confirm the efficacy of TURBT and guide post-operative decision-making. Emerging data also suggest that improved tumor detection – and resection - with blue light cystoscopy reduces the risk of progression. However, it must be emphasized that blue light cystoscopy is not a stand-alone technique and must be performed in conjunction with white light cystoscopy. ■

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Global Conferences

Halifax, Nova Scotia

Acupulco, Mexico

GLOBAL CONFERENCE COVERAGE

Canadian Urological Association Meeting
Halifax, Nova Scotia // June 23-24

Mexican Urologic Oncology Association Meeting
Acapulco, Mexico // July 26-28

International conferences offer a multi- specialty of clinicians the unique opportunity to interact directly with their colleagues based in different regions of the world. With many global meetings taking place during the summer of 2018, here we showcase two such conferences, and some of the breaking presentations on prostate, kidney and bladder cancer given and discussed there.

For more information presented at these meetings, including further covered focused on these disease areas and others, please visit the "Conference Coverage" page on UroToday.com.

Prostate Cancer

CANADIAN UROLOGICAL ASSOCIATION ANNUAL MEETING 2018

Current Management of M0 CRPC


Dr. Kim Chi

Kim Chi, MD, gave an overview of the current treatment strategies for M0 castrate resistant prostate cancer patients (MCRPC). The New England paper published by Juanita Crook in 2012[1] demonstrated that intermittent androgen deprivation therapy (ADT) was not inferior to continuous ADT for rising PSA after radiotherapy for prostate cancer (PC) patients.

The value of total PSA and PSA doubling time (DT) also has a tremendous effect on the proportion of patients developing bone metastasis or dying from the disease.[2]

For patients transitioning to the status of CRPC, some "vintage" 2nd line hormonal therapies include:

- Addition/changing of non-steroidal anti androgen (NSAA)
- Withdrawal of NSAA
- Addition of corticosteroids
- Addition of Ketoconazole
- Addition of Estrogen

Adding Denosumab to these patients has been shown to improve bone metastasis free survival with a hazard ratio (HR) of 0.85 (95% C.I 0.73-0.98), but did not improve overall survival (OS) in M0 CRPC patients.[3] The STRIVE study demonstrated a clear advantage in disease progression and death, in favor of Enzalutamide, when compared to bicalutamide, in patients with non-metastatic or metastatic CRPC.[4]

Most recently, the PROSPER study,[5] showed a clear advantage when M0 CRPC patients were treated with enzalutamide, compared to placebo, in terms of:

- Metastasis free survival (MFS) (Figure 4)
- Time to PSA progression
- Time to use of new antineoplastic therapy
- PSA response

Another recently reported study is the SPARTAN trial comparing Apalutamide to Placebo in M0 CRPC patients.[6] Like the PROSPER trial, this trial showed a similar advantage to treatment with Apalutamide, when compared to placebo, in terms of MFS.

Dr. Chi concluded his great overview mentioning some important controversies and considerations. The 1st point is that it is difficult to extrapolate all these data to all M0 patients. Most patients analyzed were very high risk, with a PSA doubling time of less than 6 months (high risk is defined as PSA doubling time of less than 10 months). Another important point is that MFS is apparently a clinically meaningful and worthwhile endpoint. Furthermore, in these trials, there was no difference in the OS between the different treatment arms. This could be due to cross-over and subsequent treatment in the placebo arms, or because disease progression is different, because of androgen resistant CRPC. Additionally, the quality of life won't be able to get better, and if anything, it is just going to get worse, due to treatment toxicity.

Some additional important points included the addition of PSMA PET scans into the standard of care. This could totally re-stratify no-metastatic patients as metastatic patients, and change their allocation, and might even improve the outcomes. Lastly, we need to consider the evolving management of oligometastasis.

In summary, patients with M0 CRPC and short PSA doubling time (<6 months) are at higher risk of developing metastasis. In Canada, there is currently no approved treatment for M0 CRPC patients, and Denosumab and zoledronic acid are not indicated. The most recent trials (PROSPER, and SPARTAN) have demonstrated that both Apalutamide and Enzalutamide demonstrate substantial benefits in MFS and other progression events. To date, these trials do not show any OS benefit, and the decision to treat should be individualized and restricted to high risk patients only.

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CANADIAN UROLOGICAL ASSOCIATION ANNUAL MEETING 2018

Evolving Approaches in Diagnosing Prostate Cancer: Beyond PSA


Dr. Frank Bladou

This session covered several topics in the diagnosis of prostate cancer (PC). The topics that were covered included:

1. Usage of MRI in biopsy naïve patients
2. MRI in the optimization of surgical outcomes – role for nerve sparing planning and high-risk disease
3. Metastatic PC

Frank Bladou, MD, started this session talking about the role of MRI as a triage test in biopsy naïve patients. The problem with the current standard of diagnosis of trans-rectal ultrasound (TRUS) guided biopsy is the over-detection of insignificant PC, and under-detection of clinically significant PC. According to Dr. Bladou, image targeted biopsy would improve the results of systematic biopsy by increasing the diagnosis of clinically significant PC, decreasing the diagnosis of clinically


insignificant PC, and decreasing the need for unnecessary biopsies in general.

Currently, mpMRI in Canada is approved only after a previous negative TRUS biopsy. Dr. Bladou thinks that we can avoid 12 core systematic biopsy and do only MRI -targeted biopsies. This is not yet recommended, but there is supporting evidence from the PROMIS study[1] and the PRECISION study2. According to the PROMIS study, MPMRI can be used as a triage test before first biopsy to allow 27% of men at risk to avoid a biopsy. MRI targeted biopsies improve detection of clinically significant cancer (18% more vs. standard TRUS biopsy). MPMRI can also reduce the over-diagnosis of clinically insignificant PC in 5% of cases. Similar findings were shown in the recently published PRECISION trial[2].

Next, Freddie Hamdy, MD, discussed the topic of MRI in optimization of surgical outcomes. He began by discussing the indications for nerve sparing. This depends on a multitude of factors, including preoperative sexual activity, disease grade and volume, serum PSA, mpMRI findings, digital rectal examination (DRE) findings, operative findings, nomogram results, and additional technology developments which are underway.

Dr. Hamdy gave some details on the differences between the US and Europe, stating that approaches to indications and delivery of radical prostatectomy are similar on both continents. Open surgery is still offered with excellent results in high-volume centers in Europe. There is a clear trend showing reduction in surgery for low risk disease in both continents. The major differences between US and UK/Europe is in the speed of mpMRI uptake (majority of UK centers now perform pre-biopsy mpMRI, and most European centers have access to PSMA-PET CT). Lastly, there is greater considerable interest in genomic markers in the US compared to Europe.

Dr. Hamdy concluded his talk by sharing his opinion on radical prostatectomy for high risk disease. Preoperative mpMRI should definitely be done in these patients before attempting surgery, and recently, a nomogram developed to incorporate mpMRI results for prediction of extracapsular extension of PC has been published.[3] Additional factors to be taken into consideration in these high-risk patients before surgery, include careful pre-operative evaluation, careful patient counselling for expectations, and we need to make sure that there are no positive margins. Extended lymphadenectomy must be performed and patients must be explained the risk of salvage/adjuvant radiation, which is highly likely in high risk disease. Lastly, these patients need to be followed and treated with multimodality additional treatments as necessary.

Frederick Pouliot, MD, PhD, continued the discussion on the usage of imaging in high risk PC patients. According to the AUA-ASTRO-SUO guideline recommendations cross sectional imaging, in the form of cross sectional abdominopelvic CT or prostate and pelvis MRI, and bone scan should be done in patients with:

- Unfavorable intermediate risk disease (2 or more of the following – palpable nodule on DRE, Gleason 7 disease, and PSA above 10 ng/ml)
- High risk disease (PSA >20 ng/ml, or grade group 4-5, or clinical stage >T3)

However, the specificity and sensitivity of the currently used bone scan for detecting bone metastasis is lower than that of Choline PET/CT (96% vs. 80% sensitivity, and 91% vs. 79% specificity). Therefore, abnormal findings on conventional imaging in the form of bone scan will be false positive in 20% of patients. This leads us to use new imaging modalities in staging these patients.

Dr. Bladou gave another talk on the topic of molecular imaging of PC (Flurocholine and PSMA PET/CT). PET/CT fusion imaging is a multimodal hybrid imaging modality which delivers both anatomical and functional data at the same time. The proposed indications for PET scans in PC include:

- Restaging of biochemically recurrent disease (PSA relapse)
- Initial staging in high-risk patients
- Treatment monitoring of patients with metastatic disease

Dr. Bladou gave an overview of the F-Fluoromethcholine (FCH) PET/CT. Choline is required for synthesis of cell membrane phospholipids. It is taken up avidly by PC cells and is cleared quite quickly from the blood. It is relatively easy to synthesize on cassette-based systems and inexpensive. The Jewish General hospital experience in Montreal, Canada with FCH was then presented, demonstrating a sensitivity of 84% and specificity of 65% in patients with biochemical recurrence.[4] When assessing FCH in the staging of high risk patients, it demonstrated a sensitivity of 62-64% and specificity of 100% for both bone and lymph node metastasis. The main limitations of FCH include its limited value for T-staging at diagnosis, where mpMRI is superior. Additionally, it has poor sensitivity for N-staging in high risk patients, and poor yield in PSA recurrence when PSA levels are low, or when the Gleason score is low.

Dr. Bladou continued and gave a short summary of the PSMA PET scan. The prostate specific membrane antigen (PSMA) is located on the cell surface, and not released into circulation. It is reliably increased in PC, and is a very attractive imaging target. Its expression is increased with higher Gleason score. The PSMA used for imaging in PET scans is urea based, and is a very small molecule with very rapid blood clearance. It targets the extracellular domain of the PSMA on the cell. Importantly, it has a very high target to background ratio. This radiotracer will emerge as the PC imaging gold standard and will be used in the future for:

1. Therapy planning upon PSA recurrence
2. Whole body staging of patients with high risk disease
3. Evaluation of therapy response

The outstanding session was then summarized with the nine dimensions of molecular imaging in PC:

1. The x, y, and z dimensions which make up the volume of the lesion
2. Location of the lesion (lymph node, vs. bone, vs. visceral)
3. Intensity of lesions
4. Change with time (dynamic)
5. Polyclonality
6. Androgen receptor negative differentiation
7. Predictive biomarker for PSMA

Imaging is important for PC diagnosis, and especially metastatic PC. It helps establish prognosis and determine best therapy. Approximately 25% of metastatic castrate resistant patients progress on imaging without PSA rise, despite a median PSA around 80 ng/ml at baseline. Polyclonality has been shown in molecular studies and imaging can track polyclonality and AR-negative differentiation. Active tracking of AR negative differentiation or resistance will enable initiation of new lines of therapy earlier or multimodal treatments.

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CANADIAN UROLOGICAL ASSOCIATION ANNUAL MEETING 2018

Robotic vs. Open Prostatectomy: A Real-World, Single-Centre Canadian Experience

Current data demonstrate similar outcomes in robotic and open radical prostatectomies (RP). However, there is still a debate surrounding the benefits of robotic vs. RP. The authors presented a study aiming to compare real-world perioperative outcomes of both modalities at a large Canadian academic centre.

This was a large retrospective review of all prostatectomies performed at The Ottawa Hospital between 2009 and 2016. The authors assessed various patient factors, including age, body mass index, Association of Anesthesiologists [ASA] score), operative and perioperative outcomes (length of post-anesthetic care unit [PACU] stay, pain score, length of hospital stay, transfusion rate, readmission or return to the emergency room within 30 days, and hospital cost). The primary outcome was rate of transfusion during admission. Both univariate and multivariable analyses were performed to identify factors associated with transfusion.

Overall, A total of 1606 prostatectomies were analyzed for the purpose of this study. These were performed by 12 surgeons during the study period with 840 being robotic cases (52%), and 766 open cases (48%). The number of cases performed by year is shown in Figure 1. When assessing the rate of transfusion, it was significantly lower in the robotic cases (0.6% vs. 11.2%; p<0.001). The robotic prostatectomy cohort had fewer regional anesthetics (0% vs. 60.3%; p<0.001). Other patient and procedure characteristics are shown in table 1. Additionally, the robotic cases had shorter length of recovery room stay (155.7 minutes vs. 231.1 minutes; p<0.001), and shorter length of hospital stay (1.4 days vs. 2.8 days; p<0.001). Additional operative outcomes are shown in table 2. As expected, the financial costs were significantly higher with the robotic cases, with $800 higher cost per case (p<0.001).

The authors of this study concluded that robotic prostatectomy is associated with improved outcomes when introduced to a program with surgeons of various levels of experience and training. Transfusions and length of hospital stay are decreased when robotic surgery is used for prostatectomy compared to an open approach. In any case, additional studies are needed to determine the true impact of robotic technology on prostate surgery.

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CANADIAN UROLOGICAL ASSOCIATION ANNUAL MEETING 2018

Real-World Evidence in Patient-Related Outcomes of Metastatic Castrate-Resistant Prostate Cancer Patients Treated with Abiraterone Acetate Plus Prednisone

Dr. Geoffrey Gotto

Abiraterone acetate, given in conjunction with prednisone (AA+P), is an oral androgen biosynthesis inhibitor that targets the androgen axis. It is one of two androgen-receptor axis targeted therapies (the other being enzalutamide) that has dramatically altered the management of advanced prostate cancer. As an oral agent, it is an excellent alternative to chemotherapy (docetaxel) and has become a standard of care for metastatic castration-resistant prostate cancer (mCRPC). Indeed, newer studies have demonstrated benefit in earlier stages of the disease and it may soon be used for hormone-sensitive metastatic prostate cancer.

However, continued work is looking at the patient-reported outcomes, rather than just oncologic benefit, to these novel agents. The COSMiC study (Canadian Observational Study in Metastatic Cancer of the Prostate; ClinicalTrials.gov: NCT02364531) is one such study and set out to prospectively amass real-world data on mCRPC patients managed with AA+P within Canada. In this presentation, they report the interim analysis.

At a median follow-up of 39.8 weeks, 264 patients were enrolled from 39 sites. The median age of patients was 77 years. Time from metastasis diagnosis is 16.8 months. Bone metastases predominated (84%) in this population. 47% have Gleason 8-10 disease.

All patients were assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) and Montreal Cognitive Assessment (MoCA) tests at baseline and then again at weeks 12, 24, 48, and 72 after AA+P initiation. A 10-point drop denotes clinically significant degradation in FACT-P and a total MoCA score of ≥26 is considered normal.

- In term of available responses, response rates dropped significantly throughout the study trial period
- Starting at 100% at baseline, response rates dropped to 72% week 24, and 24% at week 72 and 22% at the end of the study

Mean baseline FACT-P total score was 111.2 (19.44). On follow-up, at all time points, there was a <3-point absolute change from baseline, denoting no clinically significant change in functional status over time.

The mean baseline MoCA score was 25.2 (4.50) – lower than normal at baseline. Yet all subsequent assessments after baseline scored above 26 and a mean absolute change from baseline of <1, showing an absence of cognitive decline over time.

In terms of oncologic outcomes, which was not the primary outcome, prostate-specific antigen (PSA) value was available for 221 patients; 64.3% (142/221) and 34.4% (76/221) achieved a PSA decline of >50% and 90%, respectively. This was in line with COU-AA 302 results.

Lastly, in terms of tolerability, all-grade treatment-related adverse events were reported in 63 patients, with 11% who have had AA+P discontinuation/interruption. This was less than previously reported.

Ultimately, in this interim analysis of the COSMiC study, AA+P, in a real-world setting, appears to maintain men's quality of life and cognitive status over the course of treatment.

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CANADIAN UROLOGICAL ASSOCIATION ANNUAL MEETING 2018

Prostate Cancer: A Disease of our Time

Dr. Freddie Hamdy

Freddie Hamdy, MD, gave an interesting overview of prostate cancer (PC). He began with statistics regarding the United Kingdom and Canada. In the UK and Canada, 31 and 11 men die of PC every day, respectively. Dr. Hamdy then described the paradigm changes in PC over the past century. In the 19th Century microscopy appeared and cases were increasingly described in the literature. In the early 20th century all men with PC presented with advanced disease and eventually died. During this period, Huggins and Hodges discovered androgen dependence. In the mid-20th century most men with PC still presented with advanced disease and died, but surgery and radiation were starting to be used. In the 1980s PSA was discovered, transrectal ultrasound (TRUS) guided biopsies are developed, and the anatomical radical prostatectomy was introduced. We know today, that PC diagnosis is correlated to PSA levels, with 6.6% of patients with PSA < 0.5 ng/ml harboring cancer, and 26.9% of patients with PSA 3.1-4 ng/ml harboring cancer.

PC is a global problem with increased rates of diagnosis in all countries. However, it is clear, that we are over-detecting, over- and undertreating many cases. This led to the development of active surveillance for low risk indolent disease.

When looking at the ERSPC large screening trial after 13 years of follow-up, the number needed to survey to save one life was 781, with the number needed to treat being 27.[1]

The ProtecT trial, led and published by Dr. Hamdy in the UK and published in the New England Journal of medicine[2] took place between 1998-2008, encompassing 82,429 men, with 2,965 PC cases diagnosed. This is the largest randomized controlled trial comparing active monitoring, surgery, and radiotherapy for PSA-detected localized PC. The 3 compared treatment arms included active monitoring (AM), which is a surveillance program, with men followed up with PSA testing and re-evaluation of their disease. The purpose was to avoid unnecessary treatment, but keep patients in a 'window-of-curability' if treatment became necessary. The other two treatment arms included surgery, in the form of open radical prostatectomy with routine follow-up and additional treatments as needed; and radiotherapy with neoadjuvant androgen deprivation therapy (ADT) and 74 Gray 3-D conformal external beam, with regular follow-up and additional interventions as required.

The CAP trial (2001-2009) is the Cluster Randomized Trial of PSA testing. This is a trial developing out of the ProtecT trial. It is an intention to treat analysis comparing standard NHS treatment to the patients in the ProtecT trial, with the primary outcome being PC mortality in 10 years.

The main results from the ProtecT trial included 1% disease specific mortality in all arms, 10% all cause mortality in all arms, and 50%

reduction in metastasis in the radical treatment arms. In the AM arm, more than 50% had received treatment by 10 years, approximately 80% of the AM arm had no sign of progression, and 44% of AM patients avoided treatment.

Significant differences were noted n the erectile dysfunction (ED) and urinary incontinence rates between the arms, with the surgery arm having significantly higher rates of ED, and urinary incontinence, and the radiotherapy arm having significantly lower bowel function score. No significant difference was demonstrated in the anxiety and depression rates between the different arms.

The most important lessons learned from the ProtecT study include:

1. The risk of death from PC over an average of 10 years is very low – 1%.
2. Surgery and radiotherapy reduce the risk of cancer progression and spread, but cause bothersome urinary, sexual and bowel symptoms
3. AM avoids treatment side effects, but there is increased risk of cancer progression and spread.
4. Longer follow-up (5-10 years) is essential in ProtecT to provide data about the 'trade-off' between the shorter-term effects of radical treatments, the risks of disease progression, and if any, the long-term benefits in cancer cure and survival.

The new messages given to us by the PRTECT study are:

1. The ProtecT cohort represents patients with low and intermediate risk clinically localized disease
2. The risk stratification at diagnosis was inaccurate, and may be improved by pre-biopsy imaging, targeting and genomics
3. Patient reported outcomes are like those reported by patients who receive modern treatments
4. Patients over 65 years benefit from radical treatment
5. The results are generalizable, and there is a place for each of the 3 treatment arms in disease management
6. Longer follow-up (15-20 years) is essential in ProtecT and is required to fully comprehend the outcomes.

Multiparametric MRI was not used in the ProtecT study, and one often thinks what would the usage of this modality have changed in this study. It is important to remember that there is a 5-15% risk of missing significant cancer in the absence of a PI-RADS lesion. Also, there was no usage of any new molecular and genetic biomarkers, and their potential effect on the results is also unknown.

Before concluding his talk, Dr. Hamdy lastly discussed genetic diversity, which according to him, is our greatest Achilles heal in PC. Analysis of genetic phylogeny of multifocal PC identifies multiple independent clonal expansions in neoplastic and morphologically normal prostate tissue. Mutations can appear in high levels in tissue that is morphologically benign, and distant but shared by the cancer. Our knowledge in this field of genetic testing is just starting to expand. Currently, the 2017 Philadelphia consensus driven framework for multigene testing for inherited PC recommends these genes to be factored into management considerations: BRCA 1/ BRCA 2, ATM, and HOXB13.

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CANADIAN UROLOGICAL ASSOCIATION ANNUAL MEETING 2018

PROSPER: A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Enzalutamide in Men with Non-metastatic Castration-resistant Prostate Cancer

Dr. Fred Saad

Fred Saad, MD, presented an overview of the PROSPER trial.[1] Non-metastatic castration resistant prostate cancer (NMCRPC) is an area of unmet need with no currently approved therapies. The risk of metastasis is associated with increasing baseline PSA and short PSA doubling time. Delaying time to all metastasis is clinically relevant, with potential to delay cancer related morbidity and prolong overall survival (OS). Enzalutamide significantly improved OS and radiographic progression free survival (RPFS) in men with CRPC. Enzalutamide was superior to bicalutamide in improving RPFS in the subgroup of patients with chemotherapy -naïve NMCRPC (the STRIVE trial).[2]

The PROSPER study design is shown in Figure 1. Its primary endpoint was metastasis free survival (MFS) in nmCRPC patients. Secondary endpoints included safety, time to PSA progression, time to use of new antineoplastic treatment, OS, PSA response, and quality of life.

Radiographic progression was seen in 20% of the Enzalutamide arm compared to 48% of the placebo arm. The proportion of progression events in the Enzalutamide arm was 50% less than that of the placebo arm. Median MFS was ~22 months longer with Enzalutamide than with placebo. Also, time to PSA progression was ~33 months longer with Enzalutamide than with placebo (93% relative risk reduction). Median time to first use of new antineoplastic therapy was ~22 months longer with Enzalutamide than with placebo (79% relative risk reduction). The median follow-up for each arm was ~ 22 months and there was a 20% reduction in the relative risk of death with Enzalutamide vs. placebo, but this was not statistically significant. Adverse events as the primary reason for treatment discontinuation occurred in 9% of patients in the Enzalutamide arm compared to 6% of the placebo arm. No

statistically or clinically meaningful changes in health-related quality of life were observed over 97 weeks.

Dr. Saad concluded his talk stating that in men with NMCRPC and rapid PSA doubling time (median of 3.7 months), Enzalutamide resulted in clinically meaningful and statistically significant 71% reduction in the relative risk of developing metastatic CRPC. Therapy was well tolerated, and adverse events were generally consistent with those reported in prior clinical trials in men with CRPC. All secondary endpoints except OS were significantly better with the Enzalutamide arm. Median OS was not reached in either group in the first interim analysis. However, there was a 20% lower relative risk of death in the Enzalutamide group than in the placebo group.

References:

1. M Hussain, et al. J Clin Oncol 36, 2018 (suppl 6s; abstr 3)

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CANADIAN UROLOGICAL ASSOCIATION ANNUAL MEETING 2018

Optimizing Therapy in Localized Prostate Cancer – ProtecT Study

Dr. Freddie Hamdy

Freddie Hamdy, MD, gave an overview of the ProtecT study.[1] He began with some examples of real life cases of prostate cancer (PC) patients who were over- or under-treated. These led him to explain what men worried about PC want to know:

1. Whether they need to be screened
2. What is the optimal way to be tested
3. How accurate are the tests
4. Do they have PC
5. The want more detailed information about the cancer itself (PSA, grade, clinical stage)
6. The prognostic significance of the information they receive
7. The best treatment to prevent them from dying from the cancer
8. The advantages and disadvantages of the treatments on offer
9. The balance of risks when making management decisions

The big screening and treatment trials (SPCG-4, PIVOT, ERSPC, PLCO) had several fundamental factors missing. These include:

1. Non-screen detected cases (SPCG-4 and PIVOT)
2. Cohorts are no longer contemporary (SPCG-4 and PIVOT)
3. Surveillance was watchful waiting
4. Radiotherapy was not evaluated against other options
5. Competing morbidity high and randomization low (PIVOT)
6. Genomic diversity unknown, poor risk stratification
7. 'Trade-off' insufficiently considered between oncological outcomes and patient reported outcomes
8. Effective but unacceptable over-detection and over-treatment by PSA testing/biopsy (ERSPC)
9. Heavy contamination in control arm (PLCO)

The ProtecT trial took place in the UK, between 1998-2008, encompassing 82,429 men, with 2,965 PC cases diagnosed. To date, this is the largest randomized controlled trial comparing active monitoring, surgery, and radiotherapy for PSA-detected localized PC. The 3 compared treatment arms included active monitoring (AM), which is a surveillance program, with men followed up with PSA testing and re-evaluation of their disease. The purpose was to avoid unnecessary treatment, but keep patients in a 'window-of-curability' if treatment became necessary. The other two treatment arms included surgery, in the form of open radical prostatectomy with routine follow-up and additional treatments as needed; and radiotherapy with neoadjuvant androgen deprivation therapy (ADT) and 74 Gray 3-D conformal external beam, with regular follow-up and additional interventions as required.

The main results included 1% disease specific mortality in all arms, 10% all cause mortality in all arms, and 50% reduction in metastasis in the radical treatment arms. In the AM arm, more than 50% had received treatment by 10 years, approximately 80% of the AM arm had no sign of progression, and 44% of AM patients avoided treatment.

Significant differences were demonstrated in the erectile dysfunction (ED) and urinary incontinence rates between the arms, with the surgery arm having significantly higher rates of ED, and urinary incontinence, and the radiotherapy arm having significantly lower bowel function score. No significant difference was demonstrated in the anxiety and depression rates between the different arms.

To prevent one man from developing metastasis, 27 radical prostatectomies (RPs) had to be performed, or 33 radiotherapies. To prevent one man from developing clinical progression, 9 RPs needed to be performed. Dr. Hamdy also mentioned that economic evaluations of the ProtecT trial are currently being performed, and will be published soon.

The major points learned from the ProtecT study include:

1. The ProtecT cohort represents patients with low and intermediate risk clinically localized disease
2. The risk stratification at diagnosis was inaccurate, and may be improved by pre-biopsy imaging, targeting and genomics


3. Patient reported outcomes are like those reported by patients who receive modern treatments
4. Patients over 65 years benefit from radical treatment
5. The risk of death from PC over an average of 10 years is very low – 1%.
6. Surgery and radiotherapy reduce the risk of cancer progression and spread, but cause bothersome urinary, sexual and bowel symptoms
7. AM avoids treatment side effects, but there is increased risk of cancer progression and spread.
8. The results are generalizable, and there is a place for each of the 3 treatment arms in disease management
9. Longer follow-up (15-20 years) is essential in ProtecT to provide data about the 'trade-off' between the shorter-term effects of radical treatments, the risks of disease progression, and if any, the long-term benefits in cancer cure and survival.

References:

1. Freddie C. Hamdy, et al. N Engl J Med 2016; 375:1415-1424

Presented by: Freddie Hamdy, MD, University of Oxford, UK

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CANADIAN UROLOGICAL ASSOCIATION ANNUAL MEETING 2018

Development of a Management Algorithm for Prostate Cancer Patients with a Biochemical Recurrence after Radical Therapy


Dr. Bobby Shayegan

Biochemical recurrence, defined as a PSA recurrence without radiographic evidence of disease following definitive primary therapy for prostate cancer, is a growing clinical entity – and one identified by the Genitourinary Research Consortium (GURC) Best Practice Working Group as a priority to "develop a monitoring and treatment algorithm to support the optimal management of patients with non-metastatic prostate cancer." As more of the systemic therapies previously limited to patients with metastatic disease or castration-resistance are working their way into castration-sensitive non-metastatic setting, the authors of this multi-institutional Canadian group offer a management algorithm for these patients.

This is a Canadian national working group of uro-oncologists, radiation oncologists, and medical oncologists. They engaged in a series of best practice consensus discussions to examine the clinical trial evidence (literature review) and identify additional practice recommendations (expert opinion) that could be incorporated into an algorithm for the monitoring and treatment of patients with prostate cancer with a biochemical recurrence post-radical local therapy. It should be noted that it was done with the support of Janssen Inc., a pharmaceutical company.

Based on multiple consensus meetings, the group integrated evidence from RCTs and key retrospective studies, which was supplemented by expert consensus opinion in areas where evidence was lacking.

They did also consult 7 key guidelines statements:

This led to the development of an algorithm (Fig. 1) that provides practice guidance on the definition of biochemical failure, when to refer for local salvage options, recommended prostate-specific antigen (PSA) thresholds for use of intermittent and continuous androgen-deprivation therapy (ADT), and the use of PSA doubling time to guide frequency of laboratory and imaging investigations once patients have developed castrate-resistant prostate cancer

By no means is this the only method of management, but it is recommended based on expert review. It does take the clinician from initial biochemical recurrence all the way through management of non-metastatic castration-resistant prostate cancer (cM0 CRPC). However, it should be noted, it does limit management to what is currently available and approved by Health Canada.

Novel therapies with strong RCT support (use of enzalutamide or apalutamide in cM0 CRPC or abiraterone for metastatic hormone-sensitive prostate cancer) without approval are not included in the algorithm.

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MEXICAN UROLOGIC ONCOLOGY ASSOCIATION MEETING 2018

Rationale for Radical Prostatectomy for Non-Castrate Oligometastatic Prostate Cancer


Dr. Karim A. Touijer

The incidence of newly diagnosed synchronous M1 prostate cancer has decreased in the modern PSA era from 60 to 20% and the standard treatment for this condition is androgen deprivation therapy (ADT) with or without systemic chemotherapy. The oncological outcomes of ADT are predictably poor and there are several caveats associated with this treatment in this particular setting:

Prostate Cancer

- Firstly, overall outcomes of this therapy are inversely related to disease burden.
- ADT alone does not eliminate metastatic disease.
- Systemic therapy alone dose note eradicate the primary tumor.
- Even in the neo adjuvant setting, prostates removed after up to 8 months of treatment are rarely tumor-free.

Currently there are multiple therapies available for newly diagnosed M1 non-castrate prostate cancer that prolong survival (Figure 1). The natural history of this disease indicates that these patients will probably die from cancer and this leads us to believe that the combination of systemic therapy with local primary tumor control may halt the natural progression of this disease and may be of benefit in selected individuals.

The concept of primary tumor control in combination with effective systemic therapy is not new in oncology and is standard of care in colon cancer, ovarian cancer and renal cell cancer.

Data from the SEER database (2004-2010) suggests a survival benefit for local therapy including radical prostatectomy in men with documented stage IV (M1a-c) prostate cancer at diagnosis (75.8% vs. 48.7% in patients without surgery or radiotherapy). However, he underlines the limitations and selection bias of the SEER data. Similar results were found in a German study of 61 patients where time to castrate resistant prostate cancer, time to clinical progression and cancer specific survival was slightly better in patients treated with radical prostatectomy; 40 vs. 29 months, 38.6 vs 26.5 months and 95.6% vs. 84.2%, respectively.

Patient selection in this setting is of upmost importance. Radical prostatectomy in metastatic disease is not for everyone but certainly may be for some and it is currently an evolving strategy. The concept is based on treating the primary tumor and the metastasis sites as separate diseases with different therapeutic alternatives. An example is the following: offer radical prostatectomy for the primary tumor, with pelvic or retroperitoneal lymph node dissection associated with systemic therapy and radiation therapy to the oligometastastic foci.

An MSKCC pilot study was conducted to assess the safety and feasibility of radical prostatectomy in highly selected M1 prostate cancer with oligometastastic disease that included 20 patients and found that surgical morbidity was low and functional outcomes were acceptable in this setting. (Figure 2) Oncological outcomes were satisfactory with six patients being able to discontinue ADT without evidence of progression.

A phase 2 trial is currently active in MSKCC that combines ipilimumab and degarelix with radical prostatectomy to potentially cure patients with metastatic non-castrate prostate cancer. He highlights that this trial has encountered significant toxicity with this therapy and dose adjustments have been made. There are currently several phase 3 trials (Stampede, PEACE 1 trial, etc.) that are ongoing that will further clarify the role of surgery in this complex setting.

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MEXICAN UROLOGIC ONCOLOGY ASSOCIATION MEETING 2018

New Markers for Prostate Cancer Detection (4Kscore, PHI, PCA3, SelectMD, ConfirmMD)

Dr. Daniel Olvera Posada

PSA was approved by the FDA in the late 80´s, its sensibility is around 25-40% in the gray area (4-10). When it comes to prostate biopsies, 65-70% are negative for cancer. Other tools have been investigated, like free PSA, but it is still far from perfect por reducing the number of negative biopsies. The rising incidence of prostate cancer in Northamerica has been explained by an overdiagnosis since the introduction of PSA for screening. Of course this leads also to an overtreatment. In view of this problem, other resources for improving diagnosis have been studied.

Biomarkers are objective tools which guide our decision making, and they are indicators of normal or patologic biologic processes. The ideal biomarker is 100% effective, with a NPV of 100, cheap, and non-invasive. Biomarkers in blood (4K, PHI) urine (PCA3, SELECT MDX) and tissue have been developed.

4K score is a test which combines 4 prostate-specific kallikrein assay results (PSA, fPSA, intact PSA and HK2) with clinical information (age, previous biopsy and DRE) in an algorithm that calculates the individual patient's percent risk for aggressive prostate cancer, Gleason 7 or more. Contraindications are: DRE in the previous 96 hrs, treatment with 5-a-reductase inhibitors, and histry of BPE surgery. In the initial 4K validation study, they detected 23% cases of Gleason 7 or more, the AUC was 0.82, with a reduction of 58% of negative biopsies, with few false positives. The results are given a s a percentage of probability of having a low, intermediate or high risk cancer. This will help us decide wether or not to biopsy our patient.

PHI is a mathematical model, a formula, given by total PSA, fPSA and another kallikrein. It calculates a number, which goes from 0- 100; the higher the number, the higher the risk of having cancer Gleason 7 or more. Having score over 28.6 will spare 30% of negative biopsies. It should be used in men over 50 years with normal DRE and a PSA in the gray area.

PCA3 is a specific test for prostate cancer, a no codifing messenger RNA, which has been found to be elevated in 90% of cases with prostate cancer. The test is done in a urine sample, after a prostatic massage. The higher the results, the higher the risk of having cancer. A drawback of this test is that it doesn´t specify if it is more likely to have a low, intermediate or high risk cancer. A variation from PCA3 is the MIPs test, which adds another 3 biomarkers.


SELECT MDX is another diagnostic tool performed in a urine sample after a DRE. It measures mRNAs and combines clinical features into al algorithm. An advantage of this test is that it identifies gleason 7 or higher (intermediate-high risk).

CONFIRM MDX is an epigenetic test in tissue obtained from biopsies. It searches for metilation patterns in genes of the surrounding tissue of the biopsy. It is useful for confirmation of negative biopsies in patientes with a high clinical suspicion but with a negative biopsy, with an AUC of 0.74, NPV 96%. Its use can be limited by its high cost.

Biomarkers are useful tools that are already mentioned in international guidelines, although indications are not that clear. It is likely that they will be part of the diagnostic algorithm for prostate cancer in the near future.

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MEXICAN UROLOGIC ONCOLOGY ASSOCIATION MEETING 2018

Should Robot-assisted Laparoscopic Radical Prostatectomy Become the New Standard of Care?

Karim A. Touijer, MD presented a provocative talk on the role of robotic assisted prostatectomy. He reviewed data from the MSKCC in the transition period from open to laparoscopic surgery in a non-randomized prospective study from 2003-2005. These included1430 consecutive patients who underwent radical prostatectomy for clinically localized prostate cancer, 612 in the laparoscopic group (LRP) compared with 818 patients in the open group (RRP). Both techniques had comparable oncological efficacy (similar positive margin rates and freedom from progression) and laparoscopy was associated with less estimated blood loss, transfusion rates but with higher postoperative hospital visits and readmission rates. Erectile dysfunction was similar between study groups; however continence was superior following RRP. As laparoscopy was further developed, functional outcomes became equivalent to open surgery. Nonetheless, the steep learning curve of laparoscopy was highlighted when compared with open surgery, at about 750 cases to achieve surgical excellence, making it a very demanding surgical technique.

This paved the way for robotic surgery because the sole purpose of the robotic platform is to make laparoscopic surgery easier for the surgeon. It is ergonomic, intuitive, it facilitates execution of surgical movements and it is associated with easier skill transfer. He then followed up by comparing 1800 RRP with 1537 LRP and the first 350 robot-assisted laparoscopic radical prostatectomies at the MSKCC with no differences in recurrence, urinary function recovery and sexual function recovery. The main criticism of the MSKCC trials was that the surgeries were performed in a single center by a few surgeons and the external validity of this data came into question. This issue was assessed by the Swedish LAPPRO study that included over 4000 patients and determined that robotic surgery had less blood loss, comparable readmission rates and reoperations with equivalent oncological and functional outcomes.

A phase 3 randomized clinical trial that included 326 patients comparing open RRP with robot-assisted LRP in Australia yielded similar functional and oncological outcomes at 24 months of follow up was recently published in Lancet Oncology. This provides level 1 evidence that proves no differences between both techniques.

From a public health standpoint, robotic surgery implementation needs to be evaluated for its intrinsic value and determine if this technology is feasible for a health care system. Robot assisted LRP provides benefits for best patient outcomes (equivalent oncological outcomes with less pain and faster recovery) and helps standardize outcomes for surgeons. This taken into account, in a country such as Mexico, he cautioned that the ministry of health has to decide if this investment in technology is worthwhile for any given country. To conclude he states that buying more technology or increasing health care spending does not increase life expectancy.

Presented by: Karim A. Touijer, MD, MPH from the Memorial Sloan Kettering Cancer Center, New York, NY

Written by: Adrián M. Garza-Gangemi, MD, medical writer for UroToday.com and Ashish Kamat, MD, Professor of Urology and Director of Urologic Oncology Fellowship at M.D. Anderson Cancer Center

MEXICAN UROLOGIC ONCOLOGY ASSOCIATION MEETING 2018

Is There a Role for PET/CT Imaging in Decision Making for Localized Prostate Cancer Treatment?


Dr. Arturo Delgado Herrera

Arturo Delgado Herrera, MD, first reviewed conventional imaging techniques used for staging in localized prostate cancer and the indications of these studies based on a risk stratification model. He recognized the caveats of conventional imaging techniques such as; the limited sensitivity and specificity for the detection of bone metastasis and positive lymph nodes and how positive findings are associated with PSA level, initial Gleason score and clinical T stage. The only current indication in the 2018 NCCN guidelines for preoperative PET/CT is to evaluate equivocal lesions in a conventional bone scan with F-18 NaF.

The role of PET/CT imaging prior to definitive treatment is still unclear and he outlines uses of the current radiotracers available today:

- C-11 Choline, FDA cleared, may be used for detection of biochemically recurrent small volume disease.

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- F-18 Fluciclovine, FDA cleared, a synthetic amino acid may also be used for detection of biochemically recurrent small volume disease in soft tissues.
- Ga-68 PSMA, an increasingly popular tracer used worldwide that provides better detection of recurrences at lower PSA levels with better sensitivity (76-86%) and specificity (86-100%) than other FDA approved agents.
- F-18 NaF, has better sensitivity (87-100%) and specificity (62-89%) for the detection of bone lesions when compared with conventional bone scans.

He then recognized the importance of the "Will Rogers Phenomenon" stating that PET/CT use may increase the detection of cancer metastasis before these lesions become clinically evident and this bias may be falsely interpreted as a treatment effect.

A compelling argument was made for the use of PET/CT with Ga-PSMA for primary lymph node staging in high-risk prostate cancer. He cited a retrospective multicenter study of 51 patients where there was considerable upstaging from the clinical to the pathological stage and the value in predicting occurrence of lymph node (LN) metastasis in patients with ≥ 15 node harvest was significant, with a sensitivity of 66.6%, specificity of 88%, accuracy of 81%, positive predictive value of 72.7% and negative predictive value of 84.6%. These results are comparable with other published data and this suggests that PET/CT with PSMA may be superior to conventional studies for the detection of LN metastasis in the initial staging of patients with high risk localized prostate cancer.

The RADAR III guidelines recommend the use of new diagnostic studies when findings are equivocal or undetermined in conventional studies and they recommend that these studies should be considered for the initial staging of patients with high-risk disease or suspected locally advanced disease.

PET/CT with PSMA is not yet approved by FDA in the United States but its use has been increasing in many hospitals throughout the country.

To conclude, he stated that conventional bone scan and abdominal-pelvic CT scan are the standard of care for initial staging in patients with intermediate or high-risk disease but have intrinsic limitations, primarily a limited sensibility and specificity for the detection of positive lesions. PET/CT with F-18 NaF should be used to evaluate equivocal lesions in bone scans and the use of other tracers for primary staging are unclear at the moment, however PSMA is showing promising results in selected individuals.

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MEXICAN UROLOGIC ONCOLOGY ASSOCIATION MEETING 2018

Is Active Surveillance the New Paradigm?

Karim A. Touijer, MD provided a discussion about active surveillance (AS) in the treatment of prostate cancer. In randomized studies it has been shown that this therapy is a safe approach in patients with prostate cancer as well as radiotherapy and surgery, however, it only represents 6-8% of treatment of prostate cancer overall.

Dr. Touijer suggests that there are three factors that cause this issue: the doctor, the patient, and the disease. There is a Japanese study where they evaluated the preferences and knowledge of doctors in terms of treatments for prostate cancer, however, most doctors preferred not to opt for active surveillance and the vast majority were not sure of the results and were concerned about the oncological results in the long term. Some other doctors were concerned about the patient's anxiety. In another North American study, they think it's a good strategy to do active surveillance but they also think that it is not used as often as it should.

They mention that in their institution they identified a decrease in the use of AS and they identified that it was due to the way in which this strategy is offered to patients.

He believes that we should turn active surveillance into the standard of treatment and not as an option in patients with low-risk prostate cancer and that more education is needed from both doctors and patients.

There are different strategies for monitoring patients in active surveillance, PSA, digital rectal examination, MRI, a transrectal prostate biopsy (TRB), genomic tests, with biopsy being the most useful so far. TRB decides whether the patient can continue with monitoring or not.

He mentioned the most common follow-up schemes.

Currently, the use of AS has increased exponentially at the Memorial Sloan Kettering Cancer Center. They use annual confirmatory biopsy and subsequently biopsies every 3 years, using a baseline MRI and then every 18 months.

Touijer considers that AS is a strategy that can be useful in intermediate risk cancer as long as the scheme is modified based on the risk.

It concludes that one should not be afraid to initiate active surveillance in patients with low risk since the evidence in the literature is enough to recommend it as a standard of treatment in a patient with low risk.

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Bladder Cancer

Translating Bladder Cancer Genomics into Clinical Practice


Dr. Peter Black

Peter Black, MD, gave a talk summarizing the current status of bladder cancer genomics and its future in clinical practice; he did so by reviewing the literature in the setting of muscle-invasive bladder cancer (MIBC), highlighting some of his work in the area, and focusing on how to bring it to clinical practice. He has given variations of this talk before, but he did highlight some new work recently published.

He first focused on the molecular subtyping work that has been driving the translational work in MIBC. There are 4 major molecular classifications based on work done by 4 different groups: MDACC, Lund, UNC and TGCA. There are two major categories: basal/luminal. While each of the molecular classifications vary in terms of naming and terminology, they generally adhere to this major subdivision.

It should be noted that just this year, Robertson et al. (Cancer Cell 2018) described a 5th smaller subtype called neuronal/neuroendocrine, using TCGA data. On retrospective evaluation, patients with the genomic profile appeared to do worse with all treatment modalities (chemotherapy, surgery) – with the sole exception of chemoradiation!

However, these classification systems are based on using large datasets, unsupervised clustering and grouping. This is not practical for a patient sitting in the clinical.

At this time, neoadjuvant chemotherapy (NAC) is a standard of care based on Level 1 evidence prior to radical cystectomy for MIBC. While there is a lot of data to support the use of NAC, there are two major gaps in its widespread utilization:

- Only 40% of patients have major response to chemotherapy
- NAC is not widely used in most parts of the world

The best response to these gaps in care is better risk stratification and patient selection for chemotherapy response, with the use of biomarkers.

Three different molecular markers to discuss:

1. Molecular subtypes
2. COXEN model
3. Genomic alterations

Molecular subtypes – described above, but have been shown to be associated with clinical outcomes and response to therapy.

Subtype is associated with response to chemotherapy

- Basal tumor respond very well
- P53-like tumors respond poorly

Dr. Black worked with Genome Dx to generate a genomic test that could classify a patient sitting in front of you in clinic into 1 of 4 molecular classes

- Using discovery and validation set, proved that basal molecular subtypes are the best responders to NAC cisplatin
- Luminal tumors do well regardless of NAC – so maybe they don't need chemotherapy

COXEN Model "Coexpression Extrapolation"

- Being developed based on 60 cell lines and their drug response
- Test a patient's gene expression against the pool of cell line data to determine the best "match"
- Shown an accuracy ~80%
- Currently in a prospective study with SWOG

Genomic Alterations

- Individual Gene alterations, particularly DNA repair genes
- Will likely gain more recognition as predictors of response
- I.e. ERCC2 gene alterations were found only in patients with chemotherapy response – validated in a second cohort in FCCC
  - Therefore those patients with ERCC2 mutations treated with chemotherapy do well
- Mutations in ATM, Rb1, FANC – 3 gene panel
  - Patients with mutation in at least one of these genes had a high rate of response to chemotherapy
- ERBB2 (Her2)
  - Predictive of chemotherapy response, but not yet validated

He did focus a little bit on combining some of these biomarkers – specifically by including patients with basal subtype and patients with DNA damage repair gene mutations, approximately 50% of patients would be considered potential NAC responders. This may help select out patients who wouldn't respond to NAC and avoid unnecessary treatment.

- In early, retrospective analyses of a TCGA non-NAC cohort and a separate institutional NAC therapy cohort, there did appear to be a prognostic value to having either basal subtype of DDR gene mutations – better response and survival seen with NAC administration.

However, all of these markers have yet to be validated in prospective clinical trials. When they are validated, they should prioritize marker positive patients for NAC and marker-negative patients for immediate cystectomy.

He lastly touched on patients treated with NAC – what is their genomic profile like? Dr. Black's group has begun to address this already by profiling patients' TURBT tissue (pre-NAC) and cystectomy specimens (post-NAC). Unsupervised consensus clustering yielded four distinct consensus clusters (CC) or subtypes – however, they did not match up perfectly with the original molecular subtypes. Two CC's expressed genes known from previously described molecular subtypes of chemotherapy naïve BC: CC1 and 2 expressed genes consistent with a basal-like (KRT5/6, KRT14) and a luminal-like

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(GATA3, PPARG) phenotype and were called, CC1 basal and CC2 luminal, respectively. CC3 expressed a strong T-cell signature, markers for T-cell receptor signaling, chemokines and checkpoint molecules (CTLA4, CD80) and was therefore called CC3 immune. CC4 was associated with wound healing/scarring (MYH11, CNN1). This 'scar-like' character of CC4 was highly consistent with the scar samples (n=21) – and these patients did very well, likely representing a genomic marker of strong NAC response.

The future is bright for bladder cancer therapeutics, and hopefully, many of these advances will lead to clinical impact soon.

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CANADIAN UROLOGICAL ASSOCIATION ANNUAL MEETING 2018

Integrating Immune-Oncology with the Current Treatment of Advanced Urothelial Carcinoma


Dr. Bobby Shayegan

As part of the CUA 2018 education forum, Bobby Shayegan, MD, served as moderator for the immunotherapy in urothelial carcinoma session. Dr. Shayegan started by noting that bladder cancer therapies have historically lagged behind other malignancies, until the advent of immunotherapy. Secondary to bladder cancer's somatic mutational burden, immunotherapy is attractive for bladder cancer and has been one of the first significant advancements regarding systemic therapy in several decades.

The cancer immune cycle is as follows:

1. Release of cancer cell antigens at the time of death
2. Cancer antigen presentation by dendritic cells and antigen-presenting cells
3. Priming and activation of T-cells by antigen-presenting cells
4. Trafficking of T-cells to tumors
5. Infiltration of T-cells into tumors
6. Recognition of cancer cells by T-cells
7. Killing of cancer cells

CTLA-4 is an immune checkpoint receptor on T-cells that plays a key role in preventing T-cell over activation. Tumor cells use the CTLA-4 pathway to suppress initiation of an immune response, resulting in decreased –cell activation and ability to proliferate into memory cells. CTLA-4 signaling diminishes the ability of memory T-cells to sustain a response, damaging a key element of durable immunity.

PD-1 is an immune checkpoint receptor on cytotoxic T-cells that plays a key role in T-cell exhaustion and prevention of autoimmunity. Tumor-infiltrating T-cells across solid tumors and hematologic malignancies display evidence of exhaustion, including upregulation of PD-1. PD-1 blockade reinvigorates exhausted T-cells and restores their cytotoxic immune function.

Lori Wood, MD, then presenting on the role of immune checkpoint inhibitors in metastatic urothelial carcinoma. We know that second line chemotherapy demonstrates a response rate of 10-20%, with a time to progression of 2-4 months, and a median overall survival of 5-9 months. The approved immune checkpoint inhibitors for metastatic urothelial carcinoma are as follows:

- PD-1 (on T-cells):
  - Nivolumab
  - Pembrolizumab
- PD-L1 (on the cancer cell):
  - Atezolizumab
  - Durvalumab
  - Avelumab

Initial studies included multiple phase I/II studies, leading to FDA approval primarily based on phase II studies, with similar approval in Canada. As follows is a chart of immune checkpoint inhibitors in metastatic urothelial carcinoma:

Several important second-line phase III trials in metastatic urothelial carcinoma have recently reported initial results. These patients were those that progressed after platinum-based chemotherapy in the metastatic setting, or those that had recurrence within one year of adjuvant/neoadjuvant chemotherapy. The phase 3 KEYNOTE-045 study comparing pembrolizumab and investigator's choice of chemotherapy (paclitaxel, docetaxel, or vinflunine) reported results after the second planned interim analysis (at which point the trial was stopped).[1] The study found a median OS of 10.3 months (95%CI 8.0-11.8) in the pembrolizumab group, compared with 7.4 months (95%CI 6.1-8.3) in the chemotherapy group (HR 0.73, 95%CI 0.59-0.91). Furthermore, the median OS among patients who had a tumor PD-L1 combined positive score (CPS) of ≥10% was 8.0 months (95%CI 5.0-12.3) in the pembrolizumab group, as compared with 5.2 months (95%CI 4.0-7.4) in the chemotherapy group (HR 0.57, 95%CI 0.37-0.88). Based on these results, pembrolizumab was FDA approved for the treatment of locally advanced or metastatic urothelial carcinoma in the second line. The phase III IMvigor211 study tested the efficacy of atezolizumab versus chemotherapy among patients progressing on platinum-based chemotherapy.[2] There were 931 patients randomized to receive atezolizumab (n=467) or chemotherapy (n=464). In the IC2/3 population (n=234), overall survival did not differ significantly between patients in the atezolizumab group and those in the chemotherapy group (median 11.1 months, 95%CI 8.6-15.5 vs 10.6 months 95%CI 8.4-12.2) (HR 0.87, 95%CI 0.63-1.21). An exploratory analysis of the intention-to-treat population showed durable responses in line with previous phase II data from IMvigor 210 for atezolizumab in this setting.


Unfortunately, atezolizumab was not associated with significantly longer OS than chemotherapy in patients overexpressing PD-L1 (IC2/3). Atezolizumab was well tolerated compared to chemotherapy, with less all grade (60.9% vs 90.2%) and grade 3-5 (15.0% vs. 49.4%) treatment related adverse events. Furthermore, treatment discontinuation rates were less with atezolizumab (5.6% vs 11.0%).

In summary, Dr. Wood noted:

- There are many PD-1 pathway immune checkpoint inhibitors and many new inhibitors being studied
- For metastatic disease, in Canada, these agents are only approved in the second line and not approved for cisplatin ineligible at this point in time
- There are only two phase III trials currently, and only one with positive results
- Indeed, there are profound results in some patients

Several questions moving forward that Dr. Wood highlighted:

- Who are the metastatic patients with profound responses?
- Should we use in the first line setting? Alone or in combination with chemotherapy?
- Should we be using in the neoadjuvant or adjuvant setting?
- Should we be using in NMIBC?

Peter Black, MD, then proceeded to discuss the role of immune checkpoint blockade in localized bladder cancer. Dr. Black started by noting that the definition for patients that have failed BCG therapy has recently changed, focusing on BCG unresponsive NMIBC typically defined as:

- Any high-grade recurrence after induction BCG + first round of maintenance BCG, or two rounds of induction BCG [Ta/CIS failure to achieve a complete response at 6 months]
    - An exception is high-grade T1 disease at three months (after induction BCG only), which is considered "unresponsive" [T1 failure to achieve complete response at 3 months]
- For patients who achieve complete response on induction/ maintenance BCG: any high-grade recurrence within 6 months of last dose of BCG [relapse of high-grade recurrence within 6 months of last dose of BCG after a prior complete response]

Dr. Black then highlighted several common clinical caveats:

1. Recurrent low-grade Ta NMIBC does NOT constitute BCG-unresponsive NMIBC in this context
2. Do NOT deem BCG treatment to have failed after induction BCG only in patients with Ta and CIS
3. Ensure prostatic urethra and upper tracts are clear in BCG-unresponsive patients, considering that in these sanctuary sites there is up to 50% involvement

Data from the SWOG S0353 study for BCG-unresponsive NMIBC demonstrates that the best we can do with intravesical maintenance gemcitabine for BCG "refractory" NMIBC is a 28% recurrence free survival (RFS) at 1-year, and 20% RFS at 2-years.[3] Based on these results, according to Dr. Black "our best intravesical salvage therapy is not good enough." The guidelines state that in these situations, the treatment is radical cystectomy, whereas many of the experts state that it may be reasonable to administer one more round of intravesical therapy before proceeding to cystectomy for high-grade Ta and CIS (but always radical cystectomy for high-grade T1).

The rationale for testing immune checkpoint inhibitors in NMIBC is (i) there is efficacy of immunotherapy in NMIBC (BCG), (ii) there is expression of PD-L1 in Ta, T1 and CIS in patients previously treated with BCG, and (iii) there is pre-clinical efficacy data from syngeneic mouse models. There are currently two ongoing immunotherapy trials ongoing in the BCG unresponsive disease state.

Dr. Black notes that with regards to clinical trials in NMIBC, there are many trials to be done and this requires urologists to "engage". This will require more collaboration with medical oncology and strict eligibility criteria are unfortunate but essential in order to make the results interpretable.

Dr. Black concluded with discussing two phase II neoadjuvant trials that recently presented initial results last month at ASCO. The PURE-01 trial is an open-label, single-arm, phase 2 study evaluating pembrolizumab prior to radical cystectomy.[4] The primary outcome was pathologic complete response (pT0) at the time of radical cystectomy in the intention to treat (ITT) population. The first stage of enrollment included 43 patients, including 35 males/7 females, with 37.2% of patients with cT2N0 disease, 58.1% with cT3N0, and 4.7% of patients with T2-3N1. At the time of this analysis, there were 17/43 patients that were pT0 (39.5%, 95%CI: 26.3-54.4) and 5 <pT2 (total <pT2 rate: 51.2%). The ABACUS trial is a single arm, phase II study investigating two cycles of atezolizumab (1200mg every three weeks) prior to radical cystectomy among patients with T2-4N0M0 urothelial carcinoma.[5] Among 68 patients, the median age was 71 years (range 53-85), and the baseline pT2 rate was 71%, pT3 was 22%, and pT4 was 7%. The pathologic complete response rates were as follows: (i) all patients: 20/68 (29%) – pT0, n=16; pTis, n=4; (ii) PD-L1 positive patients: 10/25 (40%); (iii) PD-L1 negative patients: 5/31 (16%); (iv) cT2 patients: 17/48 (35%); (v) cT3-T4 patients: 3/20 (15%).

Dr. Black concluded with several summary points:

- BCG-unresponsive NMIBC is an important concept for clinical trials and routine practice
- Immune checkpoint blockade will likely be a part of routine therapy for NMIBC and localized MIBC in the near future single agent trials are just the tip of the iceberg
- Urologists need to familiarize themselves with these agents and also support ongoing clinical trials

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CANADIAN UROLOGICAL ASSOCIATION ANNUAL MEETING 2018

Patterns of Bladder Cancer Recurrence After Open and Robotic Radical Cystectomy

Pierre-Alain Hueber, MD, presented a study comparing open and robotic radical cystectomy in a single center. The rate /patterns of recurrence after robotic-assisted radical cystectomy (RARC) for bladder cancer may be different compared to open radical cystectomy (ORC). RARC has been thought lead to atypical recurrences, including peritoneal carcinomatosis, extra-pelvic lymph node metastasis and port side metastasis.

This study aimed to compare rates and patterns of recurrence after RARC with intra-corporeal urinary diversion (IUCD) vs. ORC in a large contemporary cystectomy series. This was a retrospective study of 837 consecutive patients who underwent ORC (n=598) or RARC with ICUD (n=238) for bladder cancer between 2009 and 2016. The recurrences were either local, distant or secondary..

Any kind of recurrence occurred in 13.4% of ORC and 14.8% of RARC with IUCD. Local recurrence occurred in 5.4% of ORC patients and 5.1% of RARC with IUCD patients. Multivariable cox regression analysis demonstrated that RARC with IUCD was not an independent predictor of recurrence after adjusting for age, sex, perioperative chemotherapy, pathological tumor and nodal status, lymphovascular invasion, and positive surgical margins.

Dr. Hueber concluded the presentation by stating that there are no differences in the rates or patterns of local or distant recurrences between RARC and ICUD and ORC. The surgical approach is not an independent predictor of recurrence after radical cystectomy for bladder cancer.

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CANADIAN UROLOGICAL ASSOCIATION ANNUAL MEETING 2018

The Revolution of Immunotherapy in Genitourinary Cancers: The Tip of the Iceberg

Dr. Yves Fradet

Yves Fradet, MD, provided a keynote CUOG lecture at the CUA 2018 annual meeting, discussing the revolution of immunotherapy in genitourinary cancers. Dr. Fradet started by noting that CUOG will celebrate its 30th anniversary next year at the CUA and that one of the first trials to come from the cooperative group was the New England Journal of Medicine clinical trial testing interferon gamma-1b compared to placebo for patients with metastatic RCC.[1] Among 197 patients from 17 Canadian centers, the overall response rate for patients treated with interferon gamma-1b was 4.4% (3.3% complete response) and 6.6% (3.3% complete response) in the placebo group (p=0.54). Dr. Fradet also highlighted that BCG immunotherapy for bladder cancer was discovered in Canada (Queen's University – Dr. Alvaro Morales) in 1976, with nearly 40 years of clinical success in Canada and subsequent FDA approval in the US in 1990.

The new era of cancer treatment is the anti-immune checkpoint therapies according to Dr. Fradet. The immune checkpoint inhibitors currently for genitourinary cancers include:

- Anti-CTLA-4:
  - Ipilimumab
  - Tremelimumab
- Anti-PD-L1:
  - Atezolizumab
  - Durvalumab
- Anti-PD-1:
  - Pembrolizumab
  - Nivolumab

Targeting PD-L1 blocks signaling between the tumor cell and both PD-1 and B7.1, and may prevent down-regulation of T cell activity. The PD-L2/PD-1interaction is preserved, and may potentially minimize effects on immune homeostasis. Targeting PD-1 blocks signaling between the tumor cell and PD-1, possibly sparing the interaction between the tumor cell and B7.1. PD-L2/PD-1 interaction is blocked and may potentially increase the chance of autoimmunity.

Dr. Fradet then discussed the KEYNOTE-045 phase III RCT, testing pembrolizumab in the second-line setting.[2] This study compared


pembrolizumab and investigator's choice of chemotherapy (paclitaxel, docetaxel, or vinflunine), and found a median OS of 10.3 months (95%CI 8.0-11.8) in the pembrolizumab group, compared with 7.4 months (95%CI 6.1-8.3) in the chemotherapy group (HR 0.73, 95%CI 0.59-0.91). Furthermore, the median OS among patients who had a tumor PD-L1 combined positive score (CPS) of ≥10% was 8.0 months (95%CI 5.0-12.3) in the pembrolizumab group, as compared with 5.2 months (95%CI 4.0-7.4) in the chemotherapy group (HR 0.57, 95%CI 0.37-0.88). Based on these results, pembrolizumab was FDA approved for the treatment of locally advanced or metastatic urothelial carcinoma in the second line.

The KEYNOTE-052 phase II trial of first-line pembrolizumab in cisplatin ineligible patients reported that among 370 patients receiving at least one dose of pembrolizumab, 89 (24%, 95%CI 20-29) patients had a centrally assessed objective response, and 74 (83%) of 89 patients had ongoing responses over a median follow-up of 5 months (IQR 3.0-8.6)[3]. Additionally, a PD-L1-expression cutoff of 10% was associated with a higher frequency of response to pembrolizumab: 42 (38%, 95%CI 29-48) of 110 patients had an objective response. Based on these results, pembrolizumab was granted FDA approval for the treatment of cisplatin-ineligible patients with advanced urothelial carcinoma. In an updated analysis of KEYNOTE-052 reported last month at ASCO, pembrolizumab appears to have clinically meaningful and durable results (follow-up time more than twice as long as reported in the initial analysis) in a heavily treated and comorbid population of which ~50% of patients were ≥75 years of age.[4]

In the neoadjuvant setting for urothelial carcinoma, Dr. Fradet highlights the PURE-01 study, a phase II open-label, single-arm trial evaluating the effects of pembrolizumab administered prior to radical cystectomy.[5] The first stage of enrollment included 43 patients, among which there were 35 males/7 females, with 37.2% of patients with cT2N0 disease, 58.1% with cT3N0, and 4.7% of patients with T2-3N1. At the time of this analysis, there were 17/43 patients that were pT0 (39.5%, 95%CI: 26.3-54.4) and 5 <pT2 (total <pT2 rate: 51.2%). Similarly, the ABACUS study is a single arm, phase II trial investigating two cycles of atezolizumab (1200mg every three weeks) prior to radical cystectomy.[6] Among 68 evaluable patients, the baseline pT2 rate was 71%, pT3 was 22%, and pT4 was 7%. The pathologic complete response rates were 29% for all patients, 40% for PD-L1 positive patients, 16% for PD-L1 negative patients, 35% for cT2 patients, and 15% for cT3-T4 patients.

Dr. Fradet concluded by highlighting several trials that will be reporting results over the next few years. Currently, there are several phase III first-line treatment trials of PD-1/PD-L1 inhibitors vs chemotherapy in advanced urothelial carcinoma. These include:

- KEYNOTE-361 (n=990): pembrolizumab + cisplatin + gemcitabine vs pembrolizumab vs standard of care chemotherapy. Estimated primary completion June 1, 2019.
- IMvigor 130 (n=1,200): atezolizumab + cisplatin + gemcitabine vs atezolizumab vs standard of care chemotherapy. Estimated primary completion December 31, 2018.

Similarly, there are several phase III first line trials of PD-1/PD-L1 inhibitors with or without anti-CTLA4 vs chemotherapy in advanced urothelial carcinoma:

- DANUBE (n=1,200): durvalumab + tremelimumab vs durvalumab vs standard of care chemotherapy. Estimated primary completion September 23, 2019.
- CheckMate 901 (n=897): nivolumab + ipilimumab → nivolumab vs nivolumab + cisplatin + gemcitabine → nivolumab vs standard of care chemotherapy. Estimated primary completion April 26, 2020.

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MEXICAN UROLOGIC ONCOLOGY ASSOCIATION MEETING 2018

Multimodal Management of Invasive Bladder Cancer in the Elderly


Dr. Wassim Kassouf

Life expectancy in the general population is increasing, making the presentation of bladder cancer more frequent in the elderly population. The treatment for octogenarians is the same, cystectomy and perioperative chemotherapy in selected cases, nevertheless, there are more conservative options such as partial cystectomy, transurethral resection of bladder (TURB) plus chemotherapy, radiotherapy alone and trimodal therapy (TMT). Wassim Kassouf, MD, emphasized that chronological age alone should not be used to exclude patients from definitive therapy, appropriate decisions should incorporate functional status and comorbidities, patient desire and goals, and informed understanding of the risk and benefits.

Bladder Cancer

Cystectomy is a procedure with high morbidity and mortality. The percentage of complications presented during the first 90 days after surgery is 67, as reported by Shabsigh et al in 2009. So far the advances in technology haven't changed the paradigm. All randomized studies comparing robotic vs open surgery were done with a hybrid approach, intracorporal diversion trials are still running. The only benefit demonstrated is in less bleeding.

Neoadjuvant chemotherapy (NAC) has improved survival from 45% to 50% at 5 years. Although, when it comes to the octogenarians, it´s a problem still unsolved. There aren´t any level I evidence studies about this asset, since these patients were systematically excluded from the SWOG and MRC studies, and toxicity in this group of patients hasn't been clearly defined, with toxic deaths approximately between 2.3 - 4.6%. This raises concern about adding morbidity when combining NAC and cystectomy.

In the USA, only 18% of octogenarians undergo cystectomy, 46% receive QT and RT, and 60% surveillance, the former percentage remarks the need for optional therapies in patients unfit for surgery. The TMT is gaining acceptance in patients who are not surgical candidates or who refuse surgery, incorporating maximal TURB, radiation and chemotherapy as a radiosensitizer. The response to TMT has increase through all this years with a current rate of complete response of 86.1%, in contrast to 64.5% in 1986, and the key factor is patient selection. Nowadays, the trials include patients with better condition and disease in less advanced stages. Efstathiou et al, published in 2012 a cancer-specific survival (CSS) of 64%, and only 29% had to undergo cystectomy.

About the chemotherapy as a radiosensitizer in TMT, it has proven in randomized study to improve CSS and overall survival (OS) in comparison with radiotherapy alone (Figure 1), and there aren't differences between the use of Cisplatin/5FU or a low dose of Gemcitabine, both with RT, as was shown in a randomized phase II multicenter trial published by ASCO 2018. Even when the TMT is a well-established less-invasive option, it does not preclude complications, and severe toxicity has been reported in 7% of the patients, including 2% of salvage cystectomy due to contracted bladder, 1.5% bowel obstruction requiring surgery, and 3% who developed severe frequency due to reduced bladder capacity. As before, the best way to avoid these complications is the adequate selection of patients, and some factors have been associated with favorable oncologic outcomes, those are: Organ confined tumor (cT2) and less than 5cm, ability to remove all visible tumor with TUR, absence of hydronephrosis, absence of extensive CIS or diffuse multifocal disease, adequate bladder capacity and function, tumor with urothelial histology and Dr. Kasouff strongly recommend routine re-biopsy post TMT and prompt salvage cystectomy for nonresponders or recurrences.

The recurrence after complete response to TMT is 29%, with a median time to recurrence of 18 months. High grade tumor was found in 95% of the recurrences, 60% were recurrence free after TURB and BCG, and 11% progressed to T2 disease. Therefore most of the recurrences are able to be treated conservatively, special attention must be paid in T1HG and prostatic urethral recurrences and may prefer a more aggressive approach in this cases.

Dr. Kassouf also highlighted some TMT limitations that do not apply to elderly patients. This included secondary malignancies, the fact that most series have a follow-up time less than 10 years, and neobladder not advocated following salvage cystectomy, and those are due to the lower life expectancy in this group of patients and lower renal function in the elderly. Yet some questions remain unsolved, such as if should pelvic nodes should be included in the radiation field or if neoadjuvant chemotherapy prior to TMT improves survival; new trials have to be designed to solve these matters.

Finally, Dr. Kassouf concluded his talk by stating that radical cystectomy can be morbid, especially in the elderly, however, the chronological age should not be used to exclude patients from definitive therapy, bladder preservation using TMT is a good option in selected patients and remains underutilized and NAC needs further evaluation in octogenarians.

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MEXICAN UROLOGIC ONCOLOGY ASSOCIATION MEETING 2018

When Should We Move to Cystectomy in NMIBC

Dr. Ashish M. Kamat

"When NOT removing the bladder would represent loss of an opportunity to CURE the patient" was the opening statement of Dr. Kamat's presentation.

The indications for radical cystectomy for NMIBC are: no resectability (large tumor in diverticulum), non functioning bladder and high risk bladder cancer (any T1 or high grade, including CIS; progresion rate of 25-50% @ 5 years). Early cystectomy indications for very High risk:

- T1, HG/G3 associated with concurrentlad bladder CIS
- Multiple and/or large and/or recurrent T1 HG/G3
- T1, HG/G3 with CIS in prostatic urethra
- Micropapillary variant of urotelial carcinoma

One key fact of the conference was that a T1HG tumor is not a superficial cancer (invasive to lamina propia) therefore radical cystectomy can be considered. A T1HG has the same or worse disease specific survival as a prostate cancer cT3b, gleason 5+5, 12/12 positive cores with PSA 75.


There is a common understaging of T1HG disease and the residual disease at the TURB site could be up to 62%, with muscle-invasive (T2) upstaging in up to 10% of the cases. Bladder cancers with lymphovascular invasion have a worse prognosis, a higher risk of metastatic disease and for progression outside the bladder. Initial radical cystectomy should be offered to any patient fit for surgery who has T1HG on repeat TUR or T1HG with CIS, or LVI or variant histology (44% cases of histologic variants are not recognized by community pathologists: lymphoepitelial, plasmocytoid, micropapillary and small cell).

Dr. Kamat expressed that diagnosis of prostatic urethral carcinoma can only be achieved with a TUR biopsy in those patients at risk: CIS, multifocal disease, involvement of trigone or bladder neck, prior intravesical therapy and previous involvement of the prostate.

A radical cystectomy should be considered for a T1HG because this cancer could rapidly progress to a metastatic disease before it reaches other layers of the bladder and lose the oportunity to cure the patient.

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MEXICAN UROLOGIC ONCOLOGY ASSOCIATION MEETING 2018

Issues and Controversies in Upper Tract Urothelial Carcinoma (UTUC)


Dr. Wassim Kassouf

Wassim Kassouf at the beginning of the conference pointed out the important relation between Lynch syndrome and UTUC, with a cumulated risk of developing UTUC during lifetime of these patients of 1-28%. In a recent series it was found that 5% of UTUC patients have this syndrome and the importance is: highest frequency of colorectal cancer and that MSI-high UTUC tumors have greater sensitivity to checkpoint blockade and chemotherapy sensitivity.

Ureteroscopy (URS) is the standard diagnostic tool and is being used with different technologies: narrow band imaging (increased detection rate by 23%), SPIES and hexvix; the diagnosis is challenging secondary to tangential viewing angle. Two studies differ about it's findings of bladder recurrence after URS previous to radical nephroureterectomy (RNU), the first found that URS >5 days previous to RNU was a independent predictor for recurrence and the second did not showed difference.

The indication for conservative management UTUC is low grade: unifocal disease, tumor size <2 cm, low-grade cytology, low-grade URS biopsy and no invasive aspect on CTU (EAU guidelines 2018). Second Look after endoscopic treatment should be performed 2 months later; this is the strongest prognostic factor for recurrence, progression and improvement of the oncologic outcomes.

Upper tract instillations of BCG or MMC showed no benefit for UTUC in a 30-year experience including 141 patients (Motamedinia, J Endourol016). MitoGel trial (temperature sensitive water-soluble gel formulation of mitomicyn C), for low-grade tumors and small volume, reported improved outcomes; preliminary results in 33 patients with complete response (57%) at 6 weeks, Dr. Kassouf stated that this could change the way we treat this disease.

The POUT trial data indicates that peri-operative chemotherapy after RNU (pT2-pT4) has a better metastasis free survival (Figure 1). Neoadjuvant chemotherapy improves survival in patients with UTUC (n=107 controls, n=43 neoadjuvant HG, 25% reduction ≥pT2, 42% reduction, CR 14% - Porten, Cancer 2014). When considering neoadjuvant chemotherapy, Dr. kassouf suggests following these factors to help in counseling patients: high grade on biopsy grade, sessile tumor, large tumor burden, local invasion on radiographic studies and adequate renal function (cisplatin-based regimens).

There is no doubt in patients with hilar/regional adenopathy that they should be treated upfront with chemotherapy (metastatic disease).

Bladder instillation with mitomycin C post-OP should be a standard treatment according to a RCT of 248 patients, which showed decreased bladder recurrence (1 year: 16% VS 27%, p=0.03, MMC given 7-10 post-OP).

The evidence on the benefit of extended lymphadenectomy is very weak (retrospective). Dr. Kassouf in his practice does lymphadenectomy of para-aortic nodes (left tumor) and para-caval nodes (right tumor), but not extended because of morbidity and questionable benefit.

The lecture concluded with the following take home messages: the role of NBI is uncertain, intracavitary instillation remains unclear (BCG appears to work best for CIS, emerging therapies as Mitogel may change paradigm) and the therapeutic benefit on extended lymphadenectomy remains unclear.

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Bladder Cancer

MEXICAN UROLOGIC ONCOLOGY ASSOCIATION MEETING 2018

Optimizing BCG Therapy for NMIBC

Ashish Kamat, MD, started his presentation stating that bladder cancer immunotherapy treatment, including written literature, seems only to include systemic therapy and not BCG. Actually, BCG is the original cancer immunotherapy, the most effective for NMIBC and approximately 1.2 million doses are used globally.

Six myths were explained and discussed, in order to achieve a better understanding about the use of BCG and optimize its use. He demonstrated that BCG reduces both recurrence and progression rates in NMIBC (Myth #1), but progression is only reduced when maintenance is used (2002, meta analysis of 24 RCT of BCG – 4863 pts). BCG has a 32% advantage over mitomycin C when maintenance is used, instead of induction alone (suboptimal therapy).

Optimal schedule of BCG is unknown (Myth #2). It's stated that the SWOG (induction for 6 weeks plus 3 weekly instillations at the third and sixth month, and then every 6 months for up to 3 years) protocol shows clear benefit over induction alone. In a BCG naïve bladder, cytokines continuously rise in the weeks 1 to 6, however in patients with previous BCG treatment, cytokines rise up to the 3rd week and more BCG is given after that, it will suppress the immune system. Dr. Kamat emphasized that maintenance treatment duration is more important than dosage (3 year @ full dose: 64.2%, 3 year @ 1/3rd dose: 62.6%, 5 year disease free rate).

BCG maintenance is only indicated for high risk patients (Myth #3). It is, in fact, also indicated for intermediate risk; EORTC (30911) reported that BCG in these patients reduces deaths (n=497, HR 0.35, p value 0.020), recurrence, metastatic disease and there is an improved overall survival.

Intravesical BCG is not well tolerated (Myth #4). EORTC and International IPD Survey reported respectively that <10% and 5.2% patients discontinued maintenance therapy due to toxicity. Strategies for optimizing intravesical BCG are: inspect voided urine for visible hematuria, catheterize atraumatically, minimize lubricant amount (to avoid BCG clumping), avoid lidocaine (acidity degrades BCG), use of antispasmodics and 1 dose of quinolone 6 hours after BCG [Recommendations Urol Clin North Am].

Older patients have lower efficacy with intravesical immunotherapy rather than no efficacy (Myth #5). Patients > 70 years had shorter time to progression, worse overall survival and NMIBC specific survival, but similar time to recurrence compared with younger patients. In spite of theses characteristics, BCG is still a better option than other chemotherapies.

BCG is all the same, everywhere (Myth #6). Dr. Kamat's opinion differs and he expressed that a better response to local BCG (from the patient´s country) instead of international BCG has been reported; the explanation is that the epitopes of the BCG strain that mount a robust immune response are secondary to previous exposure (TB or mycobacterial linked).

Presented by: Ashish M. Kamat, MD, MBBS, Professor of Urologic Oncology, MD Anderson Cancer Center, Houston, TX

Written by: Eduardo Gonzalez-Cuenca, MD, Urology Resident, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico City & Ashish M. Kamat, MD, MBBS, Professor of Urologic Oncology, MD Anderson Cancer Center, Houston, TX

MEXICAN UROLOGIC ONCOLOGY ASSOCIATION MEETING 2018

Biomarkers in Immunotherapy for Bladder Cancer

Dr. Ashish M. Kamat

Clinical judgment and data is the key for predicting the response of intravesical BCG, actually no biomarker can supersede our clinical data.

Ashish M. Kamat, MD, MBBS, explained four biomarkers we could use to identify response to immunotherapy: PD-L1 status, molecular subtyping, tumor mutational burden and immune gene expression profiling.

The PD-L1 expression (prognostic factor) is seen in approximately 20-30% of specimens and it is associated with increased pathologic stage, increased all-cause mortality and more aggressive disease. Durvalumab correlates with PD-L1 high expression with greater efficacy (High PD-L1, objective response rate 31% VS 5.1% of low/negative PD-L1, but efficacy is still observed). Atezolizumab and pembrolizumab had no impact of PD-L1 status on overall survival.

In the IMvigor 210 trial (atezolizumab) was found that basal clusters had highest prevalence of IC 2/3 PD-L1 (60 VS 23%) and TC 2/3(39 VS 8%), but highest response was in luminal cluster II subtype (ORR=34%, p=0.0017).

The tumor mutational burden (neoantigen burden) is associated with a greater likelihood of durable responses to immune checkpoint blockade. Neoantigen burden predicts response more robustly than PD-L1 and presence of TILs. IMvigor 210: cohort II found higher mutational load in responding vs non-responding patients (12.4 VS 6.4 per megabase, p<0.0001).

Multiparameter immune gene expression profiling in the Checkmate 275 study (nivolumab) found IFN-γ signature correlated with better response to nivolumab (high IFN-γ signature: CR/Prin 20/59 patients; medium or low IFN-γ signature: CR/PR in 18/118 patientes; p=0.0003).

Dr. Kamat concluded that PD-L1 positivity inconsistenly enriches for clinical benefit, TCGA and other subtypes have varied associations,


tumor mutational burden correlates with response and immune gene expression profiles studies still ongonig for findings.

Presented by: Ashish M. Kamat, MD, MBBS, Professor of Urologic Oncology, MD Anderson Cancer Center, Houston, TX

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MEXICAN UROLOGIC ONCOLOGY ASSOCIATION MEETING 2018

Should Variant Histology change management of Bladder Cancer?

Ashish M. Kamat, MD, MBBS, talked about the frequency of bladder variant histology being as high as 7,500-18,000 cases per year in the USA, representing 10-25% of all cases. Also remarked the discordance between transurethral resection and cystectomy in 39-47%.

The frequency of non-recognized histological subtypes by community pathologist is an astonishing 44% of all the biopsy samples. This remark left a take home message: Ask your pathologist if there is a histological subtype such as lymphoepithelial, plasmacytoid, nested variant, micropapillary and small cell histology present.

The later information takes importance when considering they have worst outcome regarding the higher propensity of locally advanced disease, greater degree of lymph node metastasis, a HR of 2.7 of upstaging at radical cystectomy and considering the different responses to therapy on this strains.

Micropapillary bladder cancer was first described at MD Anderson Cancer Center in 1994 as a rare subtype. It has two histological features that made this variant peculiar: the micropapillae without central vascular cores and the consisting lymphovascular invasion present in the micropapillary areas. Dr. Kamat showed evidence describing the poor performance of BCG in this variant, with 89% of recurrence and 67% of progression, 22% of them with metastasis (Figure 2), and the disease specific survival (DSS) after progression is 24% at 5 years. Dr. Kamat dramatically depicted the chance of surviving micropapillary bladder cancer is lower than playing Russian roulette when treating MPBC with BCG only. The consensus of the best treatment for cT1MPBC was the radical cystectomy, and BCG only in very selected patients.

The Small Cell Carcinoma differs biologically from urothelial carcinoma, for early metastasis, rapid growth and the unique metastasis sites (brain and bone). Approximately 50% of patients have metastasis at cystectomy, despite clinically organ confined disease, thus, is considered initially as a systemic disease, and CNS image is mandatory for all patients. In this variant, the neoadjuvant chemotherapy (NAC) improves the overall survival (OS) (159.5 vs 18.3 months) and DSS at 5 years (79 vs 20%), the drugs of choice are cisplatin with etoposide, followed by radical cystectomy. For patients unable to undergo cystectomy, NAC followed by chemoradiotherapy is an alternative.

The squamous differentiation is very common in urothelial cancer, found in up to 60%, often mixed with glandular differentiation. The biology of this tumor portends more aggressive behavior, nevertheless, has no impact in DSS, therefore it should be treated similarly as stage-matched urothelial bladder cancer, and NAC should be considered.

Dr. Kamat concluded his talk by stating the importance of awareness of bladder cancer variant histology and the impact in prognosis; treatment should be personalized by each patient.

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Kidney Cancer

CANADIAN UROLOGICAL ASSOCIATION ANNUAL MEETING 2018

Comparing Laparoscopic Cytoreductive Nephrectomy to Open Surgery: A Large, Multicentre, Retrospective Analysis

Dr. Samir Ksara

Laparoscopic surgery is known to minimize perioperative morbidity and decrease length of hospital admission, however, its benefit in cytoreductive nephrectomy continues to be a topic of debate. A previously published multi-center experience of laparoscopic cytoreductive nephrectomy found that among 120 patients, median operative time was 210 min, and median estimated blood loss was 150 cc.[1] Four (3.3 %) patients were converted to open surgery due to locally advanced disease and/or bleeding, and postoperative complications occurred in 23.3% of patients, of which 71.4 % were classified as minor (Clavien-Dindo I-II). To further assess the safety and feasibility of laparoscopic cytoreductive nephrectomy, Samir Ksara, MD, and colleagues performed a large, multicenter, retrospective analysis comparing laparoscopic radical cytoreductive nephrectomy to open cytoreductive radical nephrectomy. The objective of this study was to assess whether laparoscopic cytoreductive nephrectomy minimizes the delay to systemic therapy and offers an overall survival benefit when compared to open cytoreductive nephrectomy.

For this study, data was collected from The Canadian Kidney Cancer Information System, a prospectively maintained database from 14 Canadian centers. Patients who underwent cytoreductive nephrectomy from January 1, 2011 to June 1, 2016 were included (n=224). Cox proportional hazard modelling was used to adjust for age, gender, pathological stage, size of largest tumour, grade, and whether patient received neoadjuvant systemic therapy.

Among the 224 patients meeting inclusion criteria, 93 patients underwent laparoscopic surgery (41.5%), and 131 patients underwent open surgery. The 1-year survival estimate was 85.5% for the open group and 83.3% for the laparoscopic group, with no statistically significant difference in survival noted for those who underwent laparoscopic or open cytoreductive nephrectomy (HR 0.69; p=0.13). Furthermore, there was no significant difference noted in time to delivery of systemic therapy between the two groups (p=0.20), however there was a splitting of the Kaplan-Meier curves at six months after surgery, favoring the laparoscopic group.

The strength of this study is that it represents a real-world utilization of laparoscopic and open cytoreductive nephrectomy experience in Canada. However, the study is limited by lack of information regarding baseline characteristics, although the authors adjusted for several variables in their model. Furthermore, with the recent results of the phase III CARMENA clinical trial suggesting that not all patients may benefit from a cytoreductive nephrectomy,[2] the clinical utility of these results remains to be completely elucidated.

Dr. Ksara concluded that in the context of this analysis, laparoscopic cytoreductive nephrectomy does not lead to earlier delivery of systemic therapy and shows no benefit in overall survival when compared to open cytoreductive nephrectomy.

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CANADIAN UROLOGICAL ASSOCIATION ANNUAL MEETING 2018

1st and 2nd Line Therapy in Kidney Cancer: Practice Changing Trials

Dr. Sumanta Kumar Pal

Sumanta Pal, MD, kicked off the CUOG meeting with a talk highlighting the major changes in RCC systemic therapy management in the past year.

In the 1990s the debates in advanced RCC management were limited to "Is high-dose IL-2 appropriate for everyone?" but in the past few years has been thrown into disarray with a dizzying number of new agents in this space. Ultimately, the goal is determining which agents allow our patients to live longer (ideally for cure) and live better.

His talk focused on three major developments (amongst others):

1. ESMO 2017: Nivo/Ipi vs. sunitinib primary analysis (CheckMate 214 study)

2. SITC 2017: Nivo/ipi vs sunitinib secondary analysis (CheckMate 214 study)

3. GU ASCO 2018: Bevacizumab/atezolizumab vs. sunitinib primary analysis (InMotion 151)


All of these are in the first line setting, though he did note many of the second line therapies are now moving up to first line.

He also noted that all the studies are being compared to sunitinib, but there is increasing evidence this is no longer the standard of care.

The CheckMate 214 study compared Nivo/ipi (followed by nivo maintenance) against sunitinib (standard dosing) in the first line setting (treatment naïve advanced or metastatic RCC).

His key points included:

1. Overall survival for IMDC intermediate/poor risk patients was significantly higher in the Nivo/Ipi arm than in the sutent arm (NR vs. 26.0 months, HR 0.63, p <0.001)

2. However, in IMDC favorable risk patients, suninitib actually fared better (ORR 52% sutent vs. 29% Ipi/Nivo, 10 month PFS benefit to sunitib)

3. Twice as many patients discontinued drug in the Nivo/Ipi arm than in the sunitinib arm

4. 60% of patients in the Nivo/Ipi arm required IV corticosteroids for adverse effects

5. PFS was significantly better in PD-L1+ patients (HR 0.48), but not in PD-L1- patients (HR 1.0); however, OS benefit was significantly better with Nivo/Ipi in both subsets, but more pronounced in PD-L1+ patients

In InMotion 151, bevacizumab/atezolizumab (Bev/Atezo) was compared against standard dosing sunitinib in the first line setting (treatment naïve advanced or metastatic RCC) – however, it wasn't just clear cell histology; sarcomatoid histology was also allowed.

Key points:

1. PFS was significantly better with bev/atezo in the PD-L1+ and intent-to-treat analysis (on independent review)

2. Objective response rate higher in the Bev/Atezo cohort – notably, CR rates double the sunitinib arm (9% vs 4%)

3. In contrast to Nivo/Ipi, Bev/Atezo was very well tolerated with less adverse effects that sunitinib – and only 16% required IV steroids

4. Interestingly, the investigator-assessed outcomes did not quite sync with independent review committee – though he noted that they trended the same direction, which was reassuring, likely suggesting a true signal. IRC and INV assessment of PFS and OS benefit was generally consistent with ITT population results.

5. OS data was immature – but suggested a trend towards favoring Bev/Atezo.

When comparing the two first-line comparators, they are relatively similar – except the adverse event profile which strongly favors bev/atezo.

He did point out again that TKI's should not be discounted – sunitinib is likely not the best comparator. CABOSUN, a phase III study that compared cabozantinib and sunitinib in the first line setting, clearly demonstrated that CAB had better PFS (8.6 vs. 5.3 months, HR 0.48, p<0.0001), particularly in patients with bone metastases and poor-risk disease.

The future lies in the combination of TKI's (as bevacizumab is an earlier targeted agent, not a TKI) and immune checkpoint blocker – there is biologic rationale for this.

He then briefly reviewed the early data from early phase TKI/IO therapies, all with promising early results, including (but not limited to): axitinib/pembrolizumab, cabozantinib/nivolumab +/- Ipilimumab, tivozanib/nivolumab.

His last focus was a plug for a study that is rapidly accruing. Interestingly, it allows for adjuvant/maintenance therapy following Nivo/Ipi front-line treatment based on response.

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CANADIAN UROLOGICAL ASSOCIATION ANNUAL MEETING 2018

Outcomes Of Metastasectomy in Metastatic Renal Cell Carcinoma (mRCC) Patients: The Canadian Kidney Cancer Information System Experience


Dr. Sara Nazha

In common urological practices, it has been shown that over 25% of patients are diagnosed with metastasis at the time of renal cell carcinoma (RCC) diagnosis and up to 35% will eventually progress to metastasis after some time. There have been recent indications that state that surgical resection of these metastatic tumors can be integrated into the treatment plan with possibility of slowed disease progression and increased survival. Sara Nazha, MD, of McGill University determined to discover the efficacy of this treatment by conducting a multi-center retrospective study to assess the impact of metastasectomy in patients suffering from metastatic RCC (mRCC).

To determine an answer to this research question, the Canada Kidney Cancer information service (CKCis) was used to pool data from 9 different centers throughout Canada. Patients were screened for a diagnosis of mRCC with a pathologic confirmation of RCC between January 2011 and December 2017. Patients were stratified by whether they had received a metastasectomy (complete or


incomplete) or had not received a metastasectomy. Each patient who underwent metastasectomy was matched with up to 10 patients with no metastasectomy in regard to age, clear cell histology, use of targeted therapy prior to metastasectomy, or having a nephrectomy. Overall survival was defined as death of any kind from the initial diagnosis of mRCC.

Following study completion, it was determined that 329 patients had complete (221 pts) or incomplete (108 pts) metastasectomy for mRCC, respectively, while 1,347 mRCC patients did not undergo metastasectomy. The main endpoint of the study showed that patients who underwent a metastasectomy were associated with a significantly increased survival rate compared to no metastasectomy. When comparing complete versus incomplete metastasectomy cohorts, and additional significant increase in overall survival was seen, in the favor of complete metastasectomy.

In her closing remarks, Dr. Nazha reiterated how the metastasectomy treatments modality is capable of yielding longer overall survival in patients afflicted by mRCC. She urged the audience to please consider this treatment whenever a patient presents with this condition as it has shown to be vastly better than non-metastasectomy treatments.

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CANADIAN UROLOGICAL ASSOCIATION ANNUAL MEETING 2018

Role of Cytoreductive Nephrectomy in 2018


Dr. Ricardo Rendon

This talk focused on the role of cytoreductive nephrectomy in advanced/metastatic RCC. Ricardo Rendon, MD, gave summarized the background work and recent publications.

As systemic therapies continue to improve and change for advanced/metastatic RCC and are better tolerated, there has been increasing question of the role of cytoreductive nephrectomy (CNx) in this setting. Dr. Rendon was tasked to develop the CUA guidelines for this topic – unfortunately, after accumulating the data for this space, the recent CARMENA results were presented at ASCO 2018 and he was forced to adjust his report and slides significantly.

The current guidelines, such as the EAU guidelines, recommend CNx for favorable/intermediate risk patients with metastatic RCC and to perform immediate CNx in patients with oligometastatic disease when complete resection can be achieved; they also recommend avoiding CNx in IMDC poor-risk patients and to offer defect CNx in intermediate-risk patients with clear cell RCC who require systemic therapy. However, the strength of these recommendations is "weak" for all.

Theoretical advantages of upfront CNx:

1. palliative/reduce complications related to primary tumor
2. Remove potential sources of new metastases and new mutations
3. Improve immune function
4. Treat within window of resectability
5. Best response (CR) to systemic therapy alone is relatively low
6. Primary tumor is often minimally responsive to TT (targeted therapy)
7. 90% of patients in TT trials had CNx

Theoretical advantages of initial systemic therapy:

1. Palliation of symptoms of metastases
2. Stabilize/regression of disease
3. Shrinkage of tumor (albeit modest) – rarely affects surgery
4. "Litmus test" - ~30% of patients won't make it to CNx due to disease progression, and probably wouldn't have done well with a surgery anyway.

He then briefly reviewed the data leading to this point. In the IL-2/immunomodulator era, Flanigan et al. (NEJM 2001, JUrol 2004) and Mickisch et al. (Lancet 2001) demonstrated that removal of the kidney was associated with improved overall survival (OS). As a result, it has become an established paradigm in the management of mRCC, and patients who are surgically fit, are often recommended for cytoreductive nephrectomy prior to systemic therapy.

However, the introduction of targeted therapies, including tyrosine kinase inhibitors and mTOR inhibitors, have drastically changed the outcomes of mRCC patients. While not providing a cure, they are able to provide long-term response in some patients. In doing so, they have significantly extended the survival of patients with mRCC. Unfortunately, with this advancement in systemic therapy, the need for cytoreductive nephrectomy has been called into question. Especially in patients with advanced RCC (ntermediate and poor risk) who have high volume disease outside of the kidney, there has been increasing emphasis on providing systemic therapy up-front and avoiding delays by putting the patient through a major operation.

Retrospective series and meta-analyses have continued to demonstrate a survival benefit to CNx in the setting of mRCC. (Heng et al. EU 2014, Bhindi et al. J Urol 2018) However, this has primarily been in IMDC favorable or intermediate risk patients (IMDC 1-3

risk factors). His own recent unpublished work, a meta-analysis of all CNx trials/studies in the TT era, lookedat 18,570 patients – and found that CNx benefited patients (HR 0.57 favoring CNx).

However, he noted that patient stratification is important. A subset of patients experience rapid progression of disease (~30%) and likely won't benefit from surgery or systemic therapy. There have been different attempts to risk stratify. The IMDC nomogram is one of the more commonly used ones – but the one risk factor ("<1 year from diagnosis to treatment") makes it almost impossible for de novo mRCC patients to be considered favorable risk.

We can also use biology as a risk stratifier, which is essentially what the SURTIME study did. In SURTIME, an EORTC sponsored randomized control trial, patients were randomized to sunitinib followed by CNx (deferred CNx arm) and subsequent sunitinib versus upfront CNx followed by sunitinib. SURTIME closed early in 2016 due to poor accrual (likely due to difficulty enrollment criteria) – and was likely underpowered. SURTIME results were presented at ESMO 2017. On intent to treat analysis, deferred CNx was non-inferior to up front CNx – HR 0.57 favoring deferred nephrectomy (p=0.032). However, as they did not meet their sample size requirements, the study was technically underpowered. Yet, the data suggests that deferring CNx was likely not detrimental in targeted therapy era.

Lastly, he discussed the CARMENA study (ASCO 2018, Mejean et al.) – in this study, patients were randomized to either CNx or systemic therapy (sunitinib). Patients with low-volume metastatic disease (low-intermediate risk) were actively excluded by the investigators due to low equipoise – leaving a population that was heavily high-intermediate (60%) or poor risk (40%). They also only recruited 450 of the expected 576 patients. Sunitinib alone was not inferior to CNx + sunitinib (median OS 18.4 vs. 13.9 months, HR 0.89, favoring sunitinib). However, most of the benefit appeared to come from switching from progressive disease to stabilizing disease – no net improvement in CR or partial responses. Mortality for nephrectomy was minimal (4 deaths, 2%). Most complications were Clavian-Dindo Grade 1-2. 16% were Grade 3-4. Secondary nephrectomy in the sunitib arm was completed in 38 patients (17%) - 7 (18.9%) were due to symptoms and considered emergent. Importantly, 22.5% of patients never recovered enough after CNx to receive sunitinib.

Based on this consolidated results, he concluded, as many did, that our daily practice was unlikely to change. His recommendations, which is likely what is being done by most:

1. For patients with good performance status, young age, no systemic symptoms, relatively limited burden of disease (favorable risk or low-intermediate risk), offer CNx and manage metastases with metastatectomy and surveillance
2. For patients with high-intermediate and poor risk disease, significant systemic symptoms from metastatic burden, active CNS mets, limited burden of disease within kidney compared to extra-renal, or rapidly progressing disease, plan for systemic therapy before considering CNx.

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CANADIAN UROLOGICAL ASSOCIATION ANNUAL MEETING 2018

Predictors of a Positive Genetic Test Result in Patients with a Suspected Hereditary Kidney Cancer Syndrome: Results from a Provincial Medical Genetics Unit

Dr. Andrea Kokorovic

Andrea Kokorovic, MD, presented a study attempting to assess risk factors associated with a positive genetic test in a real-life cohort of patients referred to medical genetics for evaluation of hereditary renal cell carcinoma (RCC).

RCC has strongly been linked with hereditary kidney cancer syndromes. CUA guidelines recommend genetic referral for patients with RCC and high-risk features.[1] There is very limited data regarding outcomes of these patients. There is a single center study from MSKCC suggesting that young age is a predictor for a positive genetic test result.[2] High-risk features of RCC suggestive of a hereditary kidney cancer syndrome.

Currently, there is limited data regarding the number and outcome of patients identified as being high-risk for hereditary kidney cancer syndromes that have been referred for genetic counseling. The CUA referral criteria are derived from expert consensus and lack of support from the literature.

The presented study aimed to determine the risk factors associated with a positive genetic test in a real-life cohort of patients referred to medical genetics for evaluation of hereditary RCC.

Multivariable analysis demonstrated that family history and dermatologic findings were statistically significant predictors of a positive genetic result. Dr. Korokovic concluded that dermatologic findings and family history are the only predictors of a positive genetic test in patients undergoing evaluation for hereditary RCC. This is the largest study published to date on this important issue and suggests that current referral criteria may be too broad for application in real life patient population. In any case, further evaluation with prospective trials is warranted.

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CANADIAN UROLOGICAL ASSOCIATION ANNUAL MEETING 2018

Comparative Survival Following Initial Cytoreductive Nephrectomy versus Initial Targeted Therapy for Metastatic Renal Cell Carcinoma


Dr. Bimal Bhindi

Bimal Bhindi, MD presented a population level analysis assessing survival following upfront cytoreductive nephrectomy (CN) versus targeted therapy (TT) for patients with metastatic RCC. The optimal sequence of CN and TT for patients with mRCC remains to be established. The CARMENA study demonstrated that sunitinib was non-inferior to CN followed by sunitinib.[1] Therefore, the authors aimed to compare overall survival (OS) between patients with mRCC receiving initial CN with or without subsequent TT versus initial TT with or without subsequent CN.

For this study, the authors used the National Cancer Database (NCDB) to identify 15,068 patients diagnosed between 2006-2013 with RCC that was metastatic at diagnosis who received CN, TT, or both. Those with other prior cancer history were excluded. The cumulative incidence of receiving TT after CN and CR after TT were evaluated, with death prior to second treatment as a competing risk. To account for treatment selection bias, inverse probability of treatment weighting (IPTW) was performed based on the propensity to receive initial CN or TT. OS from diagnosis was compared using Cox regression analyses.

The cohort included 15,068 patients, of whom 6,731 (44.7%) underwent initial CN and 8,337 (55.3%) underwent initial TT. At 6 months from diagnosis, the probability of receiving TT after CN was 46.2%, with 13.6% of patients having died after initial CN prior to receiving TT. The probability at 6 months of undergoing CN after initial TT was 4.4%, with 38.3% of this group having died prior to undergoing CN. In the IPTW analysis, baseline characteristics were balanced (standardized difference < 0.1). Initial CN was associated with improved OS compared to initial TT (median 16.5 vs 9.2 months; HR 0.62, 95%CI 0.61-0.64), as shown in Figure 1. Findings were similar in all sensitivity analyses, including (i) propensity score matching and adjustment, (ii) regression adjustment, (iii) 6-month landmark analysis, (iv) clear cell mRCC subset, and (v) exclusion of patients who had metastasectomy.

Although initial CN was associated improved OS versus initial TT in this national dataset, initial CN was associated with delays in, and even death prior to, receipt of targeted therapy. As such, while the survival data here support initial CN inappropriate surgical candidates, continued efforts to develop the optimal multimodal approach to these patients are warranted.

The limitations of this study include its observational retrospective nature, unmeasured differences between groups, and incomplete capture of subsequent therapies beyond 6 months.

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1. Ravaud et al. NEJM 2018

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CANADIAN UROLOGICAL ASSOCIATION ANNUAL MEETING 2018

Surveillance Post-Radio Frequency Ablation for Small Renal Masses: Recurrence and Follow-Up


Dr. Anil Kapoor

The management of renal cell carcinoma (RCC) continues to evolve as we begin to develop a better understanding of its natural history. We now know that growth kinetics can vary significantly for renal masses, and those with slow growth kinetics can often be watched without losing the opportunity for cure. As such, there has been a shift from surgery (radical or partial nephrectomy for every renal mass) to more conservative options to help reduce morbidity, unnecessary treatment and to spare nephrons. Active surveillance for small renal masses has become more established and is now a front-line treatment option in many guidelines. Similarly, when masses are small but growing, an alternative to surgery is focal therapy – radiofrequency ablation (RFA) being one such energy source option.

While partial nephrectomy is widely accepted as the standard of care nephron-sparing approach in the management of clinically localized RCC (>90% disease-specific survival), focal therapy options have begun emerging as an alternative management strategy. It should be noted that local recurrence are noted to be slightly higher in focal therapy approaches, although overall survival, recurrence rates, and follow-up strategy after RFA has not yet been clearly established.

In this study, the authors used their institutional experience with small renal masses (SRMs) treated with RFA to evaluate the time to recurrence and recurrence rates. As a retrospective series of patients between 2011 and 2017, they found 84 patients with a solitary SRM and no evidence of metastatic disease treated with RFA; patients

with familial syndromes were excluded. Biopsy proven oncocytomas were excluded as well.

Interestingly, repeat RFAs of the ipsilateral kidney for incomplete ablation was not considered a new procedure. The primary outcome was time from initial ablation to recurrence.

In terms of demographics, the average age was 68.6±10.6 years, 71% were male, average tumor size was 2.42 ±0.81 cm. It would appear that 25 did not have prior biopsy; however, of the remaining, 40 were clear cell, 16 papillary and 3 chromophobe RCC.

Over a median follow-up of 41 months (~3.5 years), there was a total of 4 total recurrences (4.8%) post-RFA. Albeit, this is a relatively short follow-up for SRMs. In the 4 patients with recurrence, the median time to recurrence was 17 months; none of the recurrences occurred beyond 30 months.

In terms of incomplete treatment or residual disease, 5 patients had a residual disease (6%) and were identified within the first eight months post-RFA.

The only prognostic variable identified as a predictor of residual disease was tumor size (hazard ratio 2.402; p=0.047) on univariate analysis, but not on MV analysis – other variables in the model included RENAL nephrometry score, PADUA score, age, and sex. Hence, patients with larger renal masses were more likely to have residual disease. This is supported by other institutions, including ours – patients with masses greater than 3 cm need to understand that they have a higher chance of residual disease, and therefore may not warrant focal therapy.

Based on these results, the authors suggest (but need to validate on further studies) that surveillance post RFA can begin to reduce intensity beyond 30 months (though Dr. Kapoor conservatively stated 5 years). Current protocols recommend lifelong follow-up with cross-sectional imaging – this may be unnecessary beyond 3-5 years, similar to post-partial nephrectomy surveillance protocol.

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CANADIAN UROLOGICAL ASSOCIATION ANNUAL MEETING 2018

Development of a Patient Decision Aid for Complex, Localized Renal Masses

Management of renal cell carcinoma (RCC) has traditionally been a surgically managed disease, and while alternatives have risen for small renal masses (active surveillance, focal therapy), for larger cT1b+ renal masses, the standard of care is still extirpative management. Yet, the decision to proceed with either a nephron-sparing partial nephrectomy (nephron-sparing, albeit with more potential complications) or a laparoscopic radical nephrectomy (not nephron-sparing but usually with fewer complications due to the lack of reconstruction) can be a tough one. Sometimes it is determined by disease factors (ie complexity of the tumor, nephrometry score, etc) or physician factors (preference, comfort). However, sometimes both options are equal and the options are offered to the patient – but it is not an easy decision to make.

"Patient decision aids" are structured clinical tools that facilitate shared decision-making – they present therapeutic options, including their risks and benefits, in an evidence-based fashion and help patients communicate their values. The group from Ottawa worked on creating such an aid for this challenging situation which all urologic oncologists and most urologists face regularly.

They based their model off of the International Patient Decision Aids Standards (IPDAS) and the Ottawa Decision Support Framework – these are international and regional guidelines to help physicians create an aid that doesn't inappropriately influence the patient. They focused their efforts on cT1b-cT2 tumors, those which are most likely to encounter this decision point – larger tumors are more likely to require nephrectomy (even open nephrectomy) while smaller tumors are often offered more conservative management and partial nephrectomy is the preferred approach. The content of the decision aid was agreed upon by content and methodological experts using an iterative feedback process.

Once the content was created, a mixed methods survey was created to assess the decision aid. Both patients and urologists were recruited to evaluate the decision aid as this is a shared-decision making tool.

A structured patient decision aid presented evidence on options, including probabilities of benefits and risks. Open partial nephrectomy, laparoscopic radical nephrectomy, and observation were the three main options offered to patients. The outcomes for which probabilities were generated included: bleeding, urine leak, length of stay, renal failure, and survival. These are all items we routinely discuss with patients, but perhaps not in a standardized way – which may lend itself to bias. Simple language and pictures were used to present data at a level suitable for a wide range of patients – which is important for patient understanding.

They will then use a validated screening tool (SURE test) to assess patients' decisional conflict. Knowledge questions were included to verify patients' understanding and to see how well the decision aid transferred information.

Initial testing has demonstrated good results – alpha testing (11 urologists, 8 patients, 3 patient advocates). They felt the length was appropriate and that the language was easy to follow. Most felt strongly that it would be useful in clinical use. One area to improve was the inclusion of robotic partial nephrectomy.


Based on this they will finalize the final decision aid and move to beta testing.

This is a very interesting study with significant clinical impact. Also presented at other major cancer conferences, it has been well-received. We look forward to the results of their prospective evaluation of the aid in clinical practice!

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MEXICAN UROLOGIC ONCOLOGY ASSOCIATION MEETING 2018

Current Criteria for Nephron Sparing Surgery, What are the Limits?


Dr. Bernardo Gabilondo Pliego

Bernardo Gabilondo Pliego, MD, presented a talk regarding the limits of nephron sparing surgery (NSS). He stressed that surgeon experience, tumor size, and localization are critical when deciding the surgical approach in patients with localized clinical masses. The current indications for NSS include:

- Small renal masses and tumors from 4–7 cm
- Solitary Kidneys
- Chronic Kidney Disease and;
- Bilateral Renal Tumors

Patient factors (previous abdominal surgeries, BMI, presence of comorbidities and functional status) as well as tumor nephrometry evaluated with current scores determine the viability of this technique. He underlined the importance of taking into account perinephric fat which is not contemplated in many scoring systems and can potentially complicate the surgical procedure transoperatively. In addition, the benefits of the transperitoneal approach were highlighted when considering minimally invasive surgery (anatomic relationships and it facilitates surgical movements by working in a larger cavity). The use of kidney cancer predictive tools and other kidney function normograms was also encouraged.

Current treatment trends have changed the paradigm in the treatment of renal masses and renal biopsy should be done when clinically indicated. In the United States, 60% of NSS are robot-assisted laparoscopic procedures but open surgery (OPN) is still considered standard of care in many centers worldwide. Limitations of the robotic approach were evaluated in a multicenter study that compared TRIFECTA outcomes between OPN and robotic partial nephrectomy (RAPN) in completely endophytic renal tumors where no differences were found in TRIFECTA achievement between these two techniques. The learning curve for this approach was assessed by a study that compared RAPN with laparoscopy where the threshold for acceptable perioperative outcomes was 30 cases. This learning curve is reasonable when considering how technically demanding it can be when teaching complex laparoscopy cases to trainees. Several cases were described and he emphasized the use of transoperative ultrasound to obtain adequate margins in endophytic tumors.

He concluded that NSS should always be considered when clinically indicated and surgically feasible to preserve renal function as well as obtaining equivalent oncological outcomes. All techniques are acceptable and are subject to surgeon preference and experience.

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