New findings in localized and advanced prostate cancer: AUA 2011 review

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The 2011 American Urological Association (AUA) annual meeting took place in Washington, DC, USA, on May 14-19. It is the largest gathering of urologists in the world, providing unparalleled access to groundbreaking research, new guidelines and the latest advances in urologic medicine. The opportunity to exchange knowledge among urologists on a worldwide level was provided by participation of more than 80 countries in this scientific meeting. As one of the most important subjects, there were more than 500 presented studies in prostate cancer. In this review we will highlight some of the findings and the clinical significance of a few of these abstracts concerning prostate cancer staging and markers.

Key Words: prostate cancer, staging, markers, prostate-specific antigen

Prostate cancer staging

Prostate biopsy now lies beyond pure diagnostics and has become an essential tool for determining optimal therapeutic approach. Alternate approaches of saturation biopsy and transperineal approach are now under evaluation to maximize the effectiveness of repeat biopsy. McCracken et al[1] performed a study on 100 patients who required repeat biopsy based on rising prostate-specific antigen (PSA), to compare transrectal saturation and transperineal template mapping biopsy (TTMB). The first 50 patients underwent transrectal saturation biopsies and the second 50 patients underwent TTMB. This study demonstrates that cancer detection rate is higher in patients who undergo TTMB (46% versus 22%). TTMB had a complication rate of 12% (acute retention or hematuria) compared with a complication rate of 22% for the transrectal saturation biopsy group (UTI, acute retention, and hematuria). Morbidity was similar in both techniques. Cancer detection rate may be higher in TTMB due to better apical and anterior peripheral zone sampling. Despite the requirement for general anesthesia and a potential increased urinary retention rate, novel transperineal mapping schemes allow for more accurate sampling of the entire gland.

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Based on current studies, staging of newly diagnosed high grade prostate cancer with a bone scan and CT scan or MRI scan is recommended when PSA is more than 20 ng/mL, for Gleason score of 8, or T3 stage. Using a large patient population with high grade prostate cancer (Gleason 8-10), Smith et al[2] designed a study to quantify the diagnostic yield of existing staging guidelines for this high risk population. They reviewed the records of all patients who underwent a bone scan and CT abdomen/pelvis at time of initial prostate cancer diagnosis from 2003 to 2009 at the Minneapolis Veterans Affairs Medical Center. Two hundred sixty patients had both CT and bone scan at the time of diagnosis. Eighteen and a half percent were positive for metastasis based on bone scan and 19.6% were positive based on CT scan. When CT pelvis only findings plus bone scan were considered, 18.8% had evidence of metastasis. Of those with a positive bone scan, CT showed evidence of metastatic disease in 64.6% of cases. PSA > 20 ng/mL, stage T2c, and core volume > 50% were associated with increased number of positive bone scans ($p < 0.001$, $p < 0.001$, $p = 0.018$ respectively). In patients with a negative bone scan, 9.1% had CT findings of metastasis. PSA > 20 ng/mL and stage T2c were associated with positive CT after negative bone scan ($p < 0.02$). In all patients with a positive bone scan (n = 48), CT did not yield information that changed clinical management. They concluded that bone scans should be performed for staging in all patients with PSA > 20 ng/mL, stage T2c, or Gleason score of 8. If the bone scan is positive, CT will not be necessary, as the initial treatment would not be affected. If the bone scan is negative, CT should be obtained due to the modest risk of additional findings.

A commonly used method to predict the risk and select therapy for prostate cancer is Gleason score, which has a significant rate of upgrading. To evaluate the effect of age and prostate size on the risk of upgrading in Gleason score a retrospective review was performed by Gershman et al[3] in 1836 patients with Gleason score 6 prostate cancer who underwent radical prostatectomy (RP) from 2001 through 2010. They assessed clinical and pathologic variables to determine association with risk of upgrading at prostatectomy. Gland size was evaluated based on the prostate weight.

Upgrading was seen in 29.6% of patients with a final Gleason score of 3 + 4 in 25.2%, 4 + 3 in 2.7%, and 8-10 in 1.7%. Mean age, PSA, and prostate weight in upgraded patients were 60.6 years, 7.10 ng/mL, and 43.5 gm, respectively, that was significantly different compared with 58.6 years, 5.01 ng/ml, and 48.0 gm in patients without upgrading ($p < 0.0001$). Univariate logistic regression and multiple logistic regression showed that age, prostate weight, and PSA were significant predictors of Gleason score upgrading ($p < 0.0001$). Surprisingly, prostate weight was inversely related to risk of upgrading that may be related to increased high grade disease in smaller glands, possibly due to delayed diagnosis from PSA-triggered biopsy. For further assessment, they performed multiple logistic regression to examine risk of Gleason 6-10 in 2493 patients. Adjusting for age and PSA, there was a progressively increased risk of Gleason 6, 7, and 8-10 disease with decreasing prostate weight. In conclusion, older age, higher PSA, and smaller prostate gland size were associated with increased risk of Gleason score upgrading.

An increased risk of biochemical recurrence is seen in association with a positive surgical margin (PSM) status following RP. Since the impact of PSM on long term prostate cancer-specific mortality (PCSM) following RP has not been well elucidated, Dinizo et al[4] performed a study to evaluate the impact of PSM on PCSM in a large retrospective cohort of RP patients between 1982 and 2009 in 4381 men who underwent RP by a single surgeon with the median age of 58 years and the median PSA of 5.5 ng/mL. Cox proportional hazards models were utilized to determine the impact of PSM on PCSM. RP Gleason score was ≤ 6 in 63.9%, 7 in 29.9%, and 8-10 in 6.2%. PSM was found in 11.5% of cases. On follow up of 9 years, 4.1% of patients died of prostate cancer. Compared to those with negative surgical margin, men with PSM were more likely to be older (59.2 versus 57.1) and to have RP in the pre-PSA era (34.9% versus 12.5%). Also they had higher PSA level (11.6 versus 6.6), Gleason score of ≥ 7 (60.4% versus 33%), non-organ-confined tumor (90.8% versus 31.6%), and postoperative adjuvant or salvage therapy (35.3% versus 7.4%) ($p < 0.001$ for all). In a univariate model for PCSM, PSM was highly significant, HR = 4.23 (95% CI 3.13-5.73), $p < 0.0001$. However, in a multivariable model adjusting for RP year, RP Gleason, stage, and (as time dependent covariates) adjuvant or salvage treatment, PSM was no longer significant: HR = 1.03 (95% CI 0.73-1.44), $p = 0.880$.

They concluded that prostate cancer-specific survival following RP is excellent. PSM was associated with increased PCSM in a univariate analysis in contrast to the multivariable analysis, in which a PSM was not an independent predictor of PCSM.

It is very difficult to predict the presence of purely unilateral prostate cancer for the purpose of hemiablative focal therapy with high levels of accuracy. Although the contralateral untreated lobe in the prostate does

not have to be a lobe without cancer, but could also be a lobe without significant cancer (SC). To evaluate this possibility, extended 26-core prostate biopsy (3D26PBx: a combination of transrectal 12-core biopsy and transperineal 14-core biopsy) was done in a study by Numao et al,[5] to predict the lobe without SC for the purpose of hemiablative focal therapy. They studied 165 patients with prostate cancer diagnosed by 3D26PBx and underwent RP without neoadjuvant treatment between 2002 and 2009. Pathological specimens of 330 lobes (right and left) were evaluated according to the 2005 ISUP consensus. Significant cancer was defined as extraprostatic extension and/or a tumor volume ≥ 0.50 cc and/or GS ≥ 4 + 3 based on upward Gleason score (GS). They also assessed the probable role of clinical and pathological variables to predict the lobe without SC. The lobe without cancer was seen in 6.7% of the cases while 34% revealed the lobe without SC. The positive predictive value (PPV) and negative predictive value (NPV) of unilateral negative biopsy for the lobe without cancer were 22% and 99% in 3D26PBx, respectively. The PPV, NPV, sensitivity, and specificity of unilateral negative biopsy for the lobe without SC were 85%, 77%, 56%, and 94% in 3D26PBx, respectively. Clinical variables including prostate-specific antigen, prostate volume, digital rectal examination findings and age were not significantly associated with the lobe without SC in biopsy negative side. With PPV of 85%, they concluded that 3D26PBx predicted the lobe without SC and, hemiablative focal therapy may be a reasonable option in patients with a cancer negative side.

To evaluate the influence of the anatomical extent of pelvic lymph node dissection (PLND) and the therapeutic benefit of limited and extended PLND in prostate cancer management, Bivalacqua et al[6] performed a study in men with positive LN at time of RP on LN yield, biochemical recurrence-free survival (BFS), metastases free survival (MFS), and prostate cancer specific survival (CSS). Between 1992 and 2003, two surgeons at one hospital performed 2279 and 1986 RP with PLND, respectively. One surgeon routinely performed an extended PLND (EPLND; superior: bifurcation of common iliac artery; inferior: femoral canal to pelvic side wall; posterior: obturator and internal iliac vessels) while the second surgeon performed a limited PLND (LPLND, differed by posterior extent termination at obturator nerve). Of 94 men with positive LN at RP, 73 and 21 men underwent EPLND and LPLND, respectively. There was no difference in age, preoperative PSA, clinical stage, biopsy or pathological Gleason sum among groups. There was no difference in the proportion of men with extraprostatic extension, seminal vesicle invasion and positive surgical margins among groups. On average, EPLND and LPLND yielded 14.3 and 11.4 nodes respectively (p = 0.02). There was no difference in the number of positive LN or the proportion of patients with < 15% positive LN among groups. Five year BFS was 30.1% and 8.3% for EPLND and LPLND, respectively (p = 0.05); 10 year MFS was 62.2% versus 22.2% (p = 0.035) and 10 year CSS was 83.6% versus 52.6% (p = 0.2). The magnitude of the difference in BFS and MFS were accentuated in those patients with < 15% positive LN (31.9%). They concluded that patients who underwent EPLND had more LN dissected on average and experienced an improved BFS and MFS. Therefore, an EPLND at RP may provide a therapeutic benefit to patients with LN positive prostate cancer in addition to valuable staging information.

Main points

- Novel transperineal template mapping biopsy (TTMB) allow for more accurate sampling of the entire gland.
- Bone scans should be performed for staging in all patients with PSA > 20 ng/mL, stage T2c, or Gleason 8. If the bone scan is negative, CT should be obtained due to the modest risk of additional findings.
- Older age, higher PSA, and smaller prostate gland size were associated with increased risk of Gleason score upgrading.
- Prostate cancer-specific survival following RP is excellent. PSM was associated with increased PCSM in a univariate analysis in contrast to the multivariable analysis, in which a PSM was not an independent predictor of PCSM.
- Extended 26-core prostate biopsy (3D26PBx: a combination of transrectal 12-core biopsy and transperineal 14-core biopsy) predicted the lobe without SC with 85% ppv and, hemiablative focal therapy may be a reasonable option in patients with a cancer negative side.
- An EPLND at RP may provide improved BFS and MFS and a therapeutic benefit to patients with LN positive prostate cancer.

Prostate cancer markers

To evaluate the association between early onset of prostate cancer and familial prostate cancer, defined by the clustering of cases in members of a family, Helfand et al[7] performed genome-wide association studies to identify risk alleles on multiple chromosomes that are

associated with prostate cancer susceptibility and if the prostate cancer risk alleles contribute to early-onset and familial disease. In a radical prostatectomy series, 1256 Caucasian men were genotyped for 17 different risk alleles on chromosomes 2, 3, 5, 8, 10, 11, 17, 19 and X. The frequencies of these alleles were compared in men with early onset (< 55 y) and late onset (> 70 y) prostate cancer. They also compared the frequencies of these alleles in men with familial (defined by two first-degree affected family members) and sporadic (no family history) disease. 5.8% and 69.3% had familial and sporadic disease, and 43.7% and 18.3% of men had early and late onset of disease, respectively. There was a significantly higher frequency of the risk allele rs8102476 on chromosome 19q13 in men with familial versus sporadic disease (90.4% versus 79.2%; p = 0.03). They also found that risk allele SNP rs4430796 on chromosome 17q12 was significantly under-represented in men with early versus late onset disease (79.8% versus 86.1%; p = 0.04). They concluded that risk alleles on 19q13 and 17q12 may extend to hereditary and early onset prostate cancer. Such findings suggest the potential for early genetic screening in men who are at greatest risk of the disease, even in the absence of a family history.

It has been suggested that the association between high biochemical recurrence (BCR) rates after RP in obese patients may be due to poor surgical technique and greater risk of positive margins. To evaluate this possibility, Ho et al[8] performed a study on 1003 men treated with RP from 2001 to 2010 who had known data for preoperative body mass index (mean BMI of 28.5 kg/m^2) and ultrasensitive PSA nadir within 6 months after RP. PSA nadir was undetectable in 57% and, 36% had a detectable nadir but < 0.2 ng/mL, and 7% had a nadir of 0.2 ng/mL. Median follow up was 42.4 months, during which 25% developed BCR. Higher BMI was associated with higher PSA nadir on both univariate (p = 0.001) and multivariate adjusted analyses (p < 0.001). Among men with a PSA nadir < 0.2 ng/mL (i.e. those who did not recur based upon PSA nadir alone), higher BMI was associated with BCR when not adjusted for PSA nadir (p = 0.003). Adjusting for PSA nadir attenuated, but did not eliminate this association (p = 0.024). Even among men with an undetectable PSA nadir, obesity remained significantly associated with BCR (p = 0.006). It seems that obesity may play a role in higher PSA nadir and there is a probable association between obesity and prostate cancer progression suggesting technical issues confound an ideal operation and or more advanced disease in obese men. However, the increased PSA nadir does not completely explain the higher PSA recurrence rates among men with higher BMI.

Overexpression of clusterin, a stress-associated cytoprotective protein, has been found in several kinds of malignant tumors. To assess whether serum level of clusterin could be used as a novel marker predicting extension of prostate cancer, Miyake et al[9] designed a study to evaluate this possibility in 380 patients with prostate cancer and 120 patients with benign prostatic hyperplasia (BPH). Serum level of clusterin was measured by a sandwich enzyme immunoassay, and clusterin density, which was determined by dividing the serum level of clusterin by the prostate volume, was also calculated in each patient. The mean serum level of clusterin in prostate cancer patients was significantly higher than that in the BPH group. The serum clusterin level in prostate cancer patients with metastasis was significantly elevated compared with that in those without metastases; however, there was no significant difference in the serum clusterin levels among prostate cancer patients according to Gleason score. The clusterin density in patients with pathologically organ-confined prostate cancer was significantly higher than that in BPH; however, there was no significant difference in the serum levels of clusterin between these two groups. Furthermore, despite the lack of significant difference in the biochemical recurrence-free survival between patients with elevated serum clusterin level and those with normal level, the biochemical recurrence-free survival in patients with elevated clusterin density was significantly poor compared with that in those with normal density. It is suggested that measurement of the serum clusterin level and its density may provide variable information for the diagnosis of prostate cancer as well as the prediction of prostate cancer extension.

Urine PSA may increase after the local recurrence following prostatectomy originating from recurrent cancerous cells around the urethrovesical anastomosis. However, PSA may also be secreted from the periurethral glands, which make it difficult to interpret the results of the urine PSA test. To evaluate the usefulness of urine PSA test in the diagnosis of local recurrence after RP, Segawa et al[10] collected urine samples from 139 patients who underwent radical prostatectomy, before and after digital rectal examination (DRE) around the urethrovesical anastomosis from 2002 to 2007. Urine PSA concentrations before DRE for 139 patients were 0.03 ng/mL to 157.5 ng/mL (mean: 8.0 ng/mL), and were ranged from 0.03 ng/mL to 3283 ng/mL (mean: 79.1 ng/mL) after DRE. Mean PSA amount was increased from 300 ng to 1881 ng after DRE. Mean ratio

of post/pre DRE PSA amounts was 4.4 folds. Among 45 patients who experienced PSA failures, mean ratio of post/pre DRE PSA amounts was 7.1 folds, which was statistically higher ($p < 0.05$) compared with that of 3.2 folds among 94 patients without PSA failures. Among 19 patients with definitive local recurrence, (defined by the decrease of serum PSA after salvage radiation therapy), mean ratio of post/pre DRE PSA amounts was even higher, with the value of 9.9 folds. In conclusion, ratio of post/pre DRE PSA amounts in urine was higher among patients with PSA failures, especially among patients with local failures. Urine PSA test might have a potential role in the detection of local recurrence, which contributes to the selection of salvage therapy following PSA failures after radical prostatectomy for prostate cancer.

One of the important factors in following patients with prostate cancer after radical prostatectomy is PSA doubling time (PSADT). To identify that this value is constant or fluctuates throughout the course of follow up, Cary et al[11] retrospectively studied a database from 1989 to 2008. Three hundred forty-five patients in a total of 2,237 developed biochemical recurrence and PSADT was calculated. Median follow up was 5 years (0.3-18years). PSADT was recalculated at 1, 2, 3, 5, and 8 years of follow up. Pathologic Gleason score and stage, tumor volume, local recurrence and metastatic disease were analyzed as different variables. PSADTs were not stable over time. High Gleason score and higher pathologic stage were associated with a decreasing PSADT over time ($p = 0.0136$ and 0.0432 respectively). Tumor volume, local recurrence, and metastatic disease were not significantly associated with a rate of change in PSADT. Local recurrence and metastatic disease during follow up developed in 34 and 55 patients, respectively. Using all PSA values within 5 years of initial biochemical recurrence yielded an overall median PSADT of 55 months. Median time to development of metastases following biochemical recurrence was 12.9 years. It seems that pathologic stage and Gleason score significantly affect PSADT over the course of follow up. PSADT is not constant but rather it shortens over time. They suggested that the change in PSADT over time should be carefully considered when potentially offering additional therapy during follow up.

There seems to be a relation between circulating cytokine levels and disease progression in prostate cancer. Narita et al[12] performed a study on 117 prostate cancer patients who underwent radical prostatectomy to evaluate the clinical significance of preoperative serum levels of inflammatory cytokines as prognostic markers. The preoperative serum levels of interleukin (IL)-10, IL-6, tumor necrosis factor-[alpha], IL-1b, IL-8, and IL-12p70 were measured using Cytometric Bead Array. Overall, 12% of patients had PSA recurrence with a median follow up of 14.9 months. In univariate analysis, patients with IL-12p70 of 1.5 pg/mL in their serum had a significantly higher recurrence rate of PSA than those with higher values ($p = 0.019$). Also, patients with IL-6 > 2.2 pg/mL in their serum tended to have a higher recurrence rate of PSA ($p = 0.068$). Preoperative PSA level, biopsy Gleason score, and T stage were also associated with PSA recurrence. Multivariate analysis revealed that preoperative serum level of PSA, IL-6, and IL-12p70 were independent predictors for PSA recurrence-free survival [95% confidence interval, $p < 0.04$]. They concluded that, not only preoperative serum levels of IL-6 and IL-12p70 are associated with biochemical recurrence of prostate cancer treated using radical prostatectomy, serum levels may also be potential predictors of outcome in patients with localized prostate cancer.

Main points

- The potential for early genetic screening in men who are at greatest risk of prostate cancer is suggested due to the role of risk alleles on 19q13 and 17q12 chromosome, that may extend to hereditary and early onset of familial prostate cancer.
- Obesity may play a role in higher PSA nadir and there is a probable association between obesity and prostate cancer progression suggesting technical issues confound an ideal operation and or more advanced disease in obese men.
- Measurement of the serum clusterin level and its density may provide variable information for the diagnosis of prostate cancer as well as the prediction of prostate cancer extension.
- Urine PSA test might have a potential role in the detection of local recurrence, which contributes to the selection of salvage therapy following PSA failures after radical prostatectomy for prostate cancer.
- PSA doubling time (PSADT) is not constant but rather it shortens over time. The change in PSADT over time should be carefully considered when potentially offering additional therapy during follow up.
- Preoperative serum levels of IL-6 and IL-12p70 are associated with biochemical recurrence of prostate cancer treated using radical prostatectomy, and may also be potential predictors of outcome in patients with localized prostate cancer. □

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