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Editorial

Updates in prostate cancer detections and treatments — Messages from 2017 EAU and AUA☆

1. Updates in prostate cancer (PCa) detections

1.1. Screening of PCa

The discovery of prostate specific antigen (PSA) undoubtedly marked a new era for the efficient screening of PCa. In addition, the screening of PCa has been the hot area of studies all the time, and it is still the most commonly discussed topic of European Association of Urology (EAU) and American Urological Association (AUA).

1.1.1. PSA-based screening

Carlsson et al. [1] updated the Göteborg-1 screening study over 20 years ago (1995–2015). The results indicated that the effect of PSA screening on mortality was inversely associated with the age at start ($p = 0.045$), which suggested that the screening should start no later than at age 55 years. An Asian study enrolled 8086 men aged 55–69 years with baseline PSA levels of ≤1.0 ng/mL, who were screened annually for 12 years. The results revealed that 28 (0.35%) were diagnosed with PCa, and 18 (0.22%) were identified as PCa with a Gleason score ≥7 during the observation period. Besides, men with baseline PSA levels of 0.0–0.6 ng/mL might benefit from longer screening intervals (10 years) [2]. Another similar study from France demonstrated that PSA testing every 5 years should be performed in selected first-degree relatives of PCa patients, with baseline PSA level ≤1 ng/mL [3].

1.1.2. Multiparametric MRI (mpMRI)-assisted screening

Aside from the above studies on the PSA screening for PCa, Dell'Oglio et al. [4] updated the progress of the ERSPC (European Randomized Study of Screening for Prostate Cancer), which included 214 consecutive patients who underwent mpMRI of the prostate with subsequent targeted (fusion/cognitive) and concomitant systematic biopsy at a single tertiary referral center between 2013 and 2016. Multivariable logistic regression analyses indicated that inclusion of both the Prostate Imaging Reporting and Data System (PIRADS) scores and patient age into ERSPC risk calculator better identified the patients with a higher risk of positive biopsy ($p \leq 0.001$, $p < 0.001$).

1.2. Early diagnosis of PCa

Prostate biopsy is the "gold standard" for PCa diagnosis. However, such disadvantages as the low positive rate, repeated biopsies (RB), and biopsy-associated complications are still observed. PSA level is an important indicator but not an absolutely specific indicator for assisting the diagnosis of PCa, and it is demonstrated to have a relatively high false positive rate and over-diagnosis problems. Thus, the introduction of novel imaging technologies and molecular indicators of PCa is of great significance for the more precise diagnosis, which were all reported in these two meetings.

1.2.1. Messages from the Chinese Prostate Cancer Consortium (CPCC)

The CPCC led by Professor Yinghao Sun, an academician of Chinese Academy of Engineering, made several reports in EAU meetings. A multi-center study in China demonstrated

☆ The 32th Congress of the European Association of Urology (EAU) was held in London, UK on 24–28 March 2017. The 112th Annual Meeting of American Urological Association (AUA) was held in Boston, USA, on 12–16 May 2017. In retrospect, in these two meetings, the hot topics of prostate cancer (PCa) primarily focus on the screening, early diagnosis, treatments and prognosis evaluations. In this article, we review the two meetings and report some updates in the detections and treatments of PCa based on the reports and messages from EAU and AUA.

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that the incidences of PCa and high grade PCa were lower in the Chinese cohort than in the Western cohorts at any given PSA level. Besides, around 25% of patients with a PSA of 4.0—10.0 ng/mL were found to be diagnosed as PCa compared to approximately 40% [5]. Moreover, by RNA-seq technology, two novel gene fusions, *CTAGE5-KHDRBS3* (20/54 = 37.0%) and *USP9Y-TTTY15* (19/54 = 35.2%) were observed to occur notably frequently in Chinese patients. In addition, a series of long non-coding RNAs (lncRNAs) which were correlated with PCa prognosis in Chinese people were detected. For example, DD3, FR0348383, and MALAT-1 were all upregulated in PCa ($p = 0.0023$, $p = 0.0306$, and $p < 0.001$, respectively), and among them, MALAT-1 possessed the highest diagnostic value in PCa patients with a PSA level from 4 to 10 ng/mL (AUC = 0.738). This study yielded new insights into the pathogenesis of PCa in the Chinese population. In addition, MALAT-1 is reported to be developed into the corresponding PCa detection kit (Human MALAT-1 Expression Detection Kit), which helps to improve the detection of PCa [6].

1.2.2. Novel imaging analysis technologies

Our team reported a randomized controlled trial (RCT) that assessed and compared the outcomes of ultrasound CT with artificial intelligence (AI-US-CT), transrectal ultrasound guided 12-core systematic biopsy, and mpMRI assisted 12-core systematic biopsy. The results suggested that AI-US-CT group had a higher detection rate of PCa compared to systematic group and mpMRI group (38/83 (45.8%) *vs.* 36/101 (35.6%) *vs.* 23/68 (33.8%)). In a subset analysis of patients without prior biopsy, AI-US-CT group had a higher detection rate of PCa compared to systematic group and mpMRI group (29/61 (47.5%) *vs.* 36/95 (37.9%) *vs.* 23/65 (35.4%)). In a subset analysis for patients with prior negative biopsy, AI-US-CT group had a higher detection rate of PCa compared to systematic group and mpMRI group (9/22 (40.9%) *vs.* 0/6 (0%) *vs.* 0/3 (0%)). Additionally, AI-US-CT group had higher PCa detection rate (45.8%) compared to mpMRI assisted biopsy group when PI-RADS assessment category is not higher than 4 (0—43.3%). All of the above findings indicated that AI-US-CT as a novel imaging technique can be applied as an alternative method for PCa detection [7].

Studies on the values of mpMRI/US fusion biopsy are constantly emerging. In these two meetings, a prospective multi-center study reported by Ferriero et al. [8] from Italy enrolling 498 consecutive PCa patients and evaluated the diagnostic performance of mpMRI by using a per-core analysis in patients who underwent prostate fusion biopsy. The results indicated that a better detection rate (57.4% (286/498)) was achieved, especially when PI-RADS scores >3. To conclude, mpMRI-ultrasound fusion biopsy efficiently improved the PCa detection rates. Calio et al. [9] introduced the NCI experience of the effect of learning curves and changes of mpMRI/TRUS fusion biopsy in a fusion platform over 9 years. Three cohorts including 1528 PCa patients were established to compare the cancer detection rate (CDR) between fusion biopsy and systematic biopsy. It was observed from the statistical analysis that in cohort 1(July 2007 to December 2010) there was no significant difference in CDR of clinical significant diseases (Gleason scores ≥7) (24.7% *vs.* 21.5%, $p = 0.377$), however, fusion biopsy was significantly better than systematic biopsy in detection of clinical significant diseases in cohort 2 (January 2011 to May 2013) and cohort 3 (debut of UroNav platform) (31.5% *vs.* 25.3%, $p = 0.001$; 36.5% *vs.* 30.2%, $p < 0.001$, respectively). All above indicated that after an early learning period using fusion biopsy (cohort 2), clinical significant PCa was detected at significantly higher rates with fusion biopsy than with systematic biopsy, moreover, advances in software (UroNav platform) allowed for even greater detection of clinical significant disease [9].

1.2.3. Novel molecular biomarkers for PCa diagnosis

Molecular biomarkers can efficiently assist in the diagnosis of PCa. In these two meetings, several novel molecular biomarkers were reported. Ishikawa et al. [10] identified the serum PCa-associated aberrant glycosylation of PSA (S2, 3PSA) and developed an automated-microcapillary electrophoresis-based immunoassay system. The results revealed that %S2, 3PSA of PCa was significantly higher than those of non-PCa ($p < 0.0001$), and a good correlation with Gleason score was detected in this assay for the discrimination of high-risk PCa. In another retrospective study including 474 PCa patients, the logistic regression analysis revealed that the combination of the level of cathepsin D, thrombospondin 1 and %fPSA could effectively discriminate the benign disease from PCa (AUC = 0.834, $p < 0.001$; 95%CI: 0.797—0.871), thus significantly lower the rate of prostate biopsies by more than 50% that are negative for cancer [11].

2. Updates in PCa treatments

2.1. Messages from the CPCC

The conditions for the clinical treatments of PCa in China were introduced by the CPCC. Currently, there are 62 Da Vinci systems running in the Mainland of China, and the number of robot assisted laparoscopic prostatectomy (RALP) has increased rapidly. Chinese urologists performed a total of 3207 RALP procedures in 2016 (Mainland), and they will play a more important role in the future. Moreover, the first and only robotic surgery training center in the Mainland of China was established (June 2016) and officially opened (February 2017) in Shanghai Changhai Hospital, which provides opportunities for the international training of robot assisted operations for urologists.

2.2. Active surveillance (AS)

With the development of the diagnosis techniques and the comprehensive screening of PCa, increasing numbers of early-staged patients or low-risk localized PCa are being detected, thus AS treatment is attracting increasing attention. AS items primarily include the PSA level, digital rectal examination (DRE) and RB, and recently mpMRI and PSA density (PSAD) are also included in AS. In these two meetings, the above indicators were all referred.

2.2.1. RB

Luzzago et al. [12] reported that the first RB represents the most informative predictor of progression-free survival

(PFS). Univariable analyses suggested that negative 1-year biopsy were significant predictors of 3-year PFS (all $p < 0.05$). The above mentioned findings indicated that patients with negative 1-year biopsy could be followed up with less stringent biopsy protocol, so that the possible biopsy-related side effects and discomfort could be reduced.

2.2.2. mpMRI

Retter et al. [13] reported an AS cohort including 387 PCa patients which identified the relationship between mpMRI baselines and the treatment rates in AS. The Kaplan—Meier survival analysis indicated that the 5-year treatment free survival was significantly higher in men without lesions on baseline mpMRI than men with lesions on baseline mpMRI (85.1% *vs.* 78.3%, $p = 0.024$). Besides, in patients with Gleason scores of $3 + 3$ and $3 + 4$, the 5-year treatment free survival was 86.3% and 60.8%, respectively ($p < 0.001$) [13]. Above suggested mpMRI could have a role in identifying and assessing targeted patients during AS. In addition, the combination of mpMRI with other indicators were also concerned in the meetings. A study that included 101 AS patients investigated the role of mpMRI combined with PSAD in the prediction of the likelihood of upgrading to clinically significant prostate cancer (CSPC). The logistic regression analyses indicated that men with a PIRADS score of ≥ 3 with a PSAD ≥ 0.15 had a 55% chance of being upgraded to CSPC [14].

2.3. The combined therapy of PCa

2.3.1. Radical prostatectomy (RP)

RP is still the "gold standard" treatment for clinically localized PCa. Several studies that compared open RP, laparoscopic RP (LRP), and robot-assisted radical prostatectomy (RARP) were reported in these two meetings. Porpiglia et al. [15] shared the experience of 5-year follow-up of an RCT which enrolled 120 PCa patients and compared the LRP and RARP in oncological and functional outcomes. The results indicated that the probability to be continent and potent over time was more than doubled in the RARP group (OR = 2.47, $p < 0.021$ *vs.* OR = 2.35, $p < 0.028$, respectively) and 5 years biochemical recurrence-free survival was 81.6% for both the RARP and LRP groups. To conclude, RARP allows for better functional results compared to pure LRP without compromising oncological outcomes [15]. Other similar studies also observed that open RP and RARP had the equivalent curative effects and life qualities after operations, both of which were better than LRP, moreover, the outcomes were more dependent on the experience of surgeons than surgical equipment [16,17]. In addition, a multi-center study from Japan compared the postoperational complications after limited pelvic lymph node dissection (lPLND) and extended pelvic lymph node dissection (ePLND). The results indicated an increase in the number of total lymph nodes removed and a higher rate of positive lymph nodes in the ePLND cohort compared with the lPLND cohort ($p < 0.001$) [18].

2.3.2. Androgen deprivation therapy (ADT)

Zareba et al. [19] reported a retrospective study including 5909 node-positive (pN1) PCa patients after RP in America. By Cox regression analysis, four different treatment groups (ADT combined with radiation therapy (RT), ADT alone, RT alone and observation) were compared and analyzed, the results of which suggested that ADT combined with radiation therapy (RT) was found to be associated with a significantly lower all-cause mortality rate compared to both observation (multivariate HR = 0.79, 95%CI: 0.63—1.00, $p = 0.046$) and ADT alone (HR = 0.73, 95%CI: 0.57—0.94, $p = 0.014$) [19]. Another study reported by Richards et al. [20] including 87 344 PCa patients evaluated the combined effects of metformin and ADT. Multivariable Cox regression analysis revealed an improved survival in diabetics on metformin (HR = 0.77, 95%CI: 0.74—0.81, $p < 0.001$) compared with diabetics not on metformin (HR = 0.99, 95%CI: 0.95—1.03, $p = 0.5$), besides, PCa-specific survival was improved in diabetics on metformin (HR = 0.72, 95%CI: 0.67—0.78, $p < 0.001$), which indicated that the metformin combined with ADT is associated with an improved overall survival (OS) and cancer-specific survival [20].

2.3.3. RT

A multi-centers retrospective study from Japan including 524 PCa patients who underwent high-dose-rate brachytherapy revealed that the rates of biochemical no evidence of disease (bNED), OS, cause-specific survival (CSS), and metastasis-free survival (MFS) were 92%, 97%, 99% and 94%, respectively, at 5 years. Besides, certain cure effects of high-dose-rate brachytherapy were observed in all respective low intermediate/high-risk patients [21]. RT also has the advantages in the treatment of the bone and nodal oligometastases. A prospective study (POPSTAR study) reported by Siva et al. [22] enrolled 33 oligometastatic patients who underwent single fraction 20 Gy stereotactic ablative body radiotherapy (SABR) to each of the 1—3 oligometastasis for 24 months. Kaplan—Meier analysis showed the PFS was 32% (95%CI: 20%—54%), which indicated the SABR had certain cure effects in oligometastatic patients [22]. Salvage RT was also mentioned in AUA meeting, a retrospective study reported by Fossati et al. [23] including 706 patients who received salvage radiation therapy (SRT), evaluated the combined beneficial effect of concomitant hormonal therapy (HT) after SRT. The results indicated that the benefit of combined HT was minimal for PSA level <1 ng/mL, but it increased exponentially for PSA level >2 ng/mL.

2.3.4. The treatment for high-risk PCa

It has always been controversial in the treatment for high-risk PCa, which was also the hot topic discussed in these two meetings. A study reported by Hagiwara et al. [24] enrolling 1268 high-risk PCa patients compared the cost effectiveness between neoadjuvant therapy with RP (neoadjuvant group) and RP with ePLND (ePLND group). The results indicated that 5-year PSA free survival rates were 87% and 58% in neoadjuvant and ePLND groups, respectively ($p < 0.001$), but the estimated total medical expenses were US $62 506 and US $87 747, which suggested that neoadjuvant therapy following RP may reduce medical expenses approximately 29% in patients with high-risk PCa. Biochemical recurrence (BCR) usually indicates poor prognosis. ^{68}G-PSMA PET/CT examination is a promising imaging

technique and always of great significance for the prediction of BCR. A study reported by Tosco et al. [25] including 137 BCR patients after RP retrospectively analyzed the predictive factors of a positive ^{68}Ga-PSMAPET/CT in patients with PSA recurrence after RP. The results revealed a PSA $\geq$0.45 ng/mL and extra-capsular extension (ECE) were retained as independent predictors of a positive ^{68}Ga-PSMA PET/CT.

2.3.5. Castration resistant prostate cancer (CRPC)

The treatment of CRPC was also the focus in these two meetings. A retrospective study reported by Saad et al. [26] from Canada, including 708 metastatic CRPC (mCRPC) patients evaluated the efficacy and safety of sequential or concurrent use of Ra-223 and abiraterone acetate (AA) or enzalutamide (E) in mCRPC patients. The results indicated that treatment-emergent adverse events (TEAEs) were reported for fewer in Ra-223 + AA (concurrent use) than in AA/Ra-223 (sequential use) patients: any grade (77% *vs*. 83%); grade 3/4 (38% *vs*. 42%) and serious AEs (33% *vs*. 42%). However, the better curative outcomes need a further confirmation of phase III RCTs [26]. Another study from Germany including 56 mCRPC patients after AA or E treatment revealed that imaging examination efficiently detected 15% metastatic patients despite of the stable PSA level, which suggested the potential value of imaging examination in monitoring the disease progression [27].

3. Prognosis evaluations of PCa

An abundance of biomarkers associated with prognosis evaluation for PCa were reported in these two meetings. Studies from China, America *etc*. explored some meaningful novel biomarkers for prognosis evaluation. Neuropilin 2 (NRP2) served as an independent risk factor, the mutated ATM serine/threonine kinase and BRCA1/2 could be used for the discrimination between relative high-risk and indolent PCa. Rapid alkaline phosphatase velocity (APV) is a useful predictor of distant metastasis over time for CRPC patients [28–30].

A novel nomogram model predicting postoperative BCR inpatients with localized high-risk PCa was reported by Alam et al. [31]. This model included age, race, PSA, Gleason grade group, clinical stage, and number of cores with Gleason score of 8–10 for the disease. The overall BCR-free probability at 5 years was calculated by this model: 49.0% (95%CI: 0.45–0.53), and the model AUC was 0.730 after optimism-adjustment, compared to 0.700 and 0.654 in the existing and Cancer of the Prostate Risk Assessment (CAPRA) nomograms, respectively. The above mentioned findings indicated that a better discriminative ability than existing nomo-grams was achieved for the prediction of postoperative BCR [31].

A study from China proposed a P.R.O.S.T.A.T.E scoring system to predict the risk of positive surgical margin (PSM) after RP. The results suggested that preoperative P.R.O.S.T.A.T.E. scores were statistically correlated with the postoperative surgical margin status ($p < 0.001$), and the risk of PSM after RP in the low-risk, moderate-risk and high-risk groups was 21.1%, 40.1% and 87.0%, respectively [32].

4. Conclusion

Throughout the overall reports of PCa in EAU and AUA meetings, the hot topics were focused on the screening, early diagnosis, treatments and prognosis evaluations. PSA level still remains meaningful for early detection of PCa and reduction of tumor specific death. The novel imaging and analysis technologies including mpMRI, mpMRI/US fusion imaging, ^{68}Ga-PSMA PET/CT and AI-US-CT, *etc*. play great roles in the screening, early diagnosis, treatments and prognosis evaluations of PCa. Better outcomes can be accomplished by the combined therapies based on operations. In terms of the prognosis evaluations, the detection and combined analysis of novel biomarkers and nomogram model further optimize the clinical decisions after PSA examination. With the continuous improvements of medical research and technology, the reports of Chinese and other Asian scholars in EAU and AUA meetings are increasing year by year, and Asian urologists will play a more important role in the world.

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