Salvage Radiation Therapy First Found Superior for Post-RP PSA Failure

Salvage radiation therapy (SRT) prior to salvage hormone therapy (SHT) is more beneficial than SHT alone for men with PSA failure after radical prostatectomy (RP), according to results of a Japanese clinical trial published online in *European Urology*. Biochemical recurrence in the absence of evidence of tumor presents a quandary because it is unknown whether patients harbor local or metastatic disease. The former benefits more from SRT and the latter from SHT, most commonly androgen deprivation therapy (ADT).

In a phase 3 trial (JCOG0401), investigators randomly assigned 210 Japanese men with localized prostate cancer (PCA) whose PSA levels increased (*biochemical recurrence, BCR*) to 0.4 to 1.0 ng/mL after RP to receive SHT (80 mg bicalutamide, followed by luteinizing hormone-releasing hormone [LHRH] agonist if bicalutamide failed) or SRT (64.8 Gy to the prostatic bed, followed by the same hormone regimen if radiation failed).

“The time to bicalutamide failure, the primary end point, was significantly longer in the SRT group: 8.6 vs. 5.6 years,” Seiji Naito, MD, PhD, of Harasanshin Hospital in Fukuoka, Japan, and colleagues reported. In addition, 31% of men in the SRT group were successfully treated with RT and required no SHT. Overall, clinical relapse-free survival and overall survival did not differ between the SRT and SHT arms.

Even with recent advances in RP and imaging technologies, such as choline positron emission tomography (PET)/CT and prostate-specific membrane antigen-based PET/CT, the results

(Continued on page 4)

Tailored Pelvic Physical Therapy May Curb Postprostatectomy Stress Incontinence and Pain

“After radical prostatectomy (RP), individualized pelvic physical therapy (PT) to relax or strengthen the pelvic muscles may be more effective for reducing stress urinary incontinence (SUI) and pelvic pain than muscle strengthening alone,” said Gary Lemack, MD, of UT Southwestern Medical Center in Dallas, TX.

“Managing incontinence requires more than just pelvic floor muscle exercises,” he stated. “...If these exercises are unsuccessful, referral to a comprehensive pelvic floor program for a more patient-specific approach is recommended to enhance recovery of bladder function.”

The study was a retrospective chart review of 136 men (mean age, 66) with post-RP SUI treated with pelvic PT: 25 had underactive pelvic floor dysfunction (PFD) requiring only uptraining (strengthening) treatment; 13 had only overactive PFD and were treated with downtraining (relaxation); and 98 had mixed-type PFD with components of both underactivity and overactivity, and were treated with both up- and downtraining.

As reported online in *International Urology and Nephrology*, those with uptraining, as well as those with downtraining, showed significant improvement in the number of pads used per day; decreased pelvic pain on a nu-
Patient-Reported Outcomes Through Five Years for Active Surveillance, Surgery, Brachytherapy or External Beam Radiation With or Without Androgen Deprivation Therapy for Localized Prostate Cancer


JAMA 323: 149-163, 2020

Importance: Understanding adverse effects of contemporary treatment approaches for men with favorable- and unfavorable-risk localized prostate cancer (prostate cancer) could inform treatment selection.

Objective: To compare functional outcomes associated with prostate cancer treatments over five years after treatment.

Design, Setting, and Participants: Prospective, population-based cohort study of 1,386 men with favorable-risk (clinical stage cT1 to cT2bN0M0, PSA ≤20 ng/mL, and Grade Group 1-2) prostate cancer and 619 men with unfavorable-risk (clinical stage cT2cN0M0, PSA of 20-50 ng/mL, or Grade Group 3-5) prostate cancer diagnosed in 2011 through 2012, accrued from five Surveillance, Epidemiology and End Results Program sites and a US Prostate cancer registry, surveyed until September 2017.

Exposures: Treatment with active surveillance (AS; n=363), nerve-sparing radical prostatectomy (RP; n=675), external beam radiation therapy (EBRT; n=261), or low-dose-rate brachytherapy (LBR-BT; n=87) for men with favorable-risk disease and treatment with RP (n=402) or EBRT with androgen deprivation therapy (ADT; n=217) for men with unfavorable-risk disease.

Main Outcomes and Measures: Patient-reported function, based on the 26-item Expanded Prostate Index Composite (range, 0-100), five years after treatment. Regression models were adjusted for baseline function and patient and tumor characteristics. Minimum clinically important difference was 10 to 12 for sexual function, 6 to 9 for urinary incontinence, 5 to 7 for urinary irritative symptoms, and 4 to 6 for bowel and hormonal function.

Results: A total of 2,005 men met inclusion criteria and completed the baseline and at least one postbaseline survey (median [interquartile range] age, 64 [59-70] years; 1,529/1,993 [77%] subjects were non-Hispanic white). For men with favorable-risk prostate cancer, nerve-sparing RP was associated with worse urinary incontinence at five years (adjusted mean difference, -10.9 [95% Confidence Interval [CI], -14.2 to -7.6]) and sexual function at three years (adjusted mean difference, -15.2 [95% CI, 18.8 to -11.5]) vs. AS. LDR-BT was associated with worse urinary incontinence (adjusted mean difference, -7.0 [95% CI, -10.1 to -3.9]), sexual (adjusted mean difference, -10.1 [95% CI, -14.6 to -5.7]), and bowel (adjusted mean difference, -5.0 [95% CI, -7.6 to -2.4]) function at one year vs. AS. EBRT was associated with urinary, sexual, and bowel function changes that were not clinically different from AS at any time point through five years. For men with unfavorable-risk disease, EBRT with ADT was associated with lower hormonal function at six months (adjusted mean difference, -5.3 [95% CI, -8.2 to -2.4]) and bowel function at one year (adjusted mean difference, -4.1 [95% CI, -6.3 to -1.9]), but better sexual function at five years (adjusted mean difference, 12.5 [95% CI, 6.2-18.7]) and incontinence at each time point through five years (adjusted mean difference, 23.2 [95% CI, 17.7-28.7]), than RP.

Conclusions and Relevance: In this cohort of men with localized prostate cancer, most functional differences associated with contemporary management options attenuated by five years. However, men undergoing RP reported clinically meaningful worse incontinence through five years vs. all other options, and men undergoing RP for unfavorable-risk disease reported worse sexual function at five years compared with men who underwent EBRT with ADT.

Meaning: These estimates of the long-term bowel, bladder and sexual function after localized prostate cancer treatment may clarify expectations and enable men to make informed choices about care.
Doc Moyad’s What Works & What is Worthless Column – Also Known as “No Bogus Science” Column

“Resistance Training to Reduce Caliente Flashes/Flushes?!”

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.

We always need to look outside of prostate cancer to seek what is new and interesting in the world of research as it pertains to dealing with the side effects of treatment. Hot flashes (or flashes) are one of the most common and annoying side effects of androgen deprivation therapy (ADT) and the problem with treating them conventionally (aka “drugs”) is that when something works then there is a major catch in many cases and health care professionals struggle with recommending or discouraging these options. Thus, people have always been interested in lifestyle changes and over the counter (OTC) pills or supplements to reduce the frequency and/or intensity of the flash (or is it “flush”? ). However, many of the OTC products come with their own list of issues that I will not comment upon. Therefore, the interest in lifestyle changes are of constant interest. Find a way to impact them through diet or exercise then you have a big winner, but the data has been very controversial so far, or has it?

In breast cancer or in studies of post-menopausal women, there are some potential hints or a compass as to how we should be studying this issue in men with prostate cancer on ADT. Recently, a small randomized trial (n=65) from Sweden found something quite interesting. It appears in women with moderate or severe hot flashes resistance training just three times a week for 15 weeks reduced the frequency of hot flashes by 44% (almost half of the group reported over a 50% decrease). There was no significant change in the control group.

Participants in the intervention group performed the following exercises each session: chest press, leg press, leg curl, leg extension, seated row, crunches, back raises, and latissimus dorsi pull-down (aka “lats”- I hate those things because every few weeks I accidentally hit the bar with my head, which probably explains my inability to remember my in-laws birthdays etc.). Anyhow, is it possible that the body may release some compounds, such as beta-endorphin, during intense or vigorous exercise that positively impacts the brain’s temperature center unlike less intense exercises?

Maybe, but who really cares! What? Yeah, I said it! I care, but what I really care about is the potential cumulative impact of resistance training in women and men. It reduces bone loss, prevents adipose tissue gain, reduces fatigue, increases strength, tones the body, increases metabolism, reduces risk of falls, reduces insulin resistance, improves heart health, sexual health, mood, blah blah blah and now, perhaps, could reduce hot flashes! In other words, the plethora of potential benefits of resistance training just two-three times a week continues to amaze me, and it should be mandatory (not suggested) for anyone getting a little older (or on ADT). Caliente flashes (I was traveling in Mexico when I wrote this piece so give me a break Damas and Caballeros) are not fun. But perhaps it is time to give resistance training a try? Si! Adios!

References:

Effect of Extended Pelvic Lymph Node Dissection on Oncologic Outcomes in Patients with D’Amico Intermediate- and High-Risk Prostate Cancer Treated with Radical Prostatectomy: A Multi-Institutional Study


J Urol 203: 338-343, 2020

Purpose: Pelvic lymph node dissection (PLND) represents the gold standard of lymph node staging in patients with prostate cancer. We sought to assess the effect of extended PLND on oncologic outcomes in patients with characteristics of D’Amico intermediate- or high-risk prostate cancer treated with radical prostatectomy (RP).

Materials and Methods: In a multi-institutional database of four centers, we identified 9,742 patients who underwent RP from 2000 to 2017, with or without PLND. Only patients with a greater than 5% probability of lymph node invasion according to the Briganti nomogram were included in study. We performed 2:1 propensity score matching to account for potential differences between the two cohorts. Cox regression models were used to test the effect of PLND on biochemical recurrence (BCR), metastasis and cancer specific mortality.

Results: Overall 707 patients (7.3%) did not undergo PLND, of whom 520 and 187 harbored D’Amico intermediate- and high-risk prostate cancer treated with radical prostatectomy (RP). PLND cohort and 1,714 of these cases (19.0%) harbored D’Amico intermediate or high risk character-istics revealed that there was no significant difference between the two cohorts. Cox regression models were used to test the effect of PLND on biochemical recurrence (BCR), metastasis and cancer specific mortality.

Conclusions: There was no significant difference in oncologic outcomes in patients with D’Amico high or intermediate risk prostate cancer in whom PLND was or was not performed at RP. The therapeutic value of PLND remains unclear.
Given the results of the CARD trial, “it would seem that men treated with androgen-signaling inhibitors before the development of castration-resistant prostate cancer are not likely to benefit from this class of drugs if used subsequently,” they state.

“The CARD trial... shows that cross-resistance between agents targeting the androgen receptor is a factor that is likely to have a substantial effect on the planning of future research examining systemic treatments in patients with this disease,” they also suggest.

The CARD trial was conducted in 255 men with mCRPC. The median age of the cohort was 70 years, but almost one third of the patients were 75 years of age or older. All patients had received first-line treatment with docetaxel and an androgen-signaling-targeted inhibitor (either abiraterone or enzalutamide), but they showed evidence of rapid disease progression.

They were randomly assigned to receive second-line treatment with either cabazitaxel or abiraterone or enzalutamide. Cabazitaxel was administered at a dose of 25 mg/m² intravenously every three weeks with oral prednisone, 10 mg a day. Men in the cabazitaxel group were also premedicated with an antihistamine, dexamethasone, and a histamine2-receptor antagonist. Prophylactic granulocyte colony-stimulating factor was given before each cycle. In the other arm, patients received either oral abiraterone, 1000 mg/day, plus oral prednisone, 5 mg twice a day, or oral enzalutamide, 160 mg/day, repeated every three weeks.

Patients received treatment until there was evidence of disease progression or unacceptable toxic effects occurred.

“The primary endpoint of the study was imaging-based PFS, often referred to as radiographic PFS, although they are not exactly the same thing,” the authors comment. The study was designed to address a number of secondary endpoints as well.

“At a median follow-up of 9.2 months, the median imaging-based PFS was 46% longer in the cabazitaxel group, at eight months, compared with 3.7 months in the androgen-signaling-inhibitor group (P <0.001),” the study authors report. “The vast majority of patients in both arms experienced disease progression by study endpoint, but the median PFS rate was 4.4 months in the cabazitaxel arm vs. only 2.7 months in the androgen-signaling-inhibitor arm (P <0.001),” they add.

All secondary endpoints were also better among patients treated with cabazitaxel compared with those who received either abiraterone or enzalutamide. For example, median OS was 36% longer, at 13.6 months, in the cabazitaxel group, vs. 11 months in the abiraterone or enzalutamide arm.

PSA response was not available for all patients, but among those for whom it was measured, the results favored the chemotherapy group: 35.7% of cabazitaxel patients experienced a reduction in PSA levels of at least 50% from baseline, compared to only 13.5% of patients in the androgen-signaling-inhibitor group (P <0.001).

“Among patients with measurable disease at baseline, the percentage of patients with a tumor response was 37% with cabazitaxel and 12% with an androgen-signaling-targeted inhibitor (p=0.004),” de Wit and colleagues observe.

Pain response was not evaluated in all patients, but among those for whom it was, the results showed a confirmed pain response in 45% of those treated with cabazitaxel, compared with 19.3% of those treated with either abiraterone or enzalutamide.

More than half of patients in the androgen-signaling-inhibitor group were estimated to have experienced a symptomatic skeletal event at 18 months, compared to slightly more than one quarter, at approximately 29%, of those who received cabazitaxel.

In contrast, the incidence of serious adverse events of any grade was virtually identical in both groups, at 38.9% in the cabazitaxel group vs. 38.7% for those treated with either abiraterone or enzalutamide.

Importantly, there was more crossover in the androgen-signaling-inhibitor group — 33% of these patients crossed over to receive cabazitaxel, compared to about 23% of cabazitaxel patients who crossed over to abiraterone or enzalutamide.

“Thus, the fact that cabazitaxel reduced the risk for death from any cause by 36% compared with either abiraterone or enzalutamide despite the high crossover is perhaps all the more remarkable,” the authors comment.

Medscape Medical News
26 December 2019
More Veggies No Help in Active Surveillance
Findings Call Into Question Guideline-Recommended Dietary Advice

Eating more vegetables during active surveillance (AS) for early-stage prostate cancer (PCA) failed to reduce disease progression, results of a randomized trial showed. “Among nearly 500 men in the MEAL study, those told to consume seven or more servings of vegetables per day had a similar time to progression as a control group that received usual dietary advice (adjusted Hazard Ratio [HR] 0.97, 95% confidence interval [CI] 0.76-1.25),” reported J. Kellogg Parsons, MD, MHS, of UC San Diego Moores Comprehensive Cancer Center in La Jolla, CA, and colleagues.

As outlined in JAMA (Vol. 323, pp. 140-148, 2020), 43.5% of those in the intervention arm were free of disease progression at two years—defined as a PCA increasing to 10 ng/mL or above, a doubling of PSA in under three years, or tumor upgrading on biopsy—vs. 41.4% of the control arm, a non-significant difference.

At the two-year follow-up biopsy, 89.9% were free of tumor upgrading in the intervention arm vs. 90.2% of men in the control arm, also a non-significant difference.

“The behavioral intervention in this study produced robust, sustained increases in carotenoid, cruciferous-rich, and leafy green vegetable intake for two years, but did not significantly reduce the risk of clinical progression,” Parsons’ group wrote. “These data fail to support prevailing assertions in evidence-based clinical guidelines and the popular media that diets high in micronutrient-enriched vegetables improve cancer-specific outcomes among prostate cancer survivors.” By one year, the intervention group reported increases in their average daily vegetable consumption (2.43 vs. 0.45 servings), cruciferous intake (43.10 g vs. 6.44 g), and total carotenoids (13,839.31 µg vs. 2,030.79 µg, P<0.001 for all), with plasma carotenoids measured at one year confirming these self-reported data. And these gains were sustained at two years.

Clinical guidelines, based largely on expert opinion and observational data, suggest that diets high in vegetable consumption could reduce the risk for prostate cancer progression or death. Yet findings from a number of trials—testing vitamin E, C, and selenium, fish oil, and now MEAL, among others—have failed to show improved cancer outcomes with dietary interventions. “Enthusiasm for diet-based cancer interventions remains high, driven by assumptions of causality made from epidemiological data,” Parsons’ team asserted. “The overdependence of PCA nutrition guidelines on observational studies with uncertain clinical validity suggests a need to shift nutritional research toward definitive randomized clinical trials.”

From 2011 to 2015, the MEAL (Men’s Eating and Living) study randomized 478 men ages 50 to 80 with early prostate adenocarcinoma across 91 clinics in the U.S. to a telephone intervention (n=237) recommending the consumption of seven or more vegetables per day or to usual care (n=241), consisting of written information on PCA and diet.

Participants had an average age of 64 years, and most were white (80%). Men were excluded if they had clinical disease stage greater than cT2a or a PSA level of 10 ng/mL or above (mean PSA was 4.9 ng/mL).

The authors concluded that the “findings do not support use of this intervention to decrease PCA progression in this population,” but cautioned that the trial “may have been underpowered to identify a clinically important difference.”

Pelvic Physical Therapy (Continued from page 1)

Dr. Andrew Albright, a physical therapist at The Ohio State University Comprehensive Cancer Center — Arthur G. James Cancer Hospital and Richard J. Solove Research Institute in Columbus, agreed with the study’s findings. “From what I have seen within this specific patient population, performing strengthening exercises (Kegels) with an overactive and guarded pelvic floor can actually be counterproductive.”

“With most surgeries, the immediate and surrounding regions can become weak, but can also become guarded and overactive, leading to further dysfunction,” he said. “We need to treat and correct these dysfunctions to (restore) optimal function to improve the quality of lives of our patients.”

“It would definitely be beneficial to have randomized, controlled trials [conducted] in the future.”

Reuters Health Information
13 January 2020

Other limitations cited included the possibility for tumor misclassification at baseline, inconsistent use of MRI-guided biopsy, and the lack of gene testing to determine whether AS was indeed an appropriate treatment course.

MedPage Today
14 January 2020
Anterior-Dominant Prostate Cancer Harder to Detect Than Other Locations

Anterior-dominant prostate cancer is harder to detect and presents with higher prostate-specific antigen (PSA) levels than prostate cancer in other locations, according to a database study published online January 3rd in *Prostate Cancer and Prostatic Diseases*.

About 10%-25% of prostate cancers show anterior predominance. Cancers in this location tend to be underdiagnosed at biopsy and undergraded when detected.

Dr. Cristina Magi-Galluzzi of the University of Alabama at Birmingham and colleagues contrast the pathological features and clinical outcomes of 132 men with anterior-predominant prostate cancer (APCA) and 353 matched men with posterior-predominant prostate cancer (PPCA), all of whom had been treated with radical prostatectomy for localized prostate cancer.

PSA at diagnosis was slightly higher among men with PPCA (6.4 ng/mL) than among men with PPCA (5.6 ng/mL), and significantly more men with APCA (19.7%) than with PPCA (13.0%) presented with a PSA greater than 10 ng/mL.

Significantly fewer men with APCA (10.1%) than with PPCA (23.2%) had abnormal digital rectal examination at diagnosis, and surgical upgrading was more common in men with APCA than in those with PPCA 55.3% vs. 42.0%, P=0.015, the researchers report in *Prostate Cancer and Prostatic Diseases*.

Despite these differences, “freedom from biochemical failure” at three and five years did not differ significantly between men with APCA (90.1% and 85.1%, respectively) and men with PPCA (91.9% and 82.9%). “These results suggest that there are no significant differences in clinical outcomes in APCA compared to PPCA following prostatectomy, despite the diagnostic challenges of detecting these tumors with conventional prostate biopsy templates,” the authors conclude.

*Reuters Health Information 22 January 2020*

Impact of MRI and Targeted Biopsies on Eligibility and Disease Reclassification in MRI-Positive Candidates for Active Surveillance on Systematic Biopsies


To assess the impact of concomitant targeted biopsies (TB) for predicting final disease reclassification in MRI-positive low-risk prostate cancer patients eligible for active surveillance (AS) on systematic biopsies (SB).

From a prospective database, we included all pre-biopsy MRI-positive men fulfilling AS criteria at diagnosis [Toronto [n=114], UCSF [n=82], or PRIAS [n=60] criteria] on SB. All patients underwent a combination of SB and software-based fusion TB, and an immediate radical prostatectomy (RP). The primary endpoints were the pathological upgrading on final pathology and upstaging rates.

Biopsy grade group was upgraded to grade group ≥3 in 65.9%-76.7% and in 12.2-16.7%, respectively. The rate of grade group ≥3 in RP specimens varied from 31.6% to 43.3% with no relation between strictest criteria and lower upgrading rates. The proportion of not organ-confined disease (35%-39%) was comparable among the AS cohorts. Negative TB was strongly associated with the absence of final grade group ≥3. Tumor grade on TB was significantly correlated with the risk of final grade group ≥3 in both Toronto and UCSF cohorts, not in the PRIAS cohort. In the PRIAS cohort, the only significant independent predictive factor for grade group ≥3 was disease in any core (p=0.034).

In MRI-positive patients, the risk of disease reclassification was comparable whatever the SB-based AS criteria used. TB were predictive of final upgrading, with a varied impact according to the AS criteria. SB features remained relevant for reclassification prediction even in case of positive TB. The risk of upstaged disease remains important, approximately one third, and neither target-ed/systematic biopsy parameters nor MRI findings could accurately predict it.

Check out Us TOO web pages on maximizing quality of life after prostate cancer treatment:

Sexual Health/Intimacy & Erectile Dysfunction at
www.ustoo.org/intimacy

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www.ustoo.org/incontinence
Family history and specific heritable factors significantly impact the risk of developing clinically-aggressive prostate cancer. While this seems intuitive, it is remarkable how far our understanding of this has lagged behind similar research in breast and ovarian cancer. There are still many questions relevant to prostate cancer that remain unanswered, but cancer genetics is beginning to enter into the routine clinical care of men with prostate cancer, and it is imperative that providers caring for prostate cancer patients become comfortable with the salient issues.

Genetic Risk
Germline (genetic material that you are born with/inherited and have your entire life) mutations in BRCA1, BRCA2, ATM, Lynch Syndrome genes and others confer known autosomal (a chromosome that is not a sex chromosome) dominant cancer predisposition, leading to a substantially increased lifetime risk of developing a number of malignancies. The discovery of breast cancer susceptibility genes 1 and 2, in particular, was a major breakthrough in cancer research and has provided a framework for the practice of clinical genomics. BRCA1 and BRCA2 proteins are important in the recognition of, response to, and repair of double-strand DNA breaks through a process known as homologous recombination. BRCA1 and BRCA2 belong to a larger class of genes referred to as DNA damage response genes, and mutations in these DDR genes cause genetic instability that leads to a high risk of malignant transformation.

Prostate cancer is now recognized as a component of the hereditary breast and ovarian cancer (HBOC) syndrome, which is most often associated with BRCA mutations and classically characterized by a significant family history of breast and ovarian cancers. The risk of prostate cancer has been reported as high as 3.8-fold for men who carry BRCA1 mutations and up to 8.6-fold for men who carry BRCA2 mutations. Furthermore, BRCA2 mutations have been clearly associated with early onset and more aggressive prostate cancer. In a seminal study published in the New England Journal of Medicine, Pritchard and colleagues showed that 11.8% of men with metastatic prostate cancer harbored germline mutations in DDR (DNA damage repair) genes, with greater than 50% of the mutations occurring in BRCA1 or BRCA2. This was a remarkable finding as it showed both that the rate of these genetic mutations is much higher than previously thought, and that the presence of these mutations is far more common in patients with metastatic than localized cancer.

Clinical Risk Assessment for BRCA Testing
Who should undergo genetic testing? There are multiple organizations that provide genetic testing guidance. The NCCN (National Comprehensive Cancer Network), recognizing the importance of germline mutations, now includes recommendations for prostate cancer genetic testing in their Genetic/Familial High-Risk Assessment: Breast and Ovarian Guidelines. These guidelines recommend germline genetic testing in men who have a personal history of Gleason score ≥7 prostate cancer with at least 1 close blood relative (first, second, or third degree) and breast cancer diagnosed at age ≤50 years, ovarian cancer, pancreatic cancer or metastatic prostate cancer at any age; or 2 relatives with breast, pancreatic or prostate cancer; or individuals with Ashkenazi Jewish ancestry. Men with metastatic prostate cancer also meet NCCN criteria for consideration of BRCA1/2 genetic testing even without a family history.

The NCCN Prostate Cancer Early Detection Guidelines suggest screening beginning at age 40 years for men with BRCA1/2 mutations. However, it is important to recognize that this is a nuanced and rapidly changing field with a number of different guidelines, all primarily based on expert opinion. The Philadelphia Consensus Conference of 2017 published additional recommendations regarding the management of germline mutations in prostate cancer, and additional recommendations are forthcoming from the most recent consensus conference held this past October.

The role for dedicated and early screening in men with germline mutations predisposing to prostate cancer is also being evaluated in the University of Michigan Prostate Cancer Risk Clinic (https://www.rogelcancercenter.org/cancer-genetics/prostate-cancer-risk-clinic). In this clinic men who are known carriers of germline pathogenic (of a bacterium, virus, or other microorganism causing disease) mutations related to prostate cancer (e.g. BRCA1/2) are offered PSA screening and digital rectal exam starting at age 35, with a low PSA threshold for biopsy. This screening is combined with additional urine biomarker testing (SelectMDx™) with the objective of better defining the role for intensified risk-based prostate cancer screening in the United States. A similar study is open at the National Institutes of Health (NIH) Clinical Center in Bethesda, MD, with the addition of prostate MRI as part of the screening process (NCT03805919: https://clinicaltrials.gov/ct2/show/NCT03805919). Biopsies are performed for PI-RADS 3 or greater lesions, PSA 2.0 ng/mL for men under 50 years and 2.5ng/mL for men 50 years and older.

Management Implications
Patients with BRCA2 mutations have been shown in multiple studies to have more aggressive cancer and decreased survival compared to patients with sporadic disease, yet the clinical implications still require substantial investigation. For instance, the safety of active surveillance in these patients has yet to be defined and some of these patients may still be eligible for surveillance. In the metastatic setting, there is increasing-ly strong evidence regarding the role of PARP (substance that blocks an enzyme in cells called PARP, which helps cancer progress) inhibitors and platinum-based chemotherapy in patients with DDR mutations. Because PARP-inhibitors target the DNA replication machinery, tumors with homologous repair deficiencies are uniquely sensitive to PARP inhibition, a phenomenon termed synthetic lethality.

While no PARP inhibitors have been approved by the FDA for prostate cancer treatment as of yet, both olaparib and rucaparib have received FDA breakthrough therapy designations for mCRPC patients with BRCA1 or BRCA2 alterations. Results of multiple prospective randomized controlled trials assessing PARP-inhibitors in mCRPC patients with DDR alterations are pending. For example, the PROFOUND study was recently presented but is not yet published. This trial randomized mCRPC patients with DDR alterations to olaparib or the physician’s choice of abiraterone or enzalutamide, and olaparib was reported to be associated with a significant improvement in progression-free survival.

Conclusion
Men with specific germline mutations are more likely to be diagnosed with and die of prostate cancer. This is a changing landscape, and knowledge of which patients should be counseled regarding genetic testing is increasingly important. Gaining comfort with the basic concepts of genetic counseling is critical, and working in collaboration with genetic counselors will help ensure that men with prostate cancer are receiving the best care possible. While our understanding of how these mutations should alter screening and treatment of prostate cancer is still evolving, critical answers are likely coming over the next few years.
Tumor-Associated Release of Prostatic Cells Into the Blood After Transrectal Ultrasound-Guided Biopsy in Men with Histologically Confirmed PCAs


Background: Transrectal ultrasound-guided prostate biopsy (TRUS) is a standard procedure for prostate cancer (PCa) diagnosis. Because PCa is a multifocal disease in many men, multiple sampling (n ≥ 10) is required, which may bear the risk of systemic spread of cancer cells.

Design: Using the standardized CellSearch® system that allows for the detection of single epithelial cell adhesion molecule-positive circulating tumor cells (CTCs) in blood, we investigated whether prostate biopsy is associated with release of prostatic tumor cells into the circulation. Peripheral blood was obtained before and within 30 minutes of performing prostate biopsy from 115 men with increased serum PSA.

Results: The number of CTCs significantly increased after biopsy in men with histologically confirmed PCa (odds ratio, 7.8; 95% CI, 4.8-12.8), whereas no biopsy-related changes could be detected in men without confirmed PCa. Multivariable analysis showed that biopsy-related increase of CTCs was significantly correlated with a worse progression-free survival (hazard ratio, 12.4; 95% CI, 3.2-48.6) within the median follow-up of 41 months.

Conclusions: Prostate biopsies may lead to a tumor-associated release of CTCs into the blood circulation. Larger confirmatory trials with longer follow-up periods are required before any change in clinical practice can be recommended.

Salvage RT or HT
(Continued from page 1)

of this study contribute “significant clinical evidence regarding treatment of PCa,” Dr. Naito’s team stated. They explained that the newer PET/CT modalities have limitations in patients with BCR when the PSA is <1.0 ng/mL.

“Our results demonstrated that SRT may be feasible for men with post-RP PSA failure even if we do not have a histological proof of local recurrence.” Dr. Naito and colleagues wrote.

“Administration of early SRT made it possible for some men with treatment failure in our study to avoid SHT.”

Overall, the most common grade 3 to 4 adverse event was erectile dysfunction: 80% vs. 74% in the SHT and SRT groups, respectively.

Study limitations include the short follow-up and surrogate end point.

Renal & Urology News
09 January 2020

Hypofractionated or Conventionally Fractionated RT
(Continued from page 6)

cedures (24.2 vs. 21.2%). H-RT was associated with small increases in adjusted mean Expanded Prostate Cancer Index Composite short-form 26 sexual (3.3 points; 95% Confidence Interval [CI], 2.1 to 4.5; P <0.001) and hormonal function scores (3.2 points; 95% CI, 1.8 to 4.6; P <0.001). These differences failed to meet established thresholds for a clinically meaningful change. There were no statistically significant differences in urinary or bowel function and in quality of life.

Conclusion: This is the first national cohort study comparing functional outcomes after H-RT and C-RT reported by patients. These real-world results further support the use of H-RT as the standard for radiation therapy in men with nonmetastatic PCa.

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US TOO INTERNATIONAL PROSTATE CANCER EDUCATION & SUPPORT

Hot SHEET – FEBRUARY 2020
QUESTION FROM PROSTATE CANCER SURVIVOR:
I’m confused about the role of penile rehabilitation in getting erections back after surgery. I’m 67 years old and having robotic surgery in 3 weeks. I have been reading on the internet about something called penile rehabilitation and I’m not sure what to do about this. My urologist told me not to bother but a couple of my friends who have had the surgery (not by my urologist) said that their urologist told them that they must start this before the surgery. They also said that they were told different ways of doing this – pills, pumps, injections – and I don’t know what to do!

RESPONSE FROM DR. ANNE KATZ:
This can be confusing as urologists may have different beliefs about this based on what they have read or seen in their practice. A fairly recent paper in The Journal of Sexual Medicine (Liu 2019) concluded that there was “therapeutic efficacy of penile rehabilitation after RP. However, current evidence does not support that penile rehabilitation can improve spontaneous erectile function.” The authors combined the results of 16 studies that looked at the results of using pills, the penile pump and penile injections and reanalyzed the data from these studies, a method that is used to improve the evidence from single studies. Another comprehensive review (Gabrielsen 2018) concluded that penile rehabilitation is beneficial beginning immediately after surgery and continuing for one year and no longer.

In essence, what they found was that penile rehabilitation of any kind does not improve SPONTANEOUS erectile function; this is what a lot of men want – for things to be the way they were before! But from this study it appears that men still need “help” to get erections after surgery, even when they have done some form of penile rehabilitation.

Another issue is that of adherence (continuing to do the penile rehabilitation as instructed). Albaugh and colleagues looked at this issue and found that most men in their study did not follow instructions (penile pump daily and taking pills three times a week). Just 43 of the 77 men remaining in the study for the full 12 months and this dropped to 35 of the original 77 at 24 months. Of the men who had good erections before surgery, only 28% reported a return of “similar functioning at 24 months after surgery.”

Finally, other authors have concluded that “on demand” use of erectile medication may be as effective as a penile rehabilitation approach (Philippou 2018).

So where does this leave you? I think this is a personal decision based on hope and an effort to do what you can to maintain erectile functioning after treatment. There is no turning back the clock if you don’t do something, and regret is difficult to live with! It is also important to talk to your urologist about the reading you have done on the topic. It is important to have the support of your urologist and it is okay to ask him/her if they have read the latest research on the topic. You should also discuss this with your primary care provider because one or the other will be needed to write your prescriptions for medications. It is also important to remember that many men do not follow instructions on how to do this and “drop out” of the program, limiting chances of effectiveness. Cost is one of the factors that leads to difficulties in taking the medications for a long time (one or two years) to have the best chance of effectiveness. And remember that if you are not having good erections before the surgery, your chances of anything working are very low. Surgery is not going to improve poor functioning!


Watch Dr. Katz’ presentation on sexual health and intimacy from the Prostate Cancer Pathways for Patients and Caregivers event recorded at Englewood Health in Englewood, NJ on September 29, 2018. https://www.youtube.com/watch?v=A2ZdDHw2WGY&t=8542s.
Advancements in prostate cancer research provide hope for finding a cure and lead to the discovery of new treatments to minimize the impact of a man’s prostate cancer and maximize his quality of life. This regular Hot SHEET supplement includes some of the latest research from the Prostate Cancer Foundation (www.pcf.org).

The PCF is the world’s leading philanthropic organization funding and accelerating prostate cancer research. Founded in 1993, the PCF has raised more than $745 million and provided funding to more than 2,000 research programs at nearly 200 cancer centers and universities.

Focus on STAMPEDE: A Uniquely Designed Clinical Trial is Delivering Practice-Changing Findings to Patients (Part 1)

Clinical trials are necessary to determine whether a new treatment is superior to the current standard of care for improving the length and/or quality of patients’ lives. To receive FDA approval, a new treatment must typically proceed through three phases of clinical trials. The final phase (phase 3) trials can be complex, time consuming, and very costly, but are typically required for regulatory approval of a new treatment.

In an effort to streamline and reduce the cost and number of patients needed to test multiple treatments in phase 3 trials, investigators in the UK and Switzerland devised the STAMPEDE trial. Regular readers of the Hot Sheet have doubtless seen reports of previous results coming out of STAMPEDE - but it’s worthwhile to take a minute to appreciate the design of this key trial. It’s a multi-arm, multi-stage randomized phase 3 clinical trial that is comparing several different treatment regimens in prostate cancer patients who are starting long-term ADT. These are men with node-positive or metastatic disease, who are newly diagnosed or relapsing after previous primary treatment with surgery or radiation.

The unique design of the STAMPEDE trial allows for many test arms to be added over time and compared to men treated with a contemporary standard-of-care from a single ongoing control arm. Because of the trial design, only a single “control” arm is needed for many comparison arms, significantly reducing the number of patients that would have been needed if each treatment had been tested in an independent trial requiring its own control arm (see graphic). The primary outcome measure is overall survival.

STAMPEDE is headed by Professor Nicholas James, Prostate and Bladder Cancer Research Team Leader at the Institute of Cancer Research, London, and Consultant Clinical Oncologist at the Royal Marsden Hospital. Since 2005, the trial has enrolled over 11,000 men into the equivalent of 11 randomized control trials and made several practice-changing findings. Importantly, the trial demonstrated that adding new arms to the trial is fast and feasible. When the trial initiated in 2005, there was one control arm and five comparator arms. Between 2011 and 2019, five additional comparator arms have been added. While the control arm is ongoing, the first seven comparator arms have been completed.

Activating new clinical trials can be time consuming, as much paperwork and institutional and governmental reviews and approvals are needed, which must be performed for all clinical sites involved. However, the design of STAMPEDE significantly reduced the time to open new treatment arms at all of the centers involved (currently over 120). Thus far, over 3,000 investigators in the UK and Switzerland have contributed to this trial. New trial designs and data evaluation methods are being employed to efficiently add new trial arms in new international centers, including the U.S., Germany, Australia and New Zealand.

Next month, we will present an overview of some of STAMPEDE’s results to date.

For more information visit www.pcf.org, email info@pcf.org, or call 1-800-757-2873.