Addition of Docetaxel to Androgen-Metastatic Prostate Cancer Deprivation Therapy Improves Survival in alone (n = 393) or combined with docetaxel 75 mg/m² between July 2006 and December 2012 to receive standard ADT. In this open-label trial, 790 men were randomly assigned between male circumsision and prostate cancer have not been in agreement,” Dr. Noel Pabalan from Angeles University Foundation in Angeles City, Philippines, stated. “We sought to resolve discrepant results from primary studies by applying meta-analysis to statistically determine this association, to obtain a more precise estimate.”

The study, online July 28 in Prostate Cancer and Prostatic Disease, included seven case-control studies involving 8,633 men that tested the association between prostate cancer and circumcision. The studies were conducted in the U.S., Canada and England. All but two studies reported a reduced risk of prostate cancer in circumcised men, although the difference was statistically significant in only three. Overall, there was a small (12%) nonsignificant reduced risk of prostate cancer in circumcised men. But nonsignificance and heterogeneity were “erased” when the overall effect was subjected to outlier treatment and three studies omitted (odds ratio, 0.90; p=0.04), they report.

“This was also statistically significant up to 17% in our post-PSA tested subgroup, among men over 40 years of age and among blacks,” Dr. Pabalan told Reuters Health. “Stability of the reduced risks observed in key subgroups suggests that the protective feature of circumcision status against PCa is best seen in the context of the post-PSA testing and population-based studies as well as in the black race subgroup,” he and his colleagues note in their paper.

(Continued on page 3)
EBRT Defeats High-Risk Prostate Cancer
But Dose-Escalated RT Doesn’t Do Much for Low-Risk Disease

Dose-escalated external beam radiation treatment (EBRT) ≥75.6 Gy is associated with improved overall survival (OS) in men with intermediate- and high-risk prostate cancer although not in men with low-risk disease, a retrospective comparative effectiveness study suggested.

In a cohort of 12,229, 16,714, and 13,538 men with low-, intermediate- and high-risk prostate cancer, respectively, investigators found that dose-escalated EBRT was associated with a statistically significant 16% decreased hazard of death at an inverse probability weight propensity score (IPW-PS) adjusted hazard rate (HR) of 0.84 (95% CI: 0.80-0.88; \( P < 0.001 \)) for men with intermediate-risk prostate cancer compared with patients who received standard-dose EBRT.

Among men with high-risk disease, dose-escalated EBRT was associated with a statistically significant decreased hazard of death (IPW-PS adjusted HR, 0.82, 95% CI: 0.78-0.85; \( P < 0.001 \)) compared with standard-dose EBRT.

In contrast, the association between dose-escalated EBRT and reduced hazard of death was not significant in men with low-risk disease (IPW-PS adjusted HR, 0.98, 95% CI: 0.92-1.05; \( P = 0.54 \)).

“Our findings are concordant with the growing literature that most men with low-risk prostate cancer have excellent survival without radical treatment,” Anusha Kalbasi, MD, Hospital of the University of Pennsylvania, Philadelphia, and colleagues wrote in JAMA Oncology. “And our results add to the body of evidence questioning aggressive local treatment strategies in men with low-risk prostate cancer but supporting such treatment in men with greater disease severity.”

Investigators identified 360,142 men with prostate cancer reported to the National Cancer Data Base (NCDB) between 2004 and 2006. Men receiving EBRT with or without androgen-deprivation therapy (ADT) were included in the analysis.

Each of the low-, intermediate-, and high-risk groups were separated into men who had received EBRT at a dose of less than 75.6 Gy and those who received EBRT at a dose of 75.6 Gy or greater. As the authors note, the dose of 75.6 Gy was chosen as a cut-off point to reflect the division between high- and low-dose arms of randomized clinical trials of EBRT in prostate cancer.

The median follow-up for surviving men was 85 to 86 months for all risk cohorts. For the low-risk cohort, incremental increases in dose were not associated with a survival difference, the authors note. However, for the intermediate-risk cohort, every ≥2-Gy dose increase was associated with a 7.8% reduction in the hazard of death (IPW-PS HR, 0.92, 95% CI: 0.90-0.95; \( P < 0.001 \)).

For men in the high-risk group, every approximate 2-Gy increase in dose was associated with a 6.3% reduction in the hazard of death (HR, 0.94, 95% CI: 0.91-0.97; \( P < 0.001 \)).

New Data on Prostate Cancer, Salvage Radiotherapy & Survival

Men experiencing biochemical failure (BCF) – defined as an increased PSA level after radical prostatectomy (RP) for prostate cancer – often receive salvage radiotherapy (SRT) for disease control and to prevent metastatic spread. However, despite SRT, some men still exhibit BCF. Now, a long-term, single-center study, published online July 9th in the American Journal of Clinical Oncology, demonstrated that outcomes for 61 men who experienced BCR after surgery, including a subset of 34 men who experienced failure twice (once after surgery and once after SRT), are robust.

The median overall survival (OS) was 13.6 years for the men in the study who had two BCRs and 14.7 years for the men who had just the one BCR after RP, report the authors, led by D. Nathan Kim, MD, PhD, from Texas Oncology in Waco. Furthermore, the 10-year prostate-cancer-specific, metastasis-free, and castration-resistant -free survival (from the time of PSA failure after SRT) rates were all in excess of 70% for the men who had two BCRs.

The analysis involved 61 men treated at the University of Texas Southwestern Medical Center in Dallas from 1992 to 2000 who underwent SRT following BCR after RP. BCR post-RP was defined as a persistently detectable PSA level of ≥0.05 ng/mL or two consecutive PSA increases ≥0.1 ng/mL that triggered initiation of SRT. Failure of SRT was defined as a single increase in PSA ≥2 ng/mL from nadir levels, two consecutive PSA increases ≥0.2 ng/mL, initiation of salvage treatment, or clinical disease recurrence.

(Continued on page 4)
For example, it is critical to focus on weight loss, healthy cholesterol, blood glucose, blood pressure... not just because some of these things could prevent or assist in the fight against prostate diseases, but because we know they can increase the odds, more than most things, of a person living better and longer. And, this is why the push by some “experts” and patients to take mega-doses of vitamin D for prostate cancer is beginning to worry me more than a long-tail cat in a room full of rocking chairs!

Research outside of prostate cancer continues to show that vitamin D, although important, is really weak and embellished. Until someone shows strong research that more is better, then I am sticking with less is more.

Two recent MAJOR CLINICAL trials in women highlight this fact. One two-year randomized trial essentially showed that exercise (just twice a week on average) improved muscle strength and balance in older women (70-80 years old) and reduced the rate of falls and injuries by more than 50%. Importantly, adding vitamin D supplementation did not provide any major benefit to exercise alone.1

The second major trial was conducted in the U.S. and also included postmenopausal women (average age 61). Results showed that mega-doses of vitamin D taken for one year did not work better than low daily doses of vitamin D for improving bone mineral density, muscle function, muscle mass, or falls! Oh, and the average individual in this trial had a BMI of 30-31 (obese – this is my bigger concern – not vitamin D). Vitamin D content in most multivitamins has been increased to 800-1000 IU per dose. It is also being added to all types of foods and beverages, so many folks are no longer vitamin D-deficient.

So be very, very careful because we could wake up one day and realize that mega-dosing on vitamin D actually increases the risk of prostate problems!

If you think I am being overly pessimistic, please study the history of selenium and vitamin E in prostate cancer!

BAM! OUCH! YIKES!

References:

**Circumcision and Risk of Prostate Cancer**

(Continued from page 1)

The fact that all studies included in the analysis were retrospective is a limitation, they point out. “We found no report of a prospective cohort study,” they say. “A further limitation is that in all these studies circumcision was based on self-report rather than medical examinations and therefore misclassification of exposure could occur.” Despite these limitations, this is the first meta-analysis addressing the association of circumcision status with the occurrence of prostate cancer, the authors write.

If the lower risk of prostate cancer with circumcision is mediated by a reduced risk of sexually transmitted infections and prostate infection/inflammation, “then the timing of circumcision is important and needs to precede sexual activity,” they say.

**PSA Testing Declines**

(Continued from page 1)

2013. Only white men had a significantly lower percentage in 2013 than in 2010.

**Conclusions:** Significant declines in PSA testing from 2008 to 2013 in men ≥75 years old may reflect the impact of the 2008 USPSTF recommendations. While the cause of the decreases in PSA testing between 2010 and 2013 among men aged 50 to 74 years old and white men is unknown, the decreases may suggest the early effects of the 2012 recommendations.
Testosterone replacement therapy (TRT) did not increase the risk of venous thromboembolism (VTE), irrespective of the route of administration or exposure window, a large retrospective case-control study showed.

Expanding the testosterone exposure window 30 or 60 days also did not significantly affect the risk of VTE, Jacques Baillargeon, PhD, of the University of Texas Medical Branch at Galveston, and colleagues reported online in Mayo Clinic Proceedings.

It is biologically possible for an association between VTE and testosterone use to exist, Baillargeon and colleagues acknowledged. TRT increases hematocrit, blood viscosity, platelet aggregation, and the risk of polycythemia. Some case series have documented VTE in TRT-treated patients with familial and acquired thrombophilia.

“There are many men with clearly defined hypogonadism who may be afraid to take testosterone therapy, and there may be physicians who are reluctant to prescribe testosterone therapy based on past evidence,” Baillargeon told MedPage Today. “It’s important to acknowledge that for men who are truly hypogonadal, there are clear risks to not taking testosterone therapy. These men may be at increased risk for osteoporosis, sexual dysfunction, increased adiposity, decrease in lean muscle mass, and possible metabolic syndrome and cardiovascular disease.”

To help resolve conflicting evidence and inform clinical decision-making, Baillargeon and colleagues conducted a case-control study, using 2007 to 2012 data from a large US health insurer. During that period, more than 15 million men, age ≥40, were covered by the insurer. Investigators identified 7,643 men who had an episode of VTE (deep vein thrombosis or pulmonary embolism) and also received at least one prescription for an anticoagulant or a venous filter within 60 days of VTE diagnosis. Each patient with a VTE was matched with three control patients who did not develop VTE during the study period.

Testosterone exposure was defined as at least one day of overlap between the most recent prescription period and the 15-day window prior to the VTE. Investigators included all doses and formulations of testosterone.

The primary analysis showed that exposure to testosterone within 15 days of a VTE was associated with an odds ratio for VTE of 0.90 vs. men in the control group (95% CI 0.73-1.12). Analysis of VTE risk by route of testosterone administration yielded ORs of 0.80 to 1.15 vs. controls, all of which were not statistically significant.

Use of potentially confounding drugs (prothrombotic steroids, megestrol acetate, nonsteroidal anti-inflammatory drugs, or antiplatelet agents) did not change the main results.

Results for all analyses were similar for exposure windows of 15, 30, and 60 days.

Acknowledging limitations of the study, the authors noted that they excluded men who received anticoagulants in the three months prior to VTE or who had a VTE within the previous 12 months. Additionally, the analysis was based on receipt of a prescription for testosterone, not proof that the therapy was used.

Potential inaccuracies inherent to relying on ICD-9 codes to identify VTE might also have influenced the results. “Though not definitive, the study addresses some of the shortcomings of existing data on the topic and provides reassurance to men and clinicians,” said Alex W. Pastuszak, MD, PhD, of Baylor College of Medicine in Houston.

“Prior studies looking at this relationships were small or did not adjust for confounding variables, such as the use of prothrombotic drugs, which the Baillargeon study does control for,” said Pastuszak. What the current study adds to the existing body of work is a large sample size with rigorously selected data, which provide a more accurate picture of the relationship between VTE and testosterone use.

“The findings of this study fly directly against the recent FDA mandated changes to testosterone drug labels regarding a potential increased risk of VTE, with good retrospective data across a very large sample size,” added Pastuszak. The authors acknowledge the numerous limitation of the study, and the only definitive way to truly determine a possible relationship would be to perform a prospective, controlled study.

“No one has directly examined the anti-inflammatory properties of testosterone, which might lower the risk of thrombosis, Pastuszak added.

**EBRT Defeats High-Risk Prostate Cancer**

(Continued from page 2)

First, we cannot establish a causal relationship between dose-escalated EBRT and OS based on our observational cohort, they caution. Secondly, even after traditional regression and propensity score methods, they cannot rule out residual bias from unknown variables. Thirdly, the NCDB does not record data on ADT duration nor treatment toxic effects and NCDB EBRT dose records are subject to heterogeneity as the dose prescribed by radiation oncologists can vary considerably.

Lastly, the NCDB collects data only from Commission on Cancer-approved facilities. Thus our results are generalizable to patients treated at facilities that tend to be larger and urban, the investigators acknowledged.

In an accompanying editorial, Phillip Gray, MD, and Anthony Zietman, MD, Harvard Medical School, Boston, observe that the lack of benefit seen in men with low-risk disease is “hardly surprising” because the risk of cancer-specific death in this patient group is already very low.

“Indeed, mounting evidence suggests that for many, if not most, low-risk patients, the most appropriate dose of radiation may in fact be 0 Gy,” they state.

Conversely, for men with more aggressive disease, death from prostate cancer is of significant concern. “In such men, local failure is strongly associated with later cancer-related death,” Gray and Zietman observe. “And it is these men who stand to derive the most benefit from intensification of therapy.”

MedPage Today
19 July 2015
The great hope in prostate cancer is for a test that would differentiate between men with aggressive disease who need intensive treatment from those with mild forms of the disease, who may not need treatment. Much effort has gone into looking for genetic markers that could do this, and now a team of researchers from the UK says they have made a breakthrough. They have identified five distinct genetic types of prostate cancer, and say that their classification performs better than previously reported genetic signatures and that it is better at identifying the most aggressive cancers than established clinical measures such as PSA levels and Gleason score.

For the study, the researchers studied a total of 482 tissue samples from 259 men with primary prostate cancer, which included both prostate cancer tissue and benign prostate tissue. The findings were published online July 29 in *EBioMedicine*.

The work was carried out in two steps. In the first step, the team analyzed tumor samples from 156 men who had undergone radical prostatectomy (RP) in Cambridge. They then confirmed their findings in another group 103 men who had RPs in Sweden.

The team used a combined approach of looking both for abnormal chromosomes (copy-number alterations) and measuring gene activity (messenger RNA levels), and developed a refined 100-gene signature that showed five distinct patterns of genomic activity, as follows:

- One group of men had many DNA deletions and consequentially low activity of certain genes.
- Another group had high amounts of DNA repetition, which resulted in increased activity of specific genes.
- Two more groups had very few copy-number alterations or changes in activity.
- The fifth group had some – but not too many – copy-number alterations.

Next, the team traced the later medical history for both sets of men. They found that men in the subgroups with greater numbers of gene changes were more likely to relapse, compared with men who had fewer changes.

Dr. Lamb says that these gene signatures could be used alongside clinical tests to provide a more accurate idea of prognosis. “By combining the molecular information provided by this gene signature with existing clinical information, doctors might be able to identify those most at risk of relapse and treat them accordingly. For example, if a man had a low Gleason score but high levels of genetic alteration, he would be considered to be at a moderate- to high-risk of relapse,” he explained.

Dr. Lamb also discussed several caveats to the findings in the blog. The hope is that these findings will help to guide treatment at diagnosis, and for that analyses would be done on tissue samples taken from diagnostic biopsies, as opposed to RP samples used in this study. There are questions whether the diagnostic biopsy would provide enough tissue to perform this genetic analysis, and there is also the issue of tumor heterogeneity, although new techniques such as MRI-guided targeted biopsy could help to ensure that the biopsy represents the majority of cancer cells in the tumor, he suggested.

However, approached for (Continued on page 8)

**Prostate Cancer Divided Into Five Distinct Types**

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**Salvage Radiation Therapy and Survival**

(Continued from page 2)

At 10 years, OS was 67%, freedom from PSA failure was 33%, prostate-cancer-specific survival was 84%, and distant metastases-free survival was 84% for the men who failed SRT. Pathologic T-stage, Gleason score, seminal vesicle involvement, and pre-SRT PSA were associated with freedom from PSA failure. For patients who failed SRT, the median time to BCR after SRT was 30 months. A total of 19 patients (68%) received androgen-deprivation therapy.

Early SRT failure correlated with a significant decrease in distant metastases-free survival and prostate-cancer-specific survival. Ten-year distant metastases-free survival from SRT was 43% (recurrence at one year or sooner) vs. 91% (recurrence at one year or beyond).

The new retrospective data might be of service to clinicians in discussions with anxious patients because there is a “paucity” of prospective data about this clinical scenario, the authors say. This study has one of the longest follow-up periods in the medical literature. Median follow-up was 126 months after SRT and 112 months after SRT failure. Most studies have a median follow-up < 90 months after SRT.

Because of our long-term follow-up, we were able to make observations in those men who recurred despite SRT, the authors write.

Although their study was of a single group of men, and thus not comparative in any way, the authors observe that another study on natural history after PSA failure (PSAF) demonstrated that the median time to distant metastasis was eight years after PSA failure after RP (without SRT), and roughly one in three patients developed distant metastases within five years without RT.

“Patients with pathologic T3 disease or positive margins are candidates for post-RP RT,” said Colleen A.F. Lawton, MD, past chair of the American Society for Radiation Oncology (ASTRO) board of directors, who was not involved in the study. This recommendation is based on the American Urological Association/ASTRO guidelines on the use of adjuvant RT (ART) and SRT after RP, which is endorsed by the American Society of Clinical Oncology.

“Men with pathologic T3a disease should see a radiation oncologist and discuss whether they are candidates for ART or SRT,” Dr. Lawton said. “The issue is that many men do not consult with a radiation oncologist. She said that the new study findings do not challenge the guidelines, stating “The study provides food for thought, but is not practice-changing.”

The decision of whether to use ART or SRT remains an area of active debate, and prospective randomized trials are currently underway to attempt to answer this question, the authors stated. The authors were referring to the RAVES trial (NCT00860652), which is a phase III study investigating the timing of RT for high-risk prostate cancer.

The study begs the question of whether PSAF is an important surrogate for clinical care in prostate cancer. Dr. Lawton indicated that it is an important surrogate; however, there is no absolute proof about its being associated with survival.

**Medscape Medical News**

10 August 2015
Some Low-Risk Prostate Cancers Need Closer Scrutiny

 clinicians can’t safely assume that a man with newly diagnosed, clinically low-risk prostate cancer is an automatic candidate for active surveillance (AS), results of a large cohort study imply. Among more than 10,000 men diagnosed with clinically low-risk prostate cancer in 2010 and 2011, nearly half had tumor upgrades at the time of radical prostatectomy (RP) and nearly one in 10 had an increase in disease stage. Primary author Paul L. Nguyen, MD, and colleagues from Harvard Medical School and affiliated hospitals in Boston reported their findings in the August issue of the Journal of Urology.

 Current criteria for AS generally consider insignificant disease to be a Gleason score ≤ 6 and organ-confined disease. However, previous studies have also shown that these measures are not foolproof, the investigators note. To see whether they could identify characteristics that might signal higher-risk subgroups among men with clinically low-risk disease, the authors turned to the Surveillance, Epidemiology, and End Results (SEER) database. They identified 10,273 men for the final cohort. The men in the study all had newly diagnosed clinically low-risk disease (cT1c/T2a, PSA level ≤ 10 ng/mL, and a Gleason score/sum of 3+3=6).

 They found that 44% of men had disease upgraded at RP to Gleason score seven to 10. Most of these men (86%) had a Gleason pattern of 3+4=7, 11% had 4+3=7, and 1.3% had Gleason scores of 8 to 10. A total of 992 men had a tumor stage increase at the time of RP, with 88.4% of this group restaged with T3a disease. There was also a subset of 5,581 men in the study who had complete information available about the number of biopsy cores and percentage of positive cores. Investigators found factors significantly associated with upgrading on multivariate analysis were age > 60 years (adjusted odds ratio [AOR], 1.39), PSA > 5.0 ng/mL (AOR, 1.28), and >25% positive cores (AOR, 1.76) (P < 0.001 for all). The same three factors were also all significantly associated with an increase in stage, with respective AORs of 1.42, 1.44, and 2.26 (P < 0.001 for all).

 Among the 5,581 men, 60% of those with PSA levels of 7.5 to 9.9 ng/mL and more than 2% positive cores were upgraded. The findings suggest that men with these specific risk factors might be good candidates for additional studies before being followed with AS.

 “When men think of AS, they might look at guidelines and think ‘I have low-risk prostate cancer, and so I’m fine with AS,’ and that might be true for many men,” Dr. Nguyen said. “But low-risk prostate cancers are not all the same, and what we identified here is a subset of low-risk men who have a very significant risk of harboring more aggressive disease,” he added.

 These men should be considered for further testing, such as advanced imaging, before being assigned to AS, the authors write. It would not be prudent to perform advanced imaging on all low-risk patients. However, our results propose clinical features that could justify further evaluation, they said. The authors caution, however, that the decision made to choose AS has been influenced by a patient’s comorbidities and prior treatment (no local therapy in 73% in both, radiation in 7% and 8%, prostatectomy in 20% and 19%), adjuvant ADT (4.5% and 4.1%), median time from start of ADT to randomization (1.2 and 1.3 months), and no receipt of ADT before randomization (13% in both).

 At a planned interim analysis in October 2013, 53% of planned full OS information had been obtained, and prespecified criteria for significance had been met. The current report includes data with a cutoff date for survival of December 23, 2013, representing a median follow-up of 28.9 months. All other data reflect the data base as of December 23, 2014.

 Overall, 86% of men in the combination group completed six cycles of docetaxel. Median OS was 57.6 months in the ADT plus docetaxel group vs. 44.0 months in the ADT-alone group (hazard ratio [HR] = 0.61, P < 0.001).

 Benefit was more pronounced among men with high-volume disease, with a median OS of 49.2 vs. 32.2 months (HR = 0.60, P < 0.001). At the time of analysis, median OS had not been reached among men with low-volume disease in either group (HR = 0.60, 95% confidence interval = 0.32–1.13). A survival benefit of combined treatment was detected in all analyzed subgroups.

 Median time to castration-resistant prostate cancer (CRPC), i.e., biochemical, symptomatic, or radiographic progression, was 20.2 vs. 11.7 months (HR = 0.61, P < 0.001), and median time to clinical progression was 33.0 vs. 19.8 months (HR = 0.61, P < 0.001). PSA level < 0.2 ng/mL was achieved at 12 months in 27.7% vs. 16.8% of patients (P < 0.001).

 After progression, 54 men in the combination group and 137 men in the ADT-alone group received docetaxel, 57 and 37 received cabazitaxel (Jevtana®), and 29 and 27 received mitoxantrone or platinum chemotherapy. Other treatments included abiraterone, enzalutamide, sipuleucel-T and radiotherapy. Overall, 150 and 187 men received at least one agent shown to prolong OS in metastatic CRPC in the combination and ADT-alone groups, respectively.

 Among men in the combination group, 16.7% had grade 3 and 12.6 had grade 4 adverse events. The most common grade 3 adverse events were fatigue, febrile neutropenia and neutropenia. The most common grade 4 events were neutropenia and febrile neutropenia. Grade 3 sensory neuropathy or motor neuropathy occurred in 0.5%. Grade 3 or 4 thromboembolism occurred in three patients (< 1%). One patient (0.3%) died of sudden death, considered possibly related to docetaxel treatment.

 The investigators concluded: “[T]he combination of standard [ADT] and six cycles of docetaxel resulted in significantly longer OS than that with standard [ADT] alone in men with hormone-sensitive metastatic prostate cancer. The clinical benefit at this early analysis was more pronounced among patients with a higher burden of disease.”

 Content in this post has not been reviewed by the American Society of Clinical Oncology, Inc. (ASCO®) and does not necessarily reflect the ideas and opinions of ASCO®.
The report by Sweeney, et al marks an important advance in the management of metastatic prostate cancer. Since the initial discovery of androgen deprivation therapy (ADT) in the 1940’s, that treatment alone or in combination with an antiandrogen has been the standard treatment. In 2004, docetaxel was approved for progressive metastatic disease. An obvious question was whether combining the two together offered an additional benefit and indeed it does, and by a significant amount; it was 17 months for men with extensive disease and also in all subgroups. It does come with a tradeoff, however, although they are usually well managed. Now comes the challenge for patients; how to be sure they get properly counseled when initiating treatment for metastatic disease. The problem is that urologists rarely read the New England Journal of Medicine and they are the ones who are diagnosing metastatic disease but rarely administer docetaxel. The medical oncologists do that. Somehow, the American Urological Association needs to disseminate information about this study to all its members so that all men are at least made aware about the results of this study.

The Bottom Line: All men with newly diagnosed metastatic disease need to be informed of the significant survival benefit of combining docetaxel with ADT.

To be circumcised or not to be circumcised, that is the question? A debate has existed because of conflicting findings from uncontrolled reports on this topic. Now we have a meta-analysis adding further support for a real association. But, and this is a big BUT, this is still not proof that the benefit is real and the authors are clear to acknowledge that fact. Also, the abstract provides no information about the kind of tumors discovered; did it reduce with low-risk and intermediate- and high-risk tumors or did it only decrease low-risk tumors? Furthermore, were all the biopsies reviewed in each retrospective study? Because if not, there is an additional potential bias.

The Bottom Line: Unfortunately, despite the effort by the authors, this study still does not provide clear evidence that circumcision reduces the risk of getting diagnosed with prostate cancer.

In 2012, the US task Force recommended against routine PSA testing for men over age 50 because they concluded the harms outweighed the benefits. Many doctors and patient groups were significantly upset and disagreed with this recommendation. We now have some evidence that the recommendations MIGHT be having an affect. Berkowitz, et al used the National Health Interview Survey data to analyze the frequency of PSA testing between 2008-2013 and found that white men and men over 75 had a significant drop after 2010, although there is no way to know whether the task force recommendation is the reason for the change. We also do not know whether men are making an informed choice or their doctor is simply making the decision for them. Hopefully, men are getting good counseling and are having a choice to participate. If not, I am concerned about the potential for lawsuits in the future.

The Bottom Line: It appears that routine PSA testing has declined in the last few years at least in this group of men and one hopes that men are getting a chance to discuss the task force recommendation with their doctor.

Improvements in radiation therapy (RT) have enabled doctors to use higher doses than were possible many years ago. Uncontrolled studies have suggested some men benefit and the study by Kalbasi, et al adds additional evidence for men with intermediate- or high-risk cancer. Importantly, no benefit was seen for men with low-risk disease and as the editorial points out, the question is whether any dose is good for those men. BUT, here again, and as clearly pointed out by the authors, this is not a prospective, randomized trial and therefore no reliable conclusions can be made. Hopefully such a study will be forthcoming. Another question raised by this study is whether men with intermediate- or high-risk disease would be better served by dose escalated EBRT or EBRT combined with brachytherapy, the latter having been promoted by several radiation therapists.

The Bottom Line: Growing support for dose escalated RT to treat intermediate- and high-risk prostate cancer is provided, but we still have no definitive proof that it improves survival.

The study by Kim and co-workers addresses the controversy over whether men with pathologic T3 or margin positive disease are better served with adjuvant or salvage RT. The authors acknowledge that they cannot make a conclusion, but it does provide some long-term survival information for those men who forego adjuvant RT to hopefully avoid RT entirely. Proof of a true benefit, however, will have to await the results from the ongoing randomized study.

The Bottom Line: Salvage RT can confer long-term survival but a randomized study is needed to know if it is as good as adjuvant RT.

Billboards, print, and other media carry ads for testosterone replacement therapy, which has greatly increased in use. However, not all men receiving treatment are truly hypogonadal. Nevertheless, for appropriate candidates there is an ongoing question whether the risks offset the benefits and based on existing data. For that reason, the FDA has required a “black box” warning on the label. The study by Ballargeon provides some, although not definitive support, that the risk may be overstated. They used a case-control method for their analysis and found that the risk of a deep venous thrombosis was not higher in a cohort of men who received the replacement compared to a group of men who did not. Unfortunately, the FDA will not likely change their warning until a properly designed and randomized study is performed, which might require industry support.

The Bottom Line: A randomized study is needed to determine if testosterone replacement therapy reduces the risk of deep venous thrombosis.

(Continued on page 8)
comment on the study, an expert who was not involved in the research warned that there was much work yet to be done. "This is a very sophisticated genomic analysis that underscores the complexity prostate cancer," said Marc Garnick, MD, Gorman Brothers Professor of Medicine at Harvard Medical School (HMS) and the Beth Israel Deaconess Medical Center in Boston, and editor-in-chief of the HMS Annual Report on Prostate Diseases.

"This is great news and provides optimism that the years of research in trying to dissect out genomic predictors of clinical behavior are beginning to see the light at the end of the tunnel. But how long is that tunnel? Right now, pre-gFizy far away,"

“How long is that tunnel? The findings indicate significant improvement is needed in assessing AS candidates for active surveillance (AS) but underwent surgery. They found considerable upgrading and upstaging. For that reason they urge caution for men considering AS. As discussed numerous times in this column, AS is evolving and many factors must be considered before a man embarks on that approach. Some include age, health, number of positive cores, and amount of cancer in each core. Unfortunately, there are a number of reasons that these data may not be accurate as stated in the article and for now all that can be said is AS is not for every man with low-risk prostate cancer. I am optimistic that this effort will continue to improve.

Dr. Chodak’s Bottom Line (Continued from page 7)

thought to be reasonable candidates for active surveillance (AS) but underwent surgery. They found considerable upgrading and upstaging. For that reason they urge caution for men considering AS. As discussed numerous times in this column, AS is evolving and many factors must be considered before a man embarks on that approach. Some include age, health, number of positive cores, and amount of cancer in each core. Unfortunately, there are a number of reasons that these data may not be accurate as stated in the article and for now all that can be said is AS is not for every man with low-risk prostate cancer. I am optimistic that this effort will continue to improve.

The Bottom Line: All men with low-risk prostate cancer should hear the pros and cons of AS plus the uncertainties that currently exist before making their decision.

**Five Distinct Types (Continued from page 5)**

"A bigger concern," says Matthew Cooperberg, MD, from the University of California San Francisco Medical Center, a genitourinary oncologist who was not involved in the study, “is that the study relied on SEER data.” SEER administrators acknowledge that the PSA values are unreliable because of a coding and reporting issue. "It’s a little suspect because of the PSA problems," Dr. Cooperberg said. He added that further imaging is also not cost-effective.

Daniel P. Petrylak, MD, a professor of oncology at Yale Cancer Center, who was not involved in the study, said the findings indicate significant improvement is needed for assessing AS candidates.

Medscape Medical News 3 August 2015

**Closer Scrutiny (Continued from page 6)**

bilities and life expectancy, and that results may have been biased by the inclusion of only men selected for RP. "A bigger concern," says Matthew Cooperberg, MD, from the University of California San Francisco Medical Center, a genitourinary oncologist who was not involved in the study, “is that the study relied on SEER data.” SEER administrators acknowledge that the PSA values are unreliable because of a coding and reporting issue. "It’s a little suspect because of the PSA problems," Dr. Cooperberg said. He added that further imaging is also not cost-effective.

Daniel P. Petrylak, MD, a professor of oncology at Yale Cancer Center, who was not involved in the study, said the findings indicate significant improvement is needed for assessing AS candidates.

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**Dr. Chodak’s Bottom Line (Continued from page 7)**

placement does or does not increase the risk of developing a venous thrombosis.

**a7p5c1** The article by Lamb and co-workers reports a new genetic-based test that can separate prostate cancer into five distinct groups. The authors believe their work significantly improves on other risk assessment methods. At first, this sounds very, very exciting. However, as noted in the article, it is far too early to make any conclusions. It is likely we will see more data but for now patients diagnosed with the disease should not be in a hurry to have their cancer analyzed by this method until much more work is done.

The Bottom Line: A 100-gene test may one day help determine the relative aggressiveness of an individual cancer, but more work is needed to assess how well it works.

**a8p6c1** Using SEER data, Nguyen and co-workers analyzed a large cohort of men

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