New Data on RT in Prostate Cancer Are “Practice Changing”

Radiotherapy (RT) to the prostate on top of standard androgen deprivation therapy (ADT) significantly improved overall survival (OS) for men with newly diagnosed metastatic prostate cancer (mPCA) with low metastatic burden, according to new data from the STAMPEDE trial. They were presented at the European Society of Medical Oncology (ESMO) 2018 annual meeting and simultaneously published in The Lancet.

However, the OS benefit did not extend to the total unselected population of men with newly diagnosed mPCAs. The results came from the multi-arm STAMPEDE study; specifically, from a phase 3 comparison to evaluate whether or not RT improved OS in men with newly diagnosed mPCAs.

“Prostate RT should be the standard of care for men with low metastatic burden,” commented lead investigator Christopher C. Parker, MD, of the Royal Marsden NHS Foundation Trust, London, UK. “Until now, it was thought that there was no point in treating the prostate itself if the cancer had already spread because it would be like shutting the stable door after the horse has bolted,” Parker said at the press conference.

“However, this study proves the benefit of prostate RT for these men. Unlike many new drugs for cancer, RT is a simple, relatively cheap treatment that is readily available in most parts of the world,” he added.

“Standard treatment for men newly diagnosed with mPCAs is currently drug treatment alone,” Parker explained in an ESMO meeting. (Continued on page 6)

Nearly 90% Free of Prostate Cancer Progression with ADT plus Pelvic Node RT

Data Showed Trend Toward Reduction in Distant Metastases

Adding androgen deprivation therapy (ADT) and radiation therapy (RT) to the pelvic lymph nodes increased the freedom-from-progression (FFP) rate for prostate cancer in the salvage setting, an interim analysis of the SPPORT trial found.

“At five years, FFP was 89.1% when this approach was added to prostate bed radiation therapy (PBRT) for men with persistent or rising PSA levels after radical prostatectomy (RP) compared with 82.7% with PBRT plus ADT and 71.7% with PBRT alone (P <0.0001),” reported Alan Pollack, MD, PhD, of the Sylvester Comprehensive Cancer Center in Miami, FL.

In a press briefing at the American Society for Radiation Oncology (ASTRO) meeting, Pollack called the significant difference between the group receiving pelvic lymph node RT plus ADT an the PBRT alone group “striking.”

“Pelvic lymph node treatment has major effect that we haven’t seen before, and this is the first trial to document that effect in the salvage setting,” he said.

The trial compared three treatment approaches:

- PBRT alone 64.8-70.2 Gy
- PBRT plus four to six months of ADT
- PBRT and ADT plus 45 Gy RT to the pelvic lymph nodes

Among men followed for up to eight years, the rate of distant metastases trended toward benefit with the triple therapy vs. PBRT alone (Hazard Ratio [HR] 0.52, 95% (Continued on page 3)
Better Outcomes with RT for Black Prostate Cancer Patients

Population-based studies suggest that, compared with white men, black men are at higher risk of dying from prostate cancer (PCa). However, a new analysis shows that black men may achieve comparatively higher cure rates when treated with radiation therapy (RT).

This is the first study demonstrating improved PCa outcomes for this population compared with whites.

“Black men are more likely to die of PCa than white men in the USA, and black race is an independent prognostic factor for poor outcomes,” said lead author Daniel Spratt, MD, an associate professor and chief of the Genitourinary Radiotherapy Program at the University of Michigan Rogel Cancer Center, Ann Arbor. “When we started this project, we had the commonly held assumption that black men harbor more aggressive disease that leads to lower survival rates.”

Data show that this assumption may be untrue. Spratt presented his findings during the plenary session at the American Society for Radiation Oncology (ASTRO) 2018.

He explained that stage-for-stage disparities in prognosis between black and white men with PCa are primarily driven by social/cultural factors. “However, a subset of black men with PCa has distinct biology that may favor RT,” said Spratt.

Discussing the findings, Richard Den, MD, associate professor of radiation oncology, cancer biology, and urology at the Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, provided a takeaway message: “Overall, these data suggest that race should not alter the approach to PCa,” Den concluded. “Regardless of their race, we should treat patients based on the stage and characteristics of their tumor. If a patient is black, he should not get intensified treatment or de-intensified treatment.”

Compared with white men, there is a 60% higher incidence of PCa among black men, and the disease-specific mortality rate is more than two-times greater.

The reasons for these disparities are complex and multifactorial. These include racial bias in treatment, socioeconomic issues, insurance, and disparities in access to care. However, data also suggest that there may be important intrinsic biological differences between races. For example, PCa is diagnosed, on average, about five years earlier in blacks than whites.

However, in the new study, when investigators adjusted for non-biological factors, the differences between races disappeared, Spratt explained. “We looked at biologic differences that could influence treatment sensitivity, not just at the biologic differences between races.”

In this two-part study, Spratt and colleagues investigated the interplay of androgen-receptor (AR) activity and radiotherapeutic sensitivity, with the goal of providing a molecular rationale that could help explain the disparity in outcomes.

First, they investigated differences in gene expression in tumor samples from 17,003 men (1,953 or 11.5% were black men) with PCa and found that tumors from black men had lower AR activity and DNA-repair expression. Tumors with low AR activity were significantly more likely to develop distant metastases within a 10-year period (37 vs. 17%; P=0.008), and low AR activity was an independent predictor of distant metastasis. This association did not change after characteristics, including Gleason grade, T-stage, PSA, margin status after surgery, and lymph node invasion, were adjusted (P=0.03).

Their tumors also had decreased expression of the double-strand DNA repair pathway (P <0.001), increased expression of immune pathways (P <0.001), and increased radiosensitivity as predicted by a 24-gene PCa radiation sensitivity score that was developed by Spratt and his team.

“This increase in radiosensitivity suggests that black men with PCa will have better outcomes with RT,” Spratt explained.

In part two of the study, transcriptome-wide expression profiles and clinical radiosensitivity were examined in tumor samples from 5,854 men (1,129 were black) participating in four large NRG Oncology/RTOG randomized PCa trials (trials 9202, 9408, 9413, and 9910). Competing risk adjustments were used for all survival analyses for biochemical recurrence (BCR) and distant metastases.

“This meta-analysis showed that black men have lower rates of BCR and metastatic disease compared with white men,” explained Spratt.

Among black men with PCa, the rates of BCR (hazard ratio (HR), 0.82; 95% CI, 0.74, 0.92; P=0.0005) and distant metastasis (HR, 0.70; 95% CI, 0.57, 0.86; P=0.0008) were reduced, even after controlling for confounders such as age, performance status, PSA, Gleason grade, T-stage, N-
I have been waiting so long for the results of the VITAL trial (almost as long as I have been waiting for Michigan to beat Ohio State in Columbus, so hopefully by the time you read this column we accomplished this task, or else I will need a full-time therapist) that I have mentioned it at almost every lecture for years. VITAL is one of the greatest trials of vitamin D supplements (2,000 IU taken daily vs. placebo) ever conducted and it is now published in the New England Journal of Medicine. Approximately half of the participants were men and the average age was 67 years. The goal of the trial was to determine if vitamin D could prevent cancer or cardiovascular events (heart attack, stroke, or death from cardiovascular causes). There were over 25,000 participants followed a median of 5.3 years, but the researchers found no benefit of vitamin D against cancer or cardiovascular events! OUCH!

I have been saying for years to let this trial get published before you get convinced into taking more vitamin D, and now the trial has spoken but not shouted (I wish it shouted). For example, when looking at other things there appeared to be a slight non-significant reduction in deaths from cancer and even a reduction in prostate cancer risk, but these findings could have been due to luck since many other cancers were not impacted at all (breast, colorectal...). When the researchers looked at those that took vitamin D for a longer period of time, there appeared to be a reduction in cancer deaths that could be significant in that group, but again this is not what the study was designed to test. And, even if this is true, the benefits were observed primarily in normal weight individuals. There was also the suggestion that black participants might have experienced a reduction in cancer risk compared to other races in the study.

Regardless, pro-vitamin D folks will claim that these other findings are relevant and higher dosages should be tested; and anti-vitamin D folks will claim they were not relevant, and if you throw a ton of data at a wall something will stick to it (glass is always half-full rule). Regardless, there was no difference in death from all-causes between vitamin D and placebo groups (it did not help you live longer in general). What the heck should you do? Well, it appeared that 2,000 IU was as safe as a placebo and did not appear to increase the risk of prostate cancer and that is good news considering what we know now about vitamin E and selenium (SELECT trial) and the concerns over an increased risk with those supplements. Still, what received no attention was that there were more kidney stones reported in the vitamin D group (12% higher risk), but this did not reach statistical significance (close at p=0.08). It appears no benefit exists in the area of heart health at this dosage, but we need more research to determine if the anti-cancer effects could be real.

What I learned from this trial is that trying to maintain a normal weight or losing some weight not only makes you healthier but could make your pills work better, if they indeed do work! However, that is Moyad being boring again and advocating for more healthy lifestyle changes before turning toward magic pills. So, sorry, and I will now step off my soapbox sitting on top of my treadmill. Stay tuned, in the next issue we will talk about the fish oil pill results from this trial and other recent big trials! By the way, why are fish so smart? It is because they always travel in schools. “Dami!” That is what the fish said that swam into a wall.

Reference:

ADT Plus Pelvic Node RT (Continued from page 1)

Confidence Interval [CI] 0.32-0.85, P=0.014) and PBRT plus ADT (HR 0.64, 95% CI 0.39-1.06, P=0.28, not a statistically significant difference). There were 108 men with distant metastases among the nearly 1,800 patients. But Daniel Spratt, MD, of the University of Michigan, stated that, while this potential benefit has never been shown before, the three-arm trial design required a P value of less than 0.0125 to be significant. Spratt, who was not involved with the study, also cautioned that early data do not inform if giving intensive therapy for low-risk patients would be necessary. “I really think we should await longer follow-up to see if these more favorable patients benefit.”

Eric Horwitz, MD, of Fox Chase Cancer Center in Philadelphia, said that SPPORT is a modern, well-designed trial that reflects and supports how many men are treated in clinical practice. “So that’s a really big deal,” he said. “We’re pretty careful of using the data to support how we treat a person or not, and this now really fills in a piece of the puzzle,” said Horwitz, referring to the Fox Chase approach. “It’s actually a big piece of the puzzle.

“There is a group of men who do benefit from adding a short course of hormones,” he added. “And this now shows that with well-designed RT, some men actually benefit from a bigger or wider field.”

He too cautioned that while the data are not fully available, it is likely that the benefit is probably not for everybody. For men with a “superoxlow” PSA, evidence suggests that recurrence is likely confined to the prostate bed, he said. “So that’s probably a person where you can probably get away with treating the prostate bed.”

ASTRO moderator Neha Vapiwala, MD, of the University of Pennsylvania, called the study “paradigm changing,” explaining that radiation oncologists who treat prostate cancer patients have struggled with the question of whether to treat the lymph nodes or not. “It’s
There are numerous treatment options for prostate cancer (PCa) including active surveillance, chemotherapy, hormone therapy, radiation therapy (RT), high intensity focused ultrasound, cryotherapy, and surgery. That’s why it’s important for each man to consult his physician about his specific diagnosis and by shared decision-making, determine the treatment option best for him.

If RT is determined to be an appropriate treatment option, the physician, in consultation with the patient, will then decide whether to use external beam RT (EBRT), internal RT (brachytherapy), or a combination of the two. In EBRT, a machine outside the body is used to direct beams of RT focused on the prostate gland. Low-dose-rate (LDR) brachytherapy involves the permanent implantation of small radioactive seeds directly into the prostate gland, while with HDR (high-dose-rate) brachytherapy, high doses of RT are delivered via hollow catheters temporarily placed into the prostate. For some men with higher-risk, hormone therapy may also be added to the treatment regimen.

Technological innovations have significantly advanced the field of RT over the past few decades and many physicians are now using a form of EBRT called stereotactic body RT (SBRT) to treat PCa. SBRT is a type of RT used worldwide since the early 2000s that couples a high degree of targeting accuracy with high doses of extremely precise, externally delivered RT, thereby maximizing the cell-killing effect on the tumor(s) while minimizing RT-related injury in adjacent normal tissues. Treatment is generally administered in four or five sessions over one or two weeks, compared to conventional EBRT, such as intensity modulated RT, or proton therapy, that is typically delivered in 40 to 45 sessions over eight to nine weeks.

Two recently published peer-reviewed articles report on the five-year outcomes of prostate SBRT in the treatment of low- and intermediate-risk PCa. Because HDR brachytherapy has been used so successfully to treat PCa, the study investigators wanted to determine if they could achieve similar survival rates and side effect profile, but non-invasively, using SBRT. In these studies, a machine called the CyberKnife® System was used to deliver prostate SBRT. This system is unique in that it not only tracks the prostate throughout the treatment session, but it also corrects the radiation beam in real-time to account for the slightest movement, completely autonomously.

In the first SBRT study, a prospective, Phase II study, physicians at 17 institutions analyzed 259 PCa patients; 112 low-risk and 147 intermediate-risk who received a dosing regimen similar to what is delivered with HDR brachytherapy. A much greater amount of RT was delivered to the peripheral zone of the prostate, where PCa is typically located, while less RT was given centrally to spare the urethra. The entire course of RT was completed in four visits.

At five years, the disease-free survival rate for low-risk PCa patients treated with SBRT was 100% and for intermediate-risk patients was 88.5%. These results were maintained by patients followed for seven years. The five-year median serum PSA was 0.1 ng/mL for low- and intermediate-risk PCa patients and the median PSA value subsequently decreased to 0.035 ng/mL at the seven-year mark for patients followed to this time point. The lower the PSA value and the longer it continues to decline, the greater the patient’s likelihood of achieving long-term disease free survival. Patients experienced low toxicity rates despite the high SBRT dosage and heterogeneous dose distribution, with higher dosage in the peripheral zone.

In the second SBRT study, a prospective, 21 center study, 172 low-risk and 137 intermediate-risk patients were evaluated. A brachytherapy-like dose of RT was administered to the prostate gland itself, with a three to five millimeter margin of RT around the outside edge of the prostate to eradicate any microscopic cancer that could reside just outside the gland. Five-year recurrence-free survival rates were almost identical for low- and intermediate-risk patients. The five-year cancer control rate was 97.3% for low-risk PCa patients and 97.1% for intermediate-risk patients. As with the four treatment session study, the five-year median PSA was 0.1 ng/mL for all patients.

After more than five years of follow-up, serious side effects were uncommon (<2%), an incidence that compares favorably to other RT techniques, based on results from other external beam and brachytherapy studies.

There were two low-risk patients (1.2%) and two intermediate-risk patients (1.5%) who experienced grade 3 genitourinary (GU) toxicities including urinary retention, hematuria, urinary tract infection and ureteral stenosis; there were no grade 3 gastrointestinal (GI) toxicities. Additionally, there were no grade 4-5 GU or GI toxicities.

Medicare covers Prostate SBRT as do most commercial insurers. To learn more about CyberKnife, visit www.cyberknife.com. Safety information, visit: https://www.accuray.com/safety-statement/.

Editors Note: Content of this article was reviewed and edited for inclusion in the Hot SHEET, but should be recognized as information provided by Accuray Incorporated about their CyberKnife treatment. Side effects of CyberKnife treatment are usually mild and temporary, may include nausea, fatigue, and skin irritation, and may vary from patient to patient. As with any RT method, the side effects can also be severe in some patients and lead to permanent injury or even death, and results may vary from patient to patient.

References

(Continued on page 6)
Adding Radium-223 to Abiraterone No Help in Prostate Cancer (Continued from page 1)

The primary endpoint was SSE-free survival, defined as freedom from use of external-beam radiotherapy to relieve skeletal symptoms, new symptomatic pathologic bone fractures, spinal-cord compression, or tumor-related orthopedic surgical intervention.

Data analysis included 806 men, and unblinding occurred after an interim analysis showed more deaths and fractures in the radium-223 group. “All men completed study-specific treatment at that point,” Smith said. “Study procedures and treatment continued, and the protocol was amended to allow bone-targeted therapy in all men.”

The data showed a median SSE-free survival of 22.3 months in men randomized to radium-223 and 26.0 months in the placebo group (Hazard Ratio [HR] 1.12, 95% confidence interval [CI] 0.92-1.37, P=0.263, not a statistically significant difference).

Death before SSE and other primary endpoint components occurred in a similar proportion of men in each group, except for pathologic fracture, which occurred in twice as many men in the radium-223 arm. Median OS was 30.7 vs. 33.3 months in radium-223 and placebo groups, respectively (HR 1.20, 95% CI 0.95-1.50, P=0.128 not a significantly significant difference).

Analysis of TEAEs showed that fractures occurred in 103 vs. 38 men in the radium-223 and placebo groups, respectively. Independent review of men with fractures showed that 76 men in the radium-223 group had at least one fracture vs. 23 in the placebo group. All subcategories of fractures occurred more often in the radium-223 arm:

- Pathologic: 19 vs. 6
- Traumatic: 27 vs. 13
- Osteoporotic: 37 vs. 4

“Based on data from this study, the use of radium-223 combined with abiraterone is not recommended,” said Smith. “Prescribing information for radium-223 has been revised, based on these findings. Use of bone-health agents substantially reduced the risk of fracture in both treatment arms,” he noted.

Invited discussant Daniel Heinrich, MD, of Akershus University Hospital in Lørenskog, Norway, suggested that the trial “never had a chance of being positive.” He pointed out that the assumed 21-month SSE-free survival in the control arm was four to five months lower than the combination of abiraterone and prednisone achieved in a prior placebo-controlled trial. In the ERA-223 trial reported by Smith, the abiraterone-prednisone combination led to a median SSE-free survival of 26.0 months, consistent with the prior results.

Presented at the ESMO 2018 Conference, abstract LBA30.
MedPage Today
20 October 2018

Better RT Outcomes for Black Men
(Continued from page 2)

stage, and androgen depriv-ation therapy (ADT) use.

“We show that a subset of black men with PCa does have a distinct biology that may favor treatment with RT,” Spratt concluded.

“But the most important message from this presentation,” he emphasized, “is that when population registry data such as SEER show that black men have worse outcomes, this can change if the social disparities are minimized and men are analyzed in the context of a randomized clinical trial. Not only do they have potential equal outcomes, we show they have significantly improved outcomes with RT,” he added.

Dr. Den noted that the study does have limitations, such as if these data can be general-ized to the entire US and international populations. “I would argue that the answer is yes,” he said. “The difference in biology is hypothesis gener-at ing and not conclusive, and it challenges us to generate more trials to truly address these challenges.”

Den also pointed out that these data were the result of a single biopsy and, as there is significant heterogeneity in the prostate itself, it is unknown if these results would be altered if multiples sites had been used.

Presented at the 2018 annual ASTRO meeting, abstract 4
Medscape Medical News
October 23, 2018

Agent Orange Exposure Does Not Appear to Worsen Prostate Cancer Outcomes

Exposure to the defoliant Agent Orange (AO) does not appear to be associated with worse oncologic outcomes in military veterans receiving androgen deprivation therapy (ADT) for advanced prostate cancer (PCa), a large new study suggests.

“Our study is unique, as it is the first (to our knowledge) to evaluate PCa oncologic outcomes in a large cohort of U.S. veterans on ADT for advanced PCa,” stated Dr. Kyle Richards of the University of Wisconsin-Madison by email.

AO contains 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), exposure to which “has been implicated in a number of genitourinary malignancies, including cancers of the prostate, bladder, testis and kidney,” the authors note in The Journal of Urology posted online.

“TCDD is stored in fat tissue and has a half-life of about 7.5 years. Although it is not known how TCDD promotes carcinogenesis,” the authors wrote, “it probably involves interaction with the aryl hydrocarbon receptor. This protein,” they pointed out, “also interacts with the androgen receptor which is of interest given that first line treatment for metastatic PCa involves ADT.”

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ADT + Pelvic Node RT
(Continued from page 3)

a very divisive sort of question,” Vapiwala said. “What was presented here in this data are truly level 1 evidence that clearly show the separation of curves to the point that we look forward to what additional follow-up will reveal.”

From 2008 to 2015, the NRG Oncology/RTOG 0534 SPPORT trial randomized 1,792 prostate cancer patients with persistent or rising PSA levels from the U.S., Canada, and Israel to one of three treatment arms. Median patient age was 64 years and 87% were white. Nearly all (93%) had an ECOG performance status of 0.

Gastrointestinal adverse events (AEs) were significantly higher with the three-treatment regimen (grade ≥2: 6.9% versus 2.0% with PBRT alone) as were grade ≥2 (5.1% versus 2.3%, respectively) and grade ≥3 (2.6% versus 0.5%) blood-bone marrow AEs.

Men were stratified by Gleason score (7, 8-9), PSA (≥0.1 to ≤1.0 ng/mL, >1.0 to <2.0 ng/mL), and stage (pT2 and margin negative, all others). Over half the men had pT2 disease (54.3%) and positive margins (50.1%), while most had no seminal vesicle involvement (85.2%).

The primary endpoint was FFP at five years, with failure defined as an increase in PSA of 2.0 ng/mL, clinical progression, or death due to any cause.

Presented at the 2018 ASTRO meeting, abstract LBA-5.

MedPage Today
22 October 2018

New Data on RT in Prostate Cancer Are ‘Practice Changing’ (Continued from page 1)

press release. “Although outcomes have improved, men still typically die from mPCa within around five years, so there is a need for more effective treatment,” he said.

The rationale for the study was provided by animal models in which local treatment of the primary tumor not only inhibited the initiation of distant metastases, but also the progression of existing metastases,” Parker pointed out.

The STAMPEDE investigators randomized 2,061 men with newly diagnosed mPCa to standard-of-care ADT or ADT and RT. After docetaxel was approved for use in this patient population in 2015, its use was left to the discretion of the investigator. Men received lifelong ADT; docetaxel was provided at a schedule of six three-weekly cycles of 75 mg/m².

External beam RT (EBRT) to the prostate was given on a weekly (36 Gy in six fractions of six Gy) or daily (55 Gy in 20 fractions of 2.75 Gy over four weeks) schedule, which was decided before randomization. All endpoints were analyzed for the overall population and for the subpopulation of men with high and low metastatic burden.

Baseline characteristics were well balanced for patient and disease characteristics. Men were 68 years at diagnoses; PSA was 98 ng/mL; 42.5% of men had low metastatic burden, and 57.5% had high metastatic burden. Bone was the site of metastases in 89% of men; 18% of men had used docetaxel before RT.

The primary endpoint of OS was similar for men in the control group and those receiving RT (hazard ratio [HR], 0.92; P = 0.266). At three years, OS was 65% for men receiving RT and 62% for men in the control arm. OS analyzed based on the EBRT schedule showed no significant difference. “There was no evidence that effect size differed with the RT schedule. If there was a benefit, it was in men with low metastatic burden,” Parker said.

Significant improvement in OS was seen in the subgroup of men with low-burden metastatic disease (HR, 0.68; P=0.007); three-year OS rates were 73% for the control vs. 81% for the RT group. For patients with a high metastatic burden, OS was not significant, with an HR of 1.03. Three-year OS rates were 54% for the control vs. 53% for the RT group.

Parker provided a convincing rationale as to why the positive OS data in men with low metastatic burden was credible. “Our subgroup finding meets all the criteria proposed to assess credibility of subgroup effects,” he said. Among these he pointed out that low metastatic burden status was determined before randomization and before bone scans were taken; the effect was hypothesized a priori; the subgroup effect was independent of other variables tested; the subgroup effect was large; and the subgroup outcomes were consistent with other outcome measures in STAMPEDE (e.g., failure-free survival). In addition, these data mirrored data from the HORRAD study.

“It also seems plausible that the effect of local RT would be diminished in men with a greater burden of metastatic disease,” Parker and colleagues write in their published report.

RT was well tolerated. “There was a small increase in risk of bladder and bowel side effects but these were modest. The side effects are certainly outweighed by the survival benefit,” Parker said.

Commenting on the findings for ESMO, Karim Fizazi, MD, PhD, from the Gustave Roussy Institute, University of Paris Sud, France, said: “For the first time, this study provides evidence that treating the local primary tumor is associated with improvement in OS in men with mPCa and minimal disseminated disease. For men with newly diagnosed oligometastatic prostate cancer, it is quite likely that these data are practice changing,” he suggested.

Medscape Medical News
22 October 2018

Prostate SBRT Results
(Continued from page 4)

P1, “New Data...” An extremely important question in managing men with metastatic prostate cancer is whether treating the local tumor adds benefit beyond treating the metastases? Now, a large randomized trial provides some answers to that question. The STAMPEDE trial randomized men with metastases to receive androgen deprivation (ADT) alone (with or without the use of appropriate chemotherapy) or ADT plus local radiotherapy (RT). An important feature of the study design was the pre-study stratification of men into low-volume and high-volume metastases, which was defined as less than four metastatic bone sites. The study found that overall survival for the entire population was not improved by RT.

However, when the results were evaluated by extent of disease, RT did significantly improve survival in the men with low-volume metastases. Unfortunately, the improvement was relatively small. At three years, overall survival was 73% in the control arm compared to 81% in the RT arm, which translates into one man benefitting for every 12-13 receiving RT. In addition, the mean survival was improved by only three months.

While the benefit was not large, the morbidity of the therapy was low. The authors suggest that adding RT to men with low-metastatic volume should become the standard of care. It will be interesting to see the results with longer follow-up, which hopefully will improve. This finding should also encourage participation in the ongoing randomized trials for men with metastatic to assess the value of radical prostatectomy (RP), but we should not assume that the same benefit will occur.

The Bottom Line: Men with small-volume metastatic prostate cancer appear to have a small improvement in survival by adding external RT to ADT.

P1, “Nearly 90% Free...” Another recently reported RT study looked at its effect in men with a persistent or rising PSA by giving RT to the prostate bed and to the pelvic lymph nodes. This study was a three-arm randomized trial comparing prostate bed RT alone (PBRT), four to six months of ADT plus PBRT, or this combination plus RT to the pelvic lymph nodes. Although the numbers are impressive, they are not yet statistically significant. Freedom from progression (FFP) was 89% at five years in the group getting all three therapies compared to only 72% in the men getting PBRT alone. It is unclear whether all men with rising PSA do benefit or whether the added treatment of the lymph nodes is really necessary in men with a low PSA. Although more time is needed to see if the results become significant, the 17% difference seen so far may be high enough for many doctors to urge their patients to get this treatment, even though the incidence of significant side effects was greater in the group getting pelvic node RT.

The Bottom Line: The combination of PBRT, four to six months of ADT and RT to the pelvic nodes appears to result in higher progression-free survival but longer follow-up is needed to see if these results become statistically significant.

P1, “Adding Radium-223...” The concept of more is better in treating men with prostate cancer is not always true as seen in the randomized study comparing abiraterone plus prednisone with or without radium-223 for men with bone-predominant metastatic castration resistant prostate cancer. More skeletal-related events occurred in the group getting radium-223 treatment and overall survival was lower. One criticism of the study is that the assumption of the study in terms of the likelihood of not progressing was incorrect, so the study design had little chance of succeeding. Regardless, finding that the men receiving radium-223 had a higher failure rate still means that radium-223 should not be used in this setting. In addition, results indicate that another trial to make that conclusion is not required.

The Bottom Line: Radium-223 should not be combined with abiraterone and prednisone in men with bone-predominant metastatic castration resistant disease.

P2, “Better Outcomes...” Doctors have recognized that African-American men have a greater risk of dying from prostate cancer than other ethnic groups. People have debated how much was due to biology vs. other factors such as access to therapies. Now, a new randomized study has found that African-Americans have a better outcome from RT after adjusting for biological differences. This means that treatment does not need to be modified when treating African-American men.

The Bottom Line: RT therapy is not less effective in African-American men.

P5, “Agent Orange Exposure...” Since the Vietnam War, many people have been concerned about the carcinogenic effects of men exposed to Agent Orange. It has been thought to be an increased risk factor for genitourinary cancers. In this retrospective analysis of men diagnosed between 2000 and 2008 with advanced disease and treated with ADT, survival actually was higher in the men exposed to this chemical. This is not to suggest any benefit from this product but rather it means that exposure to it should not result in any changes to therapy.

The Bottom Line: Men exposed to Agent Orange who require treatment for advanced prostate cancer should receive the same treatment as men who were not exposed to this chemical.

Editor’s Note: Us TOO has invited 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.
Agent Orange Exposure Does Not Appear to Worsen Prostate Cancer (Continued from page 5)

The study used a U.S. Department of Veterans Affairs (VA) database to identify more than 87,000 men who were diagnosed with advanced PCa from 2000 to 2008 and received ADT. Of those, 4% had documented AO exposure during military service. AO-exposed men had significantly lower PSA levels at both diagnosis and at initiation of ADT. The AO-exposed group survived longer than the non-exposed group (medians 82.6 months vs. 64.2 months; P <0.001). Multivariable analysis adjusting for age, race, finasteride use, type of ADT, CCI, year of diagnosis, PSA, Gleason score, docetaxel use and local therapy also found significantly improved survival among exposed veterans.

Antiandrogen use alone was significantly associated with worse survival. The report highlights limitations in the study, including an inability to quantify AO exposure. “Physicians treating Agent Orange-exposed men with PCa should treat them similarly to men with PCa that were not exposed to Agent Orange,” Dr. Richards advised. “They can counsel patients exposed to Agent Orange that their cancer is not necessarily more aggressive and that treatment should be individualized based on their stage and grade of cancer.”

Dr. Martha K. Terris, chief of urology at the Medical College of Georgia at Augusta University, stated, “This study suggests that men with Agent Orange exposure have similar results to treatment with hormone therapy for PCa as those without Agent Orange exposure. While this is an interesting finding, it in no way suggests that Agent Orange should not be considered a potential contributor to poor PCa outcomes. “In this study, the group of men without Agent Orange exposure were a median age of 75 years as opposed to 60 years for the Agent Orange-exposed patients,” she continued. “This age difference is very significant. The study participants lived approximately seven years after starting hormone therapy regardless of exposure history. Therefore, men in the unexposed group actually lived about their normal life expectancy after starting treatment,” added Dr. Terris, who was not involved in the research. “However, the Agent Orange-exposed men, since they developed incurable cancer at a much younger age, lost almost 15 years from their life expectancy.”

“While the U.S. Department of Veterans Affairs has received a tremendous amount of bad press lately, VA providers have been exceptional in encouraging screening for PCa in young veterans exposed to Agent Orange,” she said. “I am concerned that studies erroneously suggesting Agent Orange may not be a risk factor for poor PCa prognosis could reduce enthusiasm for PCa screening in these potentially high-risk individuals.”

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This Season, Give the Gift of Hope...
We want to wish everyone a great holiday season and would like to ask you to consider contributing to the Us TOO Holiday Hope campaign. Funds raised will help Us TOO provide the prostate cancer community with educational resources and support services at no charge. Please donate to empower others with knowledge and share the gift of hope.

Please donate at: www.ustoo.org/DonateHope

Thank you for your support!
QUESTION FROM PROSTATE CANCER SURVIVOR:

After my surgery, I was surprised to find that I had an orgasm even though I did not have any erection at all. Is there any problem with having an orgasm without an erection?

RESPONSE FROM DR. JEFFREY ALBAUGH:

Although it may seem strange because you have always had an erection along with orgasm, most men will experience the orgasm/climax sensation even in the complete absence of an erection after sufficient sexual stimulation. After radical prostatectomy, you will no longer ejaculate fluid because the ejaculate came from the prostate and seminal vesicles which have been removed. Different peripheral (local) nerves control the orgasm sensation as opposed to the nerves for erections. The nerves for climax sit further away from the prostate and are less impacted by the surgery since they are not typically directly manipulated during the prostate removal.

It may take some time for healing after surgery to fully experience the orgasm/climax sensation. One study of men with bilateral nerve sparing showed improvement up to 48 months post op, with the best improving mean outcomes orgasm sensation at 24-48 months (Salonia, A. et al., 2010). In a study of 408 men who had robotic bilateral nerve sparing radical prostatectomy, 90.7% were able to achieve orgasm compared to 82.1% of men who had unilateral nerve sparing and 60.8% of men who had non-nerve sparing surgery (Tewari, A. et al., 2011). Sensation was reported better by men 60 years old or younger than by older men. In my experience with men and our unpublished research of men followed for 2 years after nerve sparing radical prostatectomy, almost all men can experience the orgasm sensation. The majority of our men either describe it as different/diminished or similar to the pre-surgical orgasm/climax sensation. A small percentage of men have a more intense climax after prostatectomy. There is no problem with having an orgasm with no erection or a partial erection. It is difficult to not compare it to your memory of pre-surgery orgasm intensity, but to fully enjoy the sexual experience and orgasm you need to be fully present (and not comparing in your mind).

As you continue to recover after radical prostatectomy, you may find it helpful to be completely open and present during your sexual experiences to enjoy each sensation and pleasurable feeling. Anxiety can impact your erections and your ability to climax, so try and keep your mind directed to sex and pleasure. Being completely present experiencing every nuance of the sexual encounter may help you enjoy sex more fully.


You can access the new edition of my book or download a free copy of my original book at www.drjeffalbaugh.com.

Do you have a question about sexual health or intimacy? If so, we invite you to send it to Us TOO. We’ll select questions to feature in future Between the Sheets columns.

Please email your question to: ustooBTS@ustoo.org

Or mail your letter to:
Us TOO International
Between the Sheets
2720 S. River Road, Suite 112
Des Plaines, IL 0018
As the year comes to a close, please consider making a donation to help Us TOO International provide educational resources, support services and personal connections within the prostate cancer community through our:

- Network of more than 200 support groups across the country and abroad
- Inspire online prostate cancer communities (UsTOO.inspire.com)
- Toll-free Us TOO Prostate Cancer HelpLine (1-800-808-7866); including connecting callers with similar survivors for peer-to-peer conversations and support
- Monthly Hot SHEET newsletter and monthly News You Can Use updates and articles
- Support group meetings/services and telephone support groups including A Forum for Her
- New website content on sexual health and intimacy, erectile dysfunction, and urinary incontinence
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Your gift and the work we do together matters now more than ever. There are nearly 3 million men in the U.S. living with a prostate cancer diagnosis. That number is estimated to climb to 4 million by 2024 as men in the baby boomer generation age. Every one of those men and his loved ones will need access to education and support to make informed decisions on the best approach to minimize the impact of the disease and maximize the quality of life.

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Thank you!