Three Novel Intrinsic Subtypes of Prostate Cancer Identified

Two Subtypes Associated with Response to Post-Operative RT

In the largest study of its kind to date, researchers have identified and validated three distinct molecular subtypes of prostate cancer that correlate with distant metastasis-free survival (DMFS) and can assist in future research to determine how patients will respond to treatment. Results were presented at the 58th Annual Meeting of the American Society for Radiation Oncology (ASTRO). Findings represent a step toward the implementation of personalized medicine in prostate cancer care.

To diagnose and determine treatment for prostate cancer, clinicians consider many factors, including a digital rectal exam, the PSA level in a patient’s blood and prostate tumor biopsy results. Molecular subtyping of tumor cells allows oncologists to individualize care and tailor treatment based on the actual biology of each patient’s individual disease.

“Tumors that appear similar under a microscope can behave very differently, from a clinical standpoint,” said Daniel E. Spratt, MD, lead author of the study and chief of the Genitourinary Radiotherapy Program at the University of Michigan in Ann Arbor, MI. “One promise of genomic analyses is to elucidate subtypes of cancer based on the genetics of the tumor rather than merely how they look or what size they are.”

To identify genomic profiles for prostate cancer, researchers analyzed RNA expression patterns in 4,236 samples from nine (Continued on page 4)

Similar 10-Year Survival Reported With Active Monitoring, Surgery, or Radiotherapy for PSA-Detected Localized Prostate Cancer

In a UK trial (ProtecT) reported in The New England Journal of Medicine, Hamdy et al. found no significant differences in prostate cancer-specific mortality (PCSM) or overall mortality among men with localized prostate cancer detected by PSA testing who underwent active surveillance (AS), radical prostatectomy (RP), or radiotherapy (RT). Metastases and disease progression were more common with monitoring.

In the study, 1,643 men aged 50 to 69 years were randomized between 1999 and 2009 to receive AS (N=545), RP (N=553), or RT (N=545). The primary outcome measure was prostate cancer mortality at a median of 10 years of follow-up. Radical treatment was received by 54.8% of the AS group by the end of November 2015; of them, 49% underwent RP, 33% received per-protocol RT, and 8% received brachytherapy.

During the median 10-year follow-up, PCSM (N=17) occurred in eight men in the AS group (1.5 deaths/1,000 person-years), five in the RP group (0.9/1,000 person-years), and four in the RT group (0.7/1,000 person-years; P=0.48 [not significant], for overall comparison). Prostate cancer-specific (Continued on page 5)
Testosterone and Prostate Cancer: Looks Safe but...  
Data Accumulating but Not Yet Definitive

Men with definitively treated prostate cancer or on active surveillance (AS) had no clear cancer-related consequences of testosterone therapy, a small retrospective cohort study showed.

During a median follow-up of 41 months after starting testosterone therapy, three of 50 men treated with radiation therapy (RT) developed biochemical relapse (BCR), but none of the PSA failures had clear associations with testosterone therapy. None of 22 men who underwent radical prostatectomy (RP) had BCRs, and none of the eight men on AS had pathologic upgrading of their prostate cancer, as reported in the October 2016 issue of *The Journal of Urology*.

Although modest in terms of sample size, the study provided additional evidence to support the view that testosterone therapy does not adversely affect prostate cancer status or risk.

“In the absence of randomized, placebo-controlled trials, our study supports the hypothesis that testosterone therapy may be oncologically safe in hypogonadal men after definitive treatment or in those on AS for prostate cancer,” Jesse Ory, MD, of Dalhousie University in Halifax, Nova Scotia, Canada, and co-authors concluded.

“The evidence has tipped in favor of testosterone’s safety with regard to prostate cancer risk, but the issue will not be resolved until evidence encompasses enough men to permit definitive conclusions,” said Alexander Pastuszak, MD, PhD, of Baylor College of Medicine in Houston.

“The piece that’s missing from the puzzle is a large cohort of men who have been objectively evaluated with the same criteria across the board,” Pastuszak, who was not involved in the study, told MedPage Today. “The problem we have with all of the studies, including mine, is that the cohorts, across the board, are small.”

“When you look at the total number of men in aggregate—who have been looked at in several different ways—there are only a few hundred,” he added. “So, while we can say, ‘yeah, it looks safe,’ we can’t say, ‘yeah, it is safe.’”

The study continued a long-standing controversy surrounding the safety of testosterone therapy that evolved from landmark studies conducted by Huggins and Hodges.

New Group of Molecules for Targeting Tumour Growth

Prostate cancer patients were offered hope after scientists at Newcastle University, UK, identified a new group of molecules that could be targeted to slow tumour growth. Experts used an advanced screening technique which found hundreds of genes were affected by the male hormone testosterone. It is believed this could lead to new diagnostic tests and treatments.

Among the 700 genes identified was an important set that add sugar groups — known as glycans — to the surface of prostate cancer cells. This group has never been investigated before. Results published in *EBioMedicine*, suggest that testosterone changes glycans to make cancer cells more likely to survive, grow and spread to other parts of the body. Scientists say it may be possible to target these glycans which could stop the growth and spread of tumours and save lives.

Dr. Jennifer Munkley, Research Associate at the Institute of Genetic Medicine, Newcastle University, co-led the three-year research project with Professor David Elliott. She said: “Our findings are very significant for future treatments as they identify a new group of molecules in prostate cancer which could be targeted therapeutically.

“Now that we have identified these glycans we will be able to develop strategies to inhibit them and help patients. Treatments targeting glycan sugar groups have been developed for other types of the illness, such as breast cancer. Our results mean these treatments could also be used for prostate cancer.”

Glycans have the potential to be used as part of a diagnostic test to help doctors decide which prostate cancers need treatment. Dr. Munkley has been awarded a Newcastle University Faculty of Medical Sciences Fellowship to continue her research.

UK researchers used a technique known as RNA-sequencing to identify the new set of genes that are important. The genes identified may provide novel ways the disease can be monitored in patients to predict the most aggressive prostate cancers that need to be treated. The research was funded in partnership between Prostate Cancer UK and the Movember Foundation.
Doc Moyad’s What Works & What is Worthless Column, Also Known As “No Bogus Science” Column

“Routine mammography screening for breast cancer just got bad news! What does that have to do with prostate cancer, Moyad?!”

Mark A. Moyad, MD, MPH, University of Michigan Medical Center, Department of Urology

Editor’s Note: Us TOO invites certain physicians and others to provide information and commentary for the Hot SHEET to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and are not necessarily those of Us TOO International.

Bottom Line:

New research from the New England Journal of Medicine suggests that breast cancer screening with mammography has resulted in a large over-diagnosis of breast cancer! Ouch! However, I believe breast cancer screening will never get a Grade D recommendation in my lifetime similar to what prostate cancer screening received a few years ago. Why? Every person reading this column has a voice but we need to do a better job of exercising these voices effectively and objectively. Remember, the squeaky wheel no longer gets the grease but the very loud wheel does get the grease!

Am I torn by the fact that my family has suffered so greatly and yet now breast cancer screening is under question? Nope! Why? Because I believe screening should always be an individual decision based on increasing objective patient knowledge about the pros and cons of screening and working with an objective health care provider you can trust. I also believe this should be the case for prostate cancer. Yet, prostate cancer screening receives a grade of D and breast cancer screening does not. Why?

I believe this is due to a unified advocacy movement. If I want 10,000 women on Capitol Hill tomorrow to protest or raise awareness on increasing breast cancer research, that will happen! If I want 10,000 men on Capitol Hill tomorrow to raise awareness or ask for increased funding for prostate cancer research, then this will be a major challenge (aka good luck with that!) and I know because I have been in this situation multiple times.

What I am trying to say is that breast cancer activism and awareness has been, and still is, way ahead of prostate cancer for many reasons – one of those reasons is that the prostate cancer community has failed to collectively become louder and louder and more unified. More unified petitions and more unified demands for more funding for research and more unified marches are needed. And, not just from patients and advocacy groups. We continue to have too many doctors and other health care professionals who sit on the bench – they make great arguments in private but publicly you can’t find them when you need them.

The bottom line is that prostate cancer screening does not deserve a D recommendation, but perhaps the US Preventive Service Task Force gave us what we deserved? Regardless, there are some movements going on now in prostate cancer that has me convinced that the screening recommendation will indeed change in the next few years so that it is more individualized instead of being fully discarded. And, the reason it will change is because ALL of the wheels on the car (NASPCC, Us TOO, PCRI, ZERO, PCPCC3, PCal, Malecare, PAACT, PCEC, PHEN, Health Care Professionals, patients, families of patients…) will get squeakier and louder together instead of just one or a few wheels at a time. Everyone reading this newsletter/this column has an obligation to be a regular activist for the cause and we will always need more unification which will then ultimately lead to the amplification of our voices. And when that happens, we will get exactly what we deserve… hey, just like with breast cancer!

Reference:

Snus (Smokeless Tobacco) May Increase Prostate Cancer Progression, Death

Use of snus may be associated with an increased risk of death among men with prostate cancer comparable to that associated with smoking, according to findings from a large cohort study. “Compared with Swedish men who did not use any tobacco products, men who smoked cigarettes or used snus had a 15% and 24% respective higher risk for death from prostate cancer,” wrote Kathryn Wilson, MD, of Harvard T.H. Chan School of Public Health, and colleagues online in the International Journal of Cancer.

The powdered tobacco product snus is widely used in Sweden and other parts of Scandinavia but is also available in the US. It is most often packaged in individual pouches that are placed under the top lip. “Because snus delivers high levels of nicotine with lower concentrations of other chemicals than cigarettes and other smokeless tobacco products do, it is widely promoted as a safer alternative to smoking,” Wilson told MedPage Today.

The nested, cohort study compared outcomes among 9,582 men with incident prostate cancer within a prospective cohort of 336,381 Swedish construction workers. Information on tobacco use was collected at study entry between 1971 and 1992, and, for the purposes of this analysis, the men were categorized into never smokers, exclusive smokers (cigarette, cigar, or pipe), exclusive snus users, or ever users of both snus and combustible tobacco products. Prostate cancer-specific and total mortality hazard ratios (HRs) for smoking and snus (Continued on page 8)
Benefit Seen with SBRT in Prostate Cancer (Continued from page 1)

at controlling cancer and be safely delivered to patients.
The trial enrolled 309 newly diagnosed men from 21 community, regional, and academic hospitals across the U.S. Of those, 172 men had low-risk disease (CS T1-T2a, Gleason 6, PSA<10 ng/mL), while 137 had intermediate-risk prostate cancer (CS T1c-T2b with Gleason 7 and PSA<10 ng/mL, or Gleason 6 and PSA 10-20 ng/mL). All men received SBRT via a robotic linear accelerator, with a RT dose to the prostate of 40 Gy administered in five treatments of 8 Gy each. Patients were followed an average of 5.1 years. Less than 2% experienced serious side effects during the course of the follow-up period, far less than the 10% rate deemed excessive by the researchers. “This is another example of how advanced technology has radically improved our ability to target cancer,” Meier said.

No grade 4 or 5 toxicities were reported, and only five grade 3 genitourinary (GU) toxicities were reported. Over 50% of the men did experience less serious side effects—53% and 59% for grade 1 GU and gastrointestinal (GI) toxicities, respectively. Over 35% and 10% for grade 2 GU and GI toxicities, respectively—most were usually temporary, the researchers reported.

As far as the efficacy of treatment, using the definition of a two-point increase in PSA as defining cancer recurrence, Meier and his colleagues found that in the entire group of 309 patients, 97.1% did not experience cancer recurrence after 5.1 years, while the rates were 97.3% and 97.1% for the low- and intermediate-risk groups respectively. Overall actuarial five-year survival for the entire population was 95.6%.

For the low-risk group, the recurrence rate “proved superior to the 93% historical control we compared against,” Meier said, adding that the results for the intermediate-risk group matched the best results for RT “and look better than dose-escalated IMRT.”

“For men with newly diagnosed prostate cancer, when appropriate technology and planning is employed, SBRT is safe, with a low rate of serious side effects,” Meier concluded. “Cancer control rates are very favorable compared to historic data, thus SBRT is a suitable option for low- and intermediate-risk prostate cancer and may be preferable to other treatment approaches.”

Colleen Lawton, MD, vice-chair of the Department of Radiation Oncology at the Medical College of Wisconsin, Milwaukee, commented that the study is encouraging because it includes multi-institutional data. “This certainly suggests that [SBRT] may become a standard treatment in time,” she said. “We certainly need more data, but we are headed in the right direction.”

MedPage Today, 29 September 2016

Three Novel Subtypes of Prostate Cancer Identified (Continued from page 1)

Researchers validated the subtypes across six additional retrospective cohorts, representing a variety of ribonucleic acid (RNA) sequencing platforms and tissue storage methods, and two prospective cohorts of 2,610 patients. The intrinsic subtypes were associated with androgen receptor (AR) activity, expression of the ERG oncogene and other known drivers of prostate tumor growth and progression, but researchers did not find a link from mutations or genetic rearrangements to the subtypes. Rates of DMFS at 10 years varied significantly among the three subtype groups. DMFS rates were 57.1 percent for subtype A, 64.4 percent for subtype B, and 73.6 percent for subtype C (B vs. A: Cox Hazard Ratio [HR], 1.31, p = 0.02; C vs. A: HR, 1.65, p = 0.0001).

After controlling for clinico-pathologic variables, the profile remained independently associated with DMFS (B vs. A: Cox HR, 1.31, p = 0.026; C vs. A: HR, 1.33, p = 0.024). Additionally, multivariate interaction analysis determined that subtypes B and C shared a significant correlation with response to postoperative radiation therapy (RT) (Wald p = 0.0016).

“We have discovered and independently validated a highly stable 100-gene intrinsic molecular profile of prostate cancer that is both prognostic and predictive for RT,” said Dr. Spratt. “We believe that these subtypes reflect truly distinctive underlying biology and that this work represents a significant advance in our understanding of prostate cancer biology.

Moreover, our findings identify numerous genes and enriched biologically active pathways in prostate cancer that have been underappreciated to date but may be potential targets to improve cure rates in this disease by developing new targeted therapies.”

Presented on 25 September 2016 at the ASTRO 58th Annual Meeting.

ASTRO News Release
25 September 2016

Adding Zoledronic Acid to ADT Does Not Delay Prostate Cancer Treatment Failure

Adding zoledronic acid (ZA) to androgen deprivation therapy (ADT) does not significantly prolong time to treatment failure in men with treatment-naive prostate cancer and bone metastasis, according to a new study conducted in Japan.

Tomomi Kamba, MD, of Kyoto University, and colleagues enrolled 227 men with treatment-naive prostate cancer (PCa) and bone metastasis, randomly assigned them to receive either...
Testosterone and PCs (Continued from page 2)

Hodges in the 1940s. Since the middle of the last decade, multiple studies have examined the relationship between testosterone therapy and prostate cancer growth and found little or no evidence to support an association. Ory and colleagues added to the data with a retrospective review of a mixed cohort of men with early prostate cancer treated by radiotherapy (RT) or RP or enrolled in AS.

The 82 men had a median age of 75.5 at last follow-up. The 50 men in the RT subgroup consisted of 37 who received external-beam RT (EBRT) and 13 who received brachytherapy (BT). One man on AS underwent cryotherapy, and another had high-intensity focused ultrasound.

Median testosterone increased from 182 ng/dL before treatment to 381 ng/dL at last follow-up. The median PSA value increased significantly during testosterone treatment for the entire cohort (P <0.000) and for the RP (P=0.048), RT (P=0.028), and AS (P=0.003) subgroups. When analyzed by D’Amico risk groups, only men with low-risk disease had a significant increase in PSA values (P=0.006), and that difference disappeared when the AS subgroup was excluded.

Of the three men who had BCR, one had high-risk Gleason 4+3 disease and a testosterone level of 254 ng/dL when he stopped testosterone therapy. He received androgen-deprivation therapy (ADT) and developed metastatic disease. The other two men had Gleason 3+4 disease and testosterone levels of 20 and 101 ng/dL. Neither man received ADT, nor neither had additional disease progression. All three patients’ PSA values remained elevated after stopping testosterone, the authors reported.

All who underwent RP had undetectable PSA velocity. All eight men on AS had low-volume Gleason 6 disease, and none exhibited clinical or pathologic progression during a median follow-up of 27 months.

In the absence of definitive, large sample-size data, Patuszak said he has no reservations about recommending testosterone therapy for men who might benefit from it.

MedPage Today
24 September 2016

AS vs. RP vs. RT (Continued from page 1)

New Group of Molecules (continued from page 2)

Simon Grieveon, head of research funding at Prostate Cancer UK, said: “There’s a desperate need for more treatments for advanced prostate cancer, which currently has too few available options. However, in order to develop new, effective treatments, we need to understand more about the genetic makeup of aggressive prostate cancers and identify what makes them tick.”

He continued: “This promising research has unearthed a new group of genes which could play a part in cancer cell survival and development, and could pave the way for new treatments in the future. Although this work is still in its infancy, and there is a long way to go before we could have a potential new treatment, we will be watching its progression with great interest.”

One man who knows first-hand the importance of this research is David Forrester, who was diagnosed with prostate cancer four years ago. The 62-year-old experienced some episodes of “urinary infections.” His brother had been diagnosed with the illness in 2004 and, therefore, Mr. Forrester was monitored by doctors.

He had annual PSA tests – a blood test that can detect the early signs of an enlarged prostate – and his PSA doubled in a short space of time. Mr. Forrester was referred to a urologist and underwent a biopsy which confirmed he had prostate cancer. As a former operating theatre manager, the grandfather-of-three decided to have surgery to remove his prostate. Although he did experience side-effects, he has recovered well and is enjoying life.

He added: “With two sons and two grandsons, who are at higher risk of developing the disease, I am especially interested in this research.”

“The results of this study offer hope to patients affected by prostate cancer and their families that improved diagnostics and treatment options will be developed in the years ahead. It is exciting that Newcastle University is leading the way and it shows what world-class research is going on.”

Newswire
16 August 2016

ZA Plus ADT (Continued from page 4)

combined ADT alone or combined ADT plus ZA. The median follow-up was 41.5 months.

The median time to treatment failure (TTTF) was similar for the combined ADT and the ADT/ZA groups (12.4 and 9.7 months, respectively), the researchers reported online ahead of print in the International Journal of Clinical Oncology. For men with baseline PSA levels below 200 ng/mL, the median TTTF was 9.8 and 23.7 months for the combined ADT and ADT/ZA groups, respectively, a significant difference that corresponded to a 42% decreased risk of treatment failure in the ADT/ZA recipients.

The median time to the first skeletal-related event was significantly longer for ADT/ZA group than the combined ADT group (64.7 vs. 45.9 months), a difference that corresponded to a 42% decrease in risk of skeletal-related events for the ADT/ZA group. Overall survival was similar between the treatment arms.

The combination, however, may delay development of castration-resistant disease in patients with lower baseline PSA levels.

Renal & Urology News
14 September 2016
Brachytherapy Enough for Intermediate-Risk Prostate Cancer

Similar Outcomes, Fewer Side Effects vs. External Beam RT

Men with intermediate-risk prostate cancer who are treated with brachytherapy (BT) alone achieve similar results, as well as fewer side effects, than men treated with BT combined with external beam radiotherapy (EBRT), investigators reported at the 2016 Annual Meeting of the American Society for Radiation Oncology (ASTRO).

“Results suggest that BT can be used alone for men with intermediate-risk prostate cancer rather than the more conventional combination technique,” said the study’s lead investigator Bradley Prestidge, MD, of the Bon Secours Cancer Institute at DePaul Medical Center in Norfolk, VA.

This study, NRG Oncology/RTOG 0232, was a phase III, multi-institutional trial conducted at 68 cancer centers throughout the U.S. and Canada from 2003 to 2012. That trial was designed to assess whether combining EBRT with BT added benefit in terms of progression-free survival (PFS) or control of cancer growth at five years following treatment.

Men were randomized into two treatment arms; 292 received BT alone and 287 men receiving 45 Gy partial EBRT to the pelvic area and BT (EBRT+BT group).

For the study, EBRT could be given by intensity-modulated RT or 3D conformal RT. BT included iodine-125 or palladium-103 (investigator preference), prescribed to 110 Gy or 100 Gy for men in the EBRT+BT group, and 145 Gy or 125 Gy respective dose for men in the BT-alone group.

Prestidge and his colleagues determined that, at five years follow-up, survival rates for men in the BT group were comparable to those in the EBRT+BT group. The five-year PFS rate was 86% for the BT group vs. 85% for the EBRT+BT group (Hazard Ratio [HR] 1.02, P=0.0006, a non-significant difference).

Overall rates of side effects were similar across the groups only for acute side effects, with 8% of men in each group reporting acute grade 3+ toxicity.

However, the more aggressive therapy given to the EBRT+BT group resulted in more late severe effects, with overall grade 3+ late toxicity rates of 12% for EBRT+BT compared to 7% for BT. Grade 3 or higher genitourinary toxicity rates for the EBT+B and BT groups were 7% and 3%, respectively, while gastrointestinal toxicity rates were 3% and 2%, respectively.

“Contrary to expectations, the more aggressive, combined treatment did not result in superior cancer control rates at five years follow-up, indicating that men can achieve a similar survival with fewer late side effects through BT alone,” he said.

That represents “a bit of a paradigm shift,” Prestidge noted, considering that the conventional treatment for intermediate-risk prostate cancer has been the combination of EBRT and BT.

He said that future work will include looking at subsets within the study cohort to compare more favorable to less favorable intermediate-risk prostate cancer patients.

Efficiency of Prostate Cancer Diagnosis by MR/Ultrasound Fusion-Guided Biopsy vs. Standard Extended-Sextant Biopsy for MR-Visible Lesions

Siddiqui MM, George AK, Rubin R, et al.
J Natl Cancer Inst 2016; 108(9)

Background: Use of magnetic resonance (MR) imaging to improve prostate biopsy efficiency is rapidly gaining in popularity. The aim of this study was to assess the biopsy efficiency of MR-ultrasound (MR/US) fusion-guided (“targeted”) biopsies vs. extended-sextant 12-core (“standard”) biopsies for overall and high-grade prostate cancer detection.

Methods: From August 2007 to February 2014, 1,003 men were enrolled in a prospective trial comparing the diagnostic yield of targeted and standard prostate biopsies performed during the same session. A total of 17,619 biopsy cores were reviewed. Biopsy efficiency was determined by dividing the total number of cores by the number of positive cores obtained. All statistical tests were two-sided.

Results: A mean of 12.3 (95% confidence interval [CI], 12.2-12.3) standard and 5.3 (95% CI, 5.1-5.5) targeted biopsy cores were obtained from each patient. Targeted biopsy detected 461 cases of prostate cancer, of which 173 (37.5%) were high-grade (Gleason score ≥ 4 + 3), while standard biopsy detected 469 cases of prostate cancer, of which 122 (26.5%) were high-grade. The percentage of biopsy cores positive for prostate cancer, irrespective of grade, was statistically significantly higher for targeted than for standard biopsies (27.9% vs. 13.5%, respectively, P <0.001), with 11.5 targeted cores vs. 26.2 standard cores utilized per diagnosis of prostate cancer. For detection of high-grade cancer, 30.7 targeted vs. 100.8 standard cores were utilized per diagnosis.

Conclusion: In men with MR-visible prostate lesions, targeted biopsy is more efficient than standard biopsy, diagnosing a similar number of cancer cases and more high-grade cases while sampling 56.1% fewer biopsy cores.

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P1, “Similar 10-Yr. Survival…”
Many people have been waiting for the results of the ProtectT trial because it is the first time radical prostatectomy (RP) and radiation therapy (RT) have been compared in a randomized study. The additional and really valuable third arm in this study is active surveillance (AS). The early findings getting so much attention in the media are that no significant difference in survival occurred between the three groups and prostate cancer mortality was about 1%. Thus far, slightly more than half of the men in AS have received definitive therapy, meaning that almost half of the men have been able to avoid definitive therapy. Does this mean that AS really is as good as the other two options? The answer is a very important NO, for several reasons. First, both metastases and disease progression were significantly higher in the AS group. That means, longer follow-up may well result in a worse survival for those men. Second, more than 10% of men assigned to each group had a different treatment than they were supposed to. That means, some men assigned to RP had either RT or AS, some assigned to AS had RP or RT and some assigned to RT had one of the other treatments. Readers should understand that these types of studies must do an intent-to-treat analysis based on the assigned group and not the actual treatment, even though not following the assigned therapy can introduce a significant bias. If surgery or RT is indeed better than AS, some men in the AS group getting one of the other two therapies would make AS look better than it truly is. Another potential bias in the results is that 23% of the men had cancers with a Gleason score ≥6. That could have made the results with AS worse than would occur if only low-risk patients were included. One final thought is that the absence of a significant difference between the RP and RT groups thus far means that for now any man presented with a choice of RT or RP should be told that there is no evidence that one is better than the other.

The Bottom Line: Whether AS will truly deliver a similar long-term survival in men with low-risk prostate cancer needs further study, but in this group of patients, RP and RT were not significantly different.

P1, “ASTRO: Benefit Seen…”
Stereotactic body radiation (SBRT) clearly looks more convenient for men than traditional intensity modulated RT (IMRT) because it can be completed in about five days rather than over 6-8 weeks. But, is it better or even as good as IMRT in terms of cancer control? That question cannot be answered until a prospective randomized study is conducted. For now, uncontrolled studies are accumulating data, some of which was published by Meier, et al. They presented SBRT results in men with low- and intermediate-risk disease from multiple centers and followed them for an average of 5.1 years. Thus far, biochemical disease-free survival looks excellent and is similar to data from other studies. Unfortunately, no valid conclusions can be made from these data for several reasons: first, more than half the group had low-risk disease so they might never have developed disease progression even without treatment. Second, the data are very immature and using PSA data to anticipate long-term outcomes is not a reliable approach. Hopefully, the investigators will use these results to justify initiating a randomized controlled trial against IMRT; because without it, we will never know which is best.

The Bottom Line: Early data suggest SBRT could be valuable long-term; but a randomized study is clearly needed.

P2, “Testosterone and…”
Is it safe to give testosterone replacement therapy to men with prostate cancer? This has been an ongoing but unresolved controversy. New data from a small, uncontrolled study found no difference in the incidence of biochemical recurrence after RP or RT for men receiving testosterone compared to those men not receiving it. Unfortunately, the study is very small and since it is not randomized, the findings could have considerable bias. Lastly, as stated above, PSA recurrence is not a reliable predictor of long-term survival after RT. Clearly better data are needed; however, readers might anticipate that the risk should be low for the following reason: men with normal testosterone do not appear to be at added risk of disease recurrence after RP or RT. Otherwise, routine castration would be a part of the treatment for localized disease. Eventually, a randomized study will be needed to settle the question.

P4, “Adding Zoledronic…”
Do men with newly diagnosed metastatic disease benefit by adding zoledronic acid to ADT? That question was addressed in a randomized study involving 227 men. So far, there has been no significant survival difference; however, this is somewhat surprising because the difference in time to treatment failure (TTTF) was almost 24% longer in the combination therapy group. One wonders whether a larger sample size would have led to a statistically different outcome. Also, there was a significant difference in TTTF in those men with a PSA <200 ng/mL and a longer median time to a first skeletal-related event.

The Bottom Line: Further analysis is needed before one can rule out possible benefit of adding zoledronic acid to ADT for men with newly diagnosed metastatic disease.

P6, “Brachytherapy…”
For many years, some centers around the US have promoted a combination of brachytherapy (BT) and external beam RT (EBRT) for intermediate-risk disease without any clear proof that it is better than either RT modality alone. Now we have results from a prospective randomized trial that enrolled men from 2003 through 2012. At five years, progression free survival was not significantly different between the two groups, but severe side effects were significantly higher in the com-

(Continued on page 8)
bination group. Although the results are too immature to make firm conclusions, the higher rate of side effects without an improvement in survival means that the combination treatment should not be used in prostate cancer patients at this time. Perhaps with longer follow-up, survival differences may appear. Until then, there is no evidence that intermediate-risk patients should be treated with both RT and BT. Some problems with the study are worth noting. First, men could receive either radioactive iodine-125 or palladium-103 as their implant and IMRT or 3D-conformal RT as EBRT. Second, androgen deprivation therapy (ADT) was not used in all men even though randomized studies show that ADT improves survival in this group. These variations could have created a bias in the results. Lastly, biochemical disease-free survival is not a reliable outcome that predicts survival.

The Bottom Line: EBRT + BT have more complications than BT alone without clearly improving survival and is not recommended for men with intermediate-risk disease.

P6, “Efficiency of Prostate...” Should MR/ultrasound fusion biopsies become the standard for men evaluated for prostate cancer? A large study involving more than 1,000 men has provided helpful data on this question. One advantage of the MR/ultrasound approach is that fewer cores can be done, which potentially might lessen the risk of complications, although little data has yet been presented. In this study, the cancer detection rate was similar in both groups, however, the MR guided group had about a 10% greater detection of tumors with a Gleason score of 4+3 or higher. Based on these results, the authors conclude that targeted biopsy is more efficient for finding high-grade disease. One problem with their analysis is that the abstract does not tell us about the difference in detection of overall Gleason 7 disease. If overall Gleason 7 disease detection were similar, under-detection of cancers more likely to require treatment might not occur using the standard biopsy approach.

The Bottom Line: Additional data is accumulating suggesting that MR fusion biopsies may be more advantageous for men; but more data are clearly needed.

Snus & PCa Progression (Continued from page 3) use were determined using Cox proportional hazards models adjusted for age, period of diagnosis, and baseline body mass index. During 36 years of follow-up, 4,758 patients died, including 2,489 due to prostate cancer. The analysis revealed:

- Compared with tobacco never-users, exclusive smokers had an increased risk of prostate cancer mortality (HR, 1.15, 95% CI 1.05–1.27) and total mortality (HR, 1.17, 95% CI 1.09–1.26);
- Exclusive snus users also had increased risks of death due to prostate cancer (HR, 1.24, 95% CI 1.03–1.49) and death from all causes (HR 1.19, 95% CI 1.04–1.37); and
- Among men diagnosed with nonmetastatic disease, the HR for prostate cancer death among exclusive snus users was 3.17 (95% CI 1.66–6.06).

Wilson said she believes the study is the first to link a smokeless tobacco product to prostate cancer progression and death. As a result of earlier studies, the US Surgeon General in 2014 declared cigarette smoking to be associated with an increased risk for prostate cancer progression and death, but not overall incidence of prostate cancer.

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13 October 2016

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Hot SHEET– NOVEMBER 2016