Editorial

Round up

THE SURVIVAL DISADVANTAGE OF LYMPH NODE DISSECTION IN NONMETASTATIC RENAL CELL CARCINOMA

The current European Association of Urology guidelines for nonmetastatic renal cell carcinoma (RCC) state that "In patients with clinically enlarged lymph nodes (LNs), perform LN dissection (LND) for staging, prognosis, and follow-up" with a weak recommendation. While the benefits of LND remain uncertain, it has also not been reported to increase morbidity or mortality of the patients. However, a systemic review and meta-analysis by Shi *et al*.[1] now suggests that LND could decrease survival in these patients. This review included around 1.3 lakh patients from 22 studies, of which 30,000 underwent LND. LND had no significant effect on the overall recurrence, metastasis, and all-cause mortality but was detrimental to the cancer-specific survival, which is a more meaningful clinical endpoint than overall survival (OS) and progression-free survival, leading the authors to recommend that surgeons choose the target population for LND carefully. The survival discrepancy is because of the statistical illusion of the so-called Will Rogers phenomenon[2] seen due to "stage migration" in patients with cancer. Changes in the criteria for assigning patients to the various stages of a disease can produce spurious improvements in stage-specific prognosis, even though the outcome of individual patients has not changed. In oncology, new imaging tools allowed the detection of cancer metastases before they became evident clinically. As a consequence, more patients are classified into the more severe metastatic disease stage from the less severe single tumor stage. Such a "stage migration" result in an improved survival of patients in both the less and the more severe disease stages.[2]

While LND increases the surgery duration and blood loss, it simultaneously increases the risk of perioperative death and complications such as lower extremity edema, deep-vein thrombosis, renal failure, adrenal insufficiency, chylous ascites, intestinal obstruction, and ischemic colitis. The reason why LND is not beneficial for even high-risk patients (T3-4/N1) is probably because the predominant route of spread for RCC is venous rather than lymphogenous. Efferent lymphatic vessels from the kidney drain directly into the thoracic duct, bypassing the retroperitoneal LNs. As a result, RCC does not have a prolonged locoregional phase compared to other urological malignancies, and therefore, LND to control the retroperitoneum does not translate into a survival benefit. While pathological LN involvement is seen in only 2%–5%[3] of patients of RCC, concurrent distant metastases are present in 60%–70% of patients with pN1 disease,[4] and in those with no concurrent metastasis, metastasis generally develops in 12 months.[5] Therefore, LND might not be suitable for all nonmetastatic RCC, and on the contrary, it could hamper survival.

PENILE REHABILITATION WITH SILDENAFIL AND RISK OF BIOCHEMICAL RECURRENCE AFTER PROSTATE RADIATION THERAPY

Penile rehabilitation with sildenafil citrate (SC) after prostate radiation therapy (PRT)/radical prostatectomy has been shown to protect sexual function.[6] However, angiogenesis and autonomic nerve development promoted by SC use have been reported to increase the risk of biochemical recurrence (BCR) leading to discouragement in its use.[6,7]

Haseltine *et al*.[8] performed a secondary analysis of the first randomized placebo-controlled trial that compared SC and placebo given concurrently and as an adjuvant with PRT to ascertain if SC use is associated with increased risk of BCR. In a multicenter, double-blind, placebo-controlled trial, patients were randomized in a 2:1 ratio to receive daily treatment with SC (50 mg) or placebo for 6 months. The BCR-free survival at 6 and 10 years was 98.8% for the SC group and 94.4% for placebo group, respectively. No significant differences in biochemical relapse-free survival outcomes were observed between the treatment arms ($P = 0.36$). In addition, the 10-year OS was also similar between the treatment arms (96% and 93% for SC and placebo, respectively).

Since androgen deprivation therapy (ADT) was a confounding factor for BCR, subgroup analysis excluding patients who received ADT was performed, and no difference was detected in the BCR-free survival between SC and placebo ($P = 0.35$). The 10-year OS remained similar between treatment arms (95% and 93% for SC and placebo, respectively). Thus, there was no difference in the BCR rate between the two arms. A potential benefit in preclinical data suggests that phosphodiesterase-5 inhibitors (PDE-5i) may suppress tumor growth. The major limitations were that this was an unplanned *post hoc* analysis, and the treatment population mainly comprised low- and intermediate-risk patients.

MIRABEGRON IMPROVES ERECTILE FUNCTION IN MEN WITH OVERACTIVE BLADDER AND ERECTILE DYSFUNCTION

PDE-5is are the only approved oral treatments for erectile dysfunction (ED), and an alternative medical management is being looked for when PDE5i fails or is contraindicated. Mirabegron is the first β3-adrenoceptor (β3-AR) agonist, which is approved for the treatment of overactive bladder (OAB). OAB symptoms are associated with an increased risk of ED[9] in men and may share a common pathophysiologic mechanism. Mirabegron acts simultaneously in the bladder, urethra, prostate, and corpus cavernosum (CC) via β3-AR activation and offers a pharmacologic target for ED. Preclinical studies have shown that mirabegron evokes CC relaxation and increases *in vivo* erection responses by activating β3-AR independent from the NO-cGMP pathway (RhoA/rho-kinase [ROCK] pathway).[10] Other studies have described its effect involving alpha-1 adrenergic receptor blockage independent of β3-AR activation and cAMP accumulation.[11]

This pilot study[12] evaluated whether mirabegron improves erectile function in men with concurrent OAB with mild-to-moderate ED. Thirteen men between ages 40 and 70, with an International Index of Erectile Function (IIEF) score of 11–25 and International Prostate Symptom Score of 8–20, were given mirabegron for 12 weeks. It was given at a dose of 25 mg daily for 14 days and increased to 50 mg for the next 10 weeks, as tolerated. Patients were followed up with IIEF-5 and OAB-questionnaire at the baseline and 2, 4, 8, and 12 weeks. A clinically meaningful improvement, defined by a change of four or more points on the IIEF-5 score, was observed in five of 13 (38.4%) men. However, definitive conclusions about the long-term efficacy of mirabegron treatment could not be determined, and the increased mean IIEF-5 scores declined following week 8. While intercourse satisfaction improved at 8 weeks, there was no effect on orgasmic function or sexual desire. As expected, mirabegron improved OAB symptoms and health-related quality-of-life without significantly increasing the postvoid residual. These findings demonstrate the potential clinical benefits and safety of mirabegron in men with ED and OAB. Limitations were the small sample size, a single-arm design with no control group, and a single-site study. However, this initial investigation could identify a possible signal of erectile function improvement with mirabegron.

Evidence suggests that the ROCK inhibitors and PDE5i enhance mirabegron-induced relaxation in the CC and potentiate its effect. These findings could, in future, lead to combination therapies of these drugs in men with ED who do not respond to PDE5i.

ISCHEMIA TIME HAS LITTLE INFLUENCE ON RENAL FUNCTION FOLLOWING PARTIAL NEPHRECTOMY

The surgeon is always wary of the ischemia time during partial nephrectomy (PN), as it directly affects the postoperative renal function. However, most studies on the correlation of warm ischemia and histopathological (HPE) changes due to ischemia are from animal models, and the HPE status of preserved renal parenchyma after PN in humans is not known.

Xiong *et al.*[13] retrospectively reviewed 65 patients with RCC from the year 2005 to 2020 who underwent PN initially and subsequent radical nephrectomy (RN) due to tumor recurrence to find out the histologic changes of preserved renal parenchyma after PN. Macroscopic normal renal parenchyma was sampled at least 5 mm away from the tumor border in PN specimens and at remote sites in RN specimens. Paraffin-embedded sections of two microns were prepared for hematoxylin and eosin (H and E) and Masson's trichrome staining as per the usual technique. H and E samples were used to evaluate histologic chronic kidney disease (CKD) scores based on the status of the glomeruli, tubules, interstitium, and vascular structures. The increase in CKD-score was similar in patients managed with cold versus warm ischemia, and ischemia time of <25 min versus >25 min also did not correlate with CKD-score changes. Patients with comorbidities of hypertension (HTN), diabetes, and/or preexisting CKD (HTN/diabetes mellitus [DM]/CKD) showed a higher median CKD-score increase than those without HTN/DM/CKD. On univariate analysis, HTN/DM/CKD was found to be the only predictor of CKD-score increase and not other factors such as type or duration of ischemia and interval from PN to RN. The authors concluded that warm ischemia and prolonged duration of ischemia were not associated with histologic deterioration after PN.

Therefore, it appears that comorbidities are the main determinants of long-term renal functional decline after PN. Most nephrons recover from ischemia, and nephron-mass loss is the primary determinant of functional recovery in the perioperative period.

PHYSICAL ACTIVITY DECREASES THE RISK OF CANCER RECLASSIFICATION IN PATIENTS ON ACTIVE SURVEILLANCE: A MULTICENTRE RETROSPECTIVE STUDY

Research suggests that diet and exercise can reduce prostate cancer risk and even progression in some trials; however, the overall body of evidence is still lacking. It has been shown that exercise modulates gene expression, improves insulin resistance, and interferes with insulin-like growth factor-1 (has mitogenic and anti-apoptotic effects) and decreases pro-inflammatory cytokines.[14-18] This study investigated the role of physical

activity (i.e., exercise) and its link with decreased advancement rates in males on active surveillance (AS).[19] The authors looked at 85 individuals with low-risk prostate cancer on AS. At the start of the study, all subjects filled out a physical activity questionnaire and were classified as inactive ($n = 24$), moderately active ($n = 46$), or active ($n = 15$). The authors then looked at the probability of grade reclassification, a typical criterion for "progression" among them. Those that progressed were found to be less physically active ($P = 0.056$). Notably, the amount of physical activity was found to be a significant predictor of who progressed over time ($P = 0.033$). Indeed, the amount of physical activity was the only significant predictor of advancement ($P = 0.016$) in multivariable analysis. It was concluded that physical activity might impact the progression of prostate cancer. While the findings of this study are significant, the paper's limitations should be noted. First and foremost, this is not a randomized study. As a result, more active subjects may have adopted other healthy habits (better diet, less smoking, etc.). Many of these additional indicators were not gathered. As a result, one cannot say that physical activity is associated with better outcomes. Second, the sample size was small. Despite these flaws, this study evidence suggests that exercise can help to prevent the growth of prostate cancer.

NONLUMINAL BLADDER CANCERS BENEFIT THE MOST FROM NEOADJUVANT CHEMOTHERAPY

Platinum-based neoadjuvant chemotherapy (NAC) confers a 5%–10% OS benefit in nonmetastatic muscle-invasive bladder cancer (MIBC) patients. There is a need of a validated biomarker to select patient subgroup likely to benefit from NAC while sparing others from the adverse effects of chemotherapy and delay in radical cystectomy (RC). Molecular classification of bladder cancer based on the Cancer Genome Atlas into the broad categories of luminal and basal subtypes may predict response to chemotherapy.[20]

The multi-institutional cohort study by Lotan *et al*.[21] included 601 patients from four cohorts with MIBC, of whom 247 received NAC and RC and 354 received only RC. NAC conferred an OS benefit of 7% and a cancer-specific survival benefit of 5% at 3 years. Patients with nonluminal tumors who received NAC had a 3-year OS of 71% versus 61% for those who directly underwent RC. Thus, NAC conferred 10% increase in OS in nonluminal tumors which was confirmed on multivariate analysis (hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.44–0.98, $P = 0.04$). No significant benefit of NAC was found in luminal tumors, with an OS of 63% for NAC and 65% without NAC.

In addition to the inherent selection bias introduced by retrospective design, the major limitation was the inclusion of multiple cohorts with a possible treatment selection bias. The authors concluded that the genomic classification may help better identify the patients who might benefit from NAC, thus affecting treatment decisions.

EMERGING ROLE OF DUAL TRACER FLUORODEOXYGLUCOSE-PROSTATE SPECIFIC MEMBRANE ANTIGEN POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY IN RENAL CELL CARCINOMA

Contrast-enhanced computed tomography (CECT) is the current imaging standard for characterization of a renal mass and staging. Up to 30% of patients present with a metastatic disease at presentation, and a similar percentage develop recurrence after surgery. Poor primary lesion characterization due to renal excretion of radio-urine in fluorodeoxyglucose-positron emission tomography (FDG-PET) has limited its widespread use. (Prostate-specific membrane antigen [PSMA]) expression is upregulated in the neovasculature of solid tumors including RCC, particularly in ccRCC, where overexpression is noted in 80%–100% of cases. Combined FDG-PET and PSMA-PET have been reported to have a potential role in RCC beyond CECT in the staging of RCC.

Tariq *et al*.[22] reported a multicenter retrospective cohort study including 11 patients with RCC who underwent "dual-tracer" (both FDG and PSMA on an intra-individual basis) PET CT for staging (36%) and re-staging after therapeutic resection (64%). A metastatic lesion was reported for moderate to intense uptake which corroborated with a lesion seen on CT. An imaging was labeled concordant if both PSMA and FDG reported the same lesions and discordant if the primary or metastatic lesions had uptake with only one tracer or had a clinically significant higher uptake with one of the tracers.

The dual-tracer PET characterization of primary tumor was concordant in 40%, discordant favoring PSMA in 20%, and FDG in 40%. On evaluation of the metastatic lesions, concordant uptake was seen in 55%, concordant negative finding in 27%, and discordant uptake favored PSMA tracer. Overall, PET outperformed CECT in 45% of patients and altered patient management in 27% of them.

Despite the limitations of a retrospective study design and small sample size, the study indicates that PET imaging may improve staging in RCC and have a potential role in response assessment to treatment.

ADDING POLY ADP-RIBOSE POLYMERASE AS INHIBITORS TO ABIRATERONE AS FIRST-LINE TREATMENT FOR METASTATIC CASTRATION-RESISTANT PROSTATE CANCER – RESULTS OF THE PROPEL AND THE MAGNITUDE TRIAL

Abiraterone + ADT + prednisolone is one of the accepted first-line treatments for metastatic castration-resistant

prostate cancer (mCRPC), among many other approved agents such as enzalutamide and docetaxel. However, the addition of abiraterone alone to ADT resulted in a meager OS improvement of 4.4 months.[23] Poly ADP-ribose polymerase(PARP) inhibitors are the newest class to join the armamentarium against prostate cancer. In prostate cancer, androgen signaling regulates DNA repair. Preclinical data suggested that a PARP inhibitor and abiraterone can potentiate each other's action.

Two trials with marked resemblance, the PROpel, and the MAGNITUDE, were discussed recently at the ASCO 2022 conference.[24,25] Both Phase 3 trials tested PARP inhibitor + abiraterone + prednisolone against placebo + abiraterone + prednisolone as first-line treatment for mCRPC with radiographic progression-free survival as the primary outcome and OS as one of the secondary outcomes.

In the magnitude trial, eligible patients with Homologous recombination repair (HRR) biomarker positive or negative were randomized 1:1 to receive either niraparib 200 mg OD + abiraterone + prednisolone or placebo abiraterone + prednisolone. The HRR-negative subgroup did not show an additional benefit with niraparib. In the HRR-positive group, the BRCA1/2 subgroup benefitted the most with niraparib compared to placebo with a 47% reduction in the risk of progression (16.6 vs. 10.9 months) at a median follow-up of 18.6 months. The researchers also presented that niraparib showed 41% improvement in time to cytotoxic chemotherapy, 31% improvement in time to symptomatic progression, and 43% improvement in PSA progression. Furthermore, the quality of life was maintained, and the drugs had a manageable safety profile. The authors concluded by emphasizing the need for genetic testing to select the patients optimally.

PROpel, randomized eligible candidates 1:1 to either receive olaparib 300 mg BD + abiraterone + prednisolone or placebo + abiraterone + prednisolone. Testing for HRR gene mutation was not done before randomization. Addition of olaparib resulted in a 34% reduction radiographic progression (HR: 0.66, 95% CI: 0.54–0.81; $P < 0.0001$) irrespective of the HHR mutation. The median rPFS was improved by 8.4 months (24.8 vs. 16.6 months). Exploratory analysis showed that patients with HRR mutation might derive greater benefit. The quality of life was maintained but with more adverse events.

OS data from both trials are immature at this point. The actual clinical advantage of adding a PARP inhibitor to the first-time treatment is unclear. Genetic testing will help in selecting patients who might benefit from combination therapy. BRCA1/2 mutation is known to cause aggressive cancers, and these patients will probably benefit from the combination therapy based on the radiographic progression-free data rather than waiting for the OS data.

ASSESSING THE SAFETY AND EFFICACY OF TWO STARTING DOSES OF LENVATINIB PLUS EVEROLIMUS IN PATIENTS WITH RENAL CELL CARCINOMA: A RANDOMIZED PHASE 2 TRIAL

For patients with advanced RCC who have failed with one or more antiangiogenic treatments, lenvatinib (18 mg) plus everolimus (5 mg) has been approved.

This randomized, open-label Phase 2 trial was conducted among patients with advanced RCC and disease progression after one prior vascular endothelial growth factor targeted therapy. The study aimed to determine if treatment with lenvatinib + everolimus with a lower beginning dose of lenvatinib has equivalent efficacy and better tolerability.[26]

The 14- or 18-mg lenvatinib beginning doses, combined with everolimus 5 mg/d, were given to patients in a 1:1 ratio. Patients in the 14-mg arm were supposed to be up titrated to lenvatinib 18 mg on day 1 of cycle 2 unless they had severe Grade 2 or Grade 3 treatment-emergent adverse events (TEAEs) that required dosage decrease in the first 28 days. The primary efficacy endpoint was objective response rate (ORR) as of week 24 (ORRwk24). The noninferiority criterion for the 14-mg versus 18-mg arm was $P < 0.045$. The primary safety endpoint was the proportion of participants experiencing unbearable Grade 2 or any Grade 3 TEAEs within 24 weeks of randomization. The ORRwk24 in the 14-mg arm was not noninferior to the ORRwk24 in the 18-mg arm (35% [95% CI 27–42]; odds ratio: 0.88; 90% CI 0.59–1.32; $P = 0.3$). The proportion of intolerable Grade 2 or any Grade 3 TEAEs was equal (14 mg, 83% vs. 18 mg, 80%; $P = 0.5$). The 18-mg arm had a numerical advantage in the secondary goals of total ORR, progression-free survival, and OS. The trial design did not allow for a comprehensive comparison of progression-free survival between treatment arms, which was one of the study's limitations.

These findings back up the FDA-approved lenvatinib 18 mg + everolimus 5 mg daily dosage regimen for individuals with advanced RCC. Although the safety outcomes were similar, the results showed that the lower dose of lenvatinib at 14 mg did not have the same efficacy as the approved dose of 18 mg, and hence, the approved dose of 18 mg should be administered.

MALARIA VACCINE: AN END OR BEGINNING?

The relentless effort that had lasted for three decades came to fruition when the World health organization approved the first-ever vaccine (RTS, S/AS01; trade name Mosquirix) targeted against a parasitic disease in October 2021. The

vaccine induces antibodies against a circumsporozoite protein that is expressed on sporozoites (infective form of Plasmodium). These antibodies immobilize the sporozoites preventing them from infecting hepatocytes. This immune response does not interfere with the infectivity of Plasmodium gametocytes to mosquitoes so most children will act as carriers, thus transmission in the general population will remain the same.

Various Phase 2 and Phase 3 trials showed promising efficacy in limiting severe infection. A phase three trial was performed in seven African countries from 2009 to 2014 in children between 5 and 17 months of age using three baseline doses and one booster dose of RTS, S/AS01 vaccine. It showed efficacy levels of 63% at the beginning which waned to 11% in 1 year and 9% at 5 years following vaccination.[27] At the time of implementation, WHO stated that the vaccine limits the severe disease in around 30% of vaccinated children.[28] Although the data on its efficacy are limited, in a study conducted in Gambia, 34% of individuals who received vaccine showed short-lived protection from malaria infection.[29]

India itself has a significant malaria burden with around 15 million cases annually with death toll reaching to 20,000 cases.[30] This vaccine holds a new hope in reducing the disease burden in tropical countries like India. Similar to the use of masks following COVID vaccination, existing mosquito control measures and other primordial prevention methods should continue to be implemented along with the vaccine.

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REFERENCES

1. Shi X, Feng D, Li D, Zhang F, Wei W. The role of lymph node dissection for non-metastatic renal cell carcinoma: An updated systematic review and meta-analysis. Front Oncol 2021;11:790381.
2. Sormani MP. The Will Rogers phenomenon: The effect of different diagnostic criteria. J Neurol Sci 2009;287 Suppl 1:S46-9.
3. Delacroix SE Jr., Chapin BF, Chen JJ, Nogueras-Gonzalez GM, Tamboli P, Matin SF, *et al.* Can a durable disease-free survival be achieved with surgical resection in patients with pathological node positive renal cell carcinoma? J Urol 2011;186:1236-41.
4. Pantuck AJ, Zisman A, Dorey F, Chao DH, Han KR, Said J, *et al.* Renal cell carcinoma with retroperitoneal lymph nodes: Role of lymph node dissection. J Urol 2003;169:2076-83.
5. Gershman B, Moreira DM, Thompson RH, Boorjian SA, Lohse CM, Costello BA, *et al.* Renal cell carcinoma with isolated lymph node involvement: Long-term natural history and predictors of oncologic outcomes following surgical resection. Eur Urol 2017;72:300-6.
6. Gallina A, Bianchi M, Gandaglia G, Cucchiara V, Suardi N, Montorsi F, *et al.* A detailed analysis of the association between postoperative phosphodiesterase type 5 inhibitor use and the risk of biochemical recurrence after radical prostatectomy. Eur Urol 2015;68:750-3.
7. Jenkins L, Eastham J, Laudone V, Scardino P, Nelson C, Mulhall J. Is there a relationship between phosphodiesterase type 5 inhibitors (PDE5i) and prostate cancer biochemical recurrence? J Sex Med 2017;14:e59.
8. Haseltine JM, Hopkins M, Schofield E, Kollmeier MA, Shasha D, Gorovets D, *et al.* Sildenafil citrate and risk of biochemical recurrence in prostate cancer patients treated with radiation therapy: Post-hoc analysis of a randomized controlled trial. J Sex Med 2021;18:1467-72.
9. Rosen R, Altwein J, Boyle P, Kirby RS, Lukacs B, Meuleman E, *et al.* Lower urinary tract symptoms and male sexual dysfunction: The multinational survey of the aging male (MSAM-7). Eur Urol 2003;44:637-49.
10. Gur S, Peak T, Yafi FA, Kadowitz PJ, Sikka SC, Hellstrom WJ. Mirabegron causes relaxation of human and rat corpus cavernosum: Could it be a potential therapy for erectile dysfunction? BJU Int 2016;118:464-74.
11. Alexandre EC, Kiguti LR, Calmasini FB, Silva FH, da Silva KP, Ferreira R, *et al.* Mirabegron relaxes urethral smooth muscle by a dual mechanism involving β3 -adrenoceptor activation and α1 -adrenoceptor blockade. Br J Pharmacol 2016;173:415-28.
12. Karakus S, Musicki B, Burnett AL. Mirabegron improves erectile function in men with overactive bladder and erectile dysfunction: A 12-week pilot study. Int J Impot Res. 2021. doi: 10.1038/s41443-021-00455-2.
13. Xiong L, Nguyen J, Peng Y, Zhou Z, Ning K, Jia N, *et al*. What happens to the preserved renal parenchyma after clamped partial nephrectomy? Eur Urol 2022. https://doi.org/10.1016/j.eururo.2022.01.036, [In press].
14. Ornish D, Lin J, Chan JM, Epel E, Kemp C, Weidner G, *et al.* Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study. Lancet Oncol 2013;14:1112-20.
15. Ornish D, Magbanua MJ, Weidner G, Weinberg V, Kemp C, Green C, *et al*. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. Proc Natl Acad Sci U S A 2008;105:8369-74.
16. Magbanua MJ, Richman EL, Sosa EV, Jones LW, Simko J, Shinohara K, *et al*. Physical activity and prostate gene expression in men with low-risk prostate cancer. Cancer Causes Control 2014;25:515-23.
17. Schenk JM, Neuhouser ML, Beatty SJ, VanDoren M, Lin DW, Porter M, *et al*. Randomized trial evaluating the role of weight loss in overweight and obese men with early stage prostate Cancer on active surveillance: Rationale and design of the Prostate Cancer Active Lifestyle Study (PALS). Contemp Clin Trials 2019;81:34-9.
18. De Nunzio C, Nacchia A, Cicione A, Cindolo L, Gacci M, Cancrini F, *et al*. Physical activity as a protective factor for lower urinary tract symptoms in male patients: A prospective cohort analysis. Urology 2019;125:163-8.
19. Brassetti A, Ferriero M, Napodano G, Sanseverino R, Badenchini F, Tuderti G, *et al*. Physical activity decreases the risk of cancer reclassification in patients on active surveillance: A multicenter retrospective study. Prostate Cancer Prostatic Dis 2021;24:1151-7.
20. Guo CC, Bondaruk J, Yao H, Wang Z, Zhang L, Lee S, *et al.* Assessment of luminal and basal phenotypes in bladder cancer. Sci Rep 2020;10:9743.
21. Lotan Y, de Jong JJ, Liu VY, Bismar TA, Boorjian SA, Huang HC, *et al.* Patients with muscle-invasive bladder cancer with nonluminal subtype derive greatest benefit from platinum based neoadjuvant chemotherapy. J Urol 2022;207:541-50.
22. Tariq A, Kwok M, Pearce A, Rhee H, Kyle S, Marsh P, *et al*. The role of dual tracer PSMA and FDG PET/CT in Renal Cell Carcinoma (RCC) compared to conventional imaging: A multi-institutional case series with intra-individual comparison. In: Urologic Oncology: Seminars and Original Investigations. Vol. 40. Amsterdam, Netherlands: Elsevier; 2022. p. 66-e1.
23. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, *et al.* Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995-2005.
24. Saad F, Armstrong AJ, Thiery-Vuillemin A, Oya M, Loredo E, Procopio G,

et al. PROpel: Phase III trial of Olaparib (ola) and Abiraterone (abi) versus Placebo (pbo) and abi as first-Line (1L) therapy for Patients (pts) with Metastatic Castration-Resistant Prostate Cancer (mCRPC). J Clin Oncol 2022;40 Suppl 6:11.
25. Chi KN, Rathkopf DE, Smith MR, Efstathiou E, Attard G, Olmos D, *et al.* Phase 3 MAGNITUDE study: First results of niraparib (NIRA) with Abiraterone Acetate and Prednisone (AAP) as first-line therapy in Patients (pts) with Metastatic Castration-Resistant Prostate Cancer (mCRPC) with and without Homologous Recombination Repair (HRR) gene alterations. J Clin Oncol 2022;40 Suppl 6:12.
26. Pal SK, Puente J, Heng D, Glen H, Koralewski P, Stroyakovskiy D, *et al*. Assessing the Safety and Efficacy of Two Starting Doses of Lenvatinib Plus Everolimus in Patients with Renal Cell Carcinoma: A Randomized Phase 2 Trial.2022. European urology, S0302-2838(21)02272-7. Advanceonlinepublication. https://doi.org/10.1016/j.eururo.2021.12.024.
27. Olotu A, Fegan G, Wambua J, Nyangweso G, Leach A, Lievens M, *et al.* Seven-year efficacy of RTS, S/AS01 malaria vaccine among young african children. N Engl J Med 2016;374:2519-29.
28. WHO Recommends Groundbreaking Malaria Vaccine for Children at Risk. Available from: https://www.who.int/news/item/06-10-2021-who-recommends-groundbreaking-malaria-vaccine-for-children-at-risk. [Last accessed on 2022 Mar 06].
29. Polhemus ME, Remich SA, Ogutu BR, Waitumbi JN, Otieno L, Apollo S, *et al.* Evaluation of RTS, S/AS02A and RTS, S/AS01B in adults in a high malaria transmission area. PLoS One 2009;4:e6465.
30. Kumar A, Valecha N, Jain T, Dash AP. Burden of Malaria in India: Retrospective and Prospective View. Defining and Defeating the Intolerable Burden of Malaria III: Progress and Perspectives: Supplement to Volume 77(6) of American Journal of Tropical Medicine and Hygiene. American Society of Tropical Medicine and Hygiene; 2007. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1720/. [Last accessed on 2022 Mar 06].

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

Access this article online	
Quick Response Code:	**Website:** www.indianjurol.com
	DOI: 10.4103/iju.iju_84_22

How to cite this article: Mandal S. Round up. Indian J Urol 2022;38:85-90.