More Radium-223 in mCRPC Means More Toxicity
Similar Efficacy and Fewer Grade 3 Events with Standard Dose

Treatment intensification with radium-223 (223Ra) dichloride offered no major benefit for men with heavily pretreated metastatic castration-resistant prostate cancer (mCRPC) and significant bone involvement, researchers found.

“Higher dose or longer treatment schedule did not prolong survival or delayed symptomatic skeletal events (SSEs) than the standard approved 223Ra regimen, and both were associated with worse grade 3 toxicity,” reported Cora Sternberg, MD, of Weill Cornell Medical Center in New York City, and colleagues.

“Median SSE-free survival from the date of randomization — the study’s primary endpoint — was 12.9 months for men in the high-dose arm vs. 12.3 months for those receiving the standard 223Ra dose in either the control or extended-dose arms (Hazard Ratio [HR] 1.06, 80% Confidence Interval [CI] 0.88-1.27, \( P=0.70 \)),” the team reported online in the Annals of Oncology.

In the extended-schedule arm (12 injections rather than the standard six), the median SSE-free survival from the time of the sixth injection was 10.8 months, as compared with 13.2 months for those in the standard-schedule arm (HR 1.26, 80% CI 0.94-1.69, \( P=0.31 \), not a statistically significant difference).

Overall survival (OS) was not significantly different between the three arms, at 15.8, 16.0 and 14.1 months in the control, high-dose and extended-treatment arms, respectively.

However, rates of grade ≥3 treatment-emergent adverse events (TEAEs) were significantly higher in the high-dose and extended-schedule arms vs. the standard-dose arm (48%, 53%, 60% of partial nephrectomies, 23% of hysterectomies and 13% of partial colectomies (colon removal).

Compared with open procedures, out-of-pocket costs averaged $138 lower for robotic RP, $641 lower for robotic hysterectomy, $1,141 lower for robotic partial colectomy, $728 lower for robotic radical nephrectomy, and $303 for robotic partial nephrectomy.

The robotic approach was also associated with lower total payments for all procedures examined, averaging $2,633 lower for robotic radical prostatectomy and $1,405 for robotic partial nephrectomy.

(Continued on page 6)

Stalling Need for ADT in Recurrent Prostate Cancer
More Evidence of Benefits with Metastasis-Directed Therapy but Overall Survival Data Remain Elusive

Immediate treatment of limited metastatic recurrence of prostate cancer (PCa) led to a fourfold improvement in the proportion of men alive without androgen deprivation therapy (ADT) at five years, according to data reported at the 2020 Genitourinary Cancers Symposium (GUeS).

The estimated five-year ADT-free survival rate was 34% for treated patients and 8% for those followed with active surveillance (AS). Metastasis-directed treatment (MDT) led to better ADT-free survival regardless of PSA doubling time or lymph node involvement. Immediate treatment also delayed the time to development of castration-resistant PCa (CRPC).

Overall survival (OS) rate was 80-90% in both groups.

“The results added to evidence that immediate treatment may delay progression and improve survival but cannot be considered definitive because predefined criteria for statistical significance were not met,” Piet Ost, MD, of Ghent University in Belgium, said. “This was a phase II screening trial, and these are initial, non-definitive results,” said Ost.

“Any p-value <0.20 is considered significant for this specific trial, but a significant result does not mean this trial will change practice.”

The findings came from the (Continued on page 4)
**Prospective Validation of Gallium-68 Prostate Specific Membrane Antigen-Positron Emission Tomography/Computerized Tomography for Primary Staging of Prostate Cancer**

van Kalmthout LWM, van Melick HHE, Lavalaye J, et al.

**J Urol 203: 537-545, 2020**

**Purpose:** Prospective validation of Gallium-68 ($^{68}$Ga) prostate specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) is lacking in initial staging of prostate cancer (PCa). In this study we evaluated the diagnostic accuracy of $^{68}$Ga PSMA PET/CT for detecting lymph node metastasis in men with intermediate- and high-risk PCa.

**Materials and Methods:** Men with newly diagnosed PCa and negative bone scan findings at greater than 10% MSKCC (Memorial Sloan Kettering Cancer Center) risk for lymph node metastasis were prospectively included in a study from October 2017 to October 2018. In candidates for extended pelvic lymph node dissection (eLND) the $^{68}$Ga PSMA PET/CT was performed prior to planned surgery.

**Results:** Seven patients had lymph node metastases on eLND, in three patients metastases were also visible on PSMA PET/CT. Overall accuracy for the diagnosis of lymph node involvement was 95.2% with a sensitivity of 90.0% and a specificity of 95.0%.

**Conclusions:** $^{68}$Ga PSMA PET/CT detected lymph node metastasis at a high sensitivity (95.0%) and specificity (95.0%) and indicates a potential role for $^{68}$Ga PSMA PET/CT in diagnostic decision making.

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**Long-Term Oncological and Functional Follow-Up in Low-Dose-Rate Brachytherapy for Prostate Cancer: Results from the Prospective Nationwide Swiss Registry**

Viktorin P, Putora PM, Schmid HP, et al.

**BJU Int. 2020 Jan 21 [Epub ahead of print]**

**Objective:** To evaluate long-term oncological, functional and toxicity outcomes of Low-Dose-Rate Brachytherapy (LDR-BT) in relation to risk factors and radiation dose in a prospective multicenter cohort.

**Patients and Methods:** Data of men from 12 Swiss centers undergoing LDR-BT from September 2004 to March 2018 were prospectively collected. Men with a follow-up ≥ three months were analyzed. Functional and oncologic outcomes were assessed at approximately six weeks, six months and 12 months after implantation and annually thereafter. LDR-BT was done with iodine-125 seeds. Dosimetry (assessment of the dose distribution of radioactivity) was done six weeks after implantation based on the European Society for Radiotherapy and Oncology recommendations. The Kaplan-Meier method was used for biochemical recurrence free survival (BRFS). A PSA rise above the PSA nadir + 2 was defined as biochemical failure. Functional outcomes were assessed by urodynamic measurement parameters and questionnaires.

**Results:** Of 1,580 men in the database, 1,291 (81.7%) were evaluable for therapy outcome. Median (range) follow up was 37.1 (3.0-141.6) months. Better BRFS was found for Gleason score ≤3+4 (P=0.03, log rank test) and initial PSA level of <10ng/mL (p <0.001). D’Amico Risk groups were significantly associated with BRFS (p <0.001), with a hazard ratio (HR) of 2.38 for intermediate- and high-risk patients vs. low-risk patients. The radiation dose covering 90% of the prostate volume (D90) after six weeks was significantly lower in men with recurrence. Functional outcomes returned close to baseline levels after two-three years. A major limitation of these findings is a substantial loss to follow-up.

**Conclusions:** Our results are in line with other studies showing that LDR-BT is associated with good oncological outcomes together with good functional results.
I am writing this column on my birthday, so feel free to send an expensive gift. Hint: I need a new car or lawn mower. Anyhow, I digress, but I still want to spend this column in a moment of serious medical reflection. I have observed an endless number of over the counter (OTC) and prescription weight loss products hit the market over 35 years. I always wanted to believe newer pills would be tantamount to better pills, but over my career I am reminded of some egregious exceptions. Belviq, another weight loss drug (aka “lorcaserin”- approved in 2012), was just pulled from the market because it might increase the risk of numerous cancers. Some of the top selling drugs or OTC weight loss products over my lifetime have also been removed because they increased the risk of cardiovascular problems or cancer. Pills, supposed to help you lose weight, which most of them did for many people, increased the chances that you will not live as long? Say what?! This is the ultimate medical paradox! Just because a pill gives you what lifestyle changes can potentially give you does NOT always equate to the same outcome. In other words, you lose weight with diet and exercise and we know you can potentially live longer, not shorter. Yet, you can lose the same amount of weight with a pill and live shorter or get some bad medical condition?! Why do we think that some pills are miracles because they get us where we wanted to get, but just much faster and without all that personal effort or work? The story of Belviq is yet another weight loss pill in the history books that should serve as a lesson to us now and in the future. When someone promises you an anti-aging or weight loss miracle, even if you win the battle then you may be destined to still lose the war. Give me a weight loss pill that is heart healthy and might reduce the risk of cancer and I will show you one that is too cheap today to put into a commercial on television. Perhaps now you know why I wrote about metformin long ago, and why I am still very excited about that pill, but it does not come close to the vevent I have for trying to lose weight via lifestyle changes first, without the use of the latest and greatest pill. We want to believe a pill can do everything lifestyle changes can do, but in some situations this has been a broken and disastrous way of thinking. Belviq and the many other weight loss pills pulled from the market serve as a reminder that sometimes the potential miracle lies within you, and not the pill.

Reference
Moyad M. “On my birthday.”

Apalutamide and Overall Survival in Non-Metastatic Castration-Resistant Prostate Cancer
Ann Oncol. 30: 1813-1820, 2019

Background: In the SPARTAN study, compared with placebo, apalutamide added to ongoing androgen deprivation therapy significantly prolonged metastasis-free survival (MFS) and time to symptomatic progression in men with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC). Overall survival (OS) results at the first interim analysis (IA1) were immature, with 104 of 427 (24%) events required for planned final OS analysis. Here, we report the results of a second pre-specified interim analysis (IA2).

Methods: 1,207 men with nmCRPC were randomized 2:1 to apalutamide (240 mg daily) or placebo. The primary endpoint of the study was MFS. Subsequent therapy for metastatic CRPC was permitted. When the primary endpoint was met, the study was unblinded. Patients receiving placebo who had not yet developed metastases were offered open-label apalutamide. At IA2, pre-specified analysis of OS was undertaken, using a group-sequential testing procedure with O’Brien-Fleming-type alpha spending function. Safety and second progression-free survival (PFS2) were assessed.

Results: Median follow-up was 41 months. With 285 (67% of required) OS events, apalutamide was associated with an improved OS compared with placebo (hazard ratio [HR] 0.75; 95% confidence interval [CI] 0.59-0.96; P=0.0197), although the P-value did not cross the pre-specified O’Brien-Fleming boundary of 0.0121. Apalutamide improved PFS2 (HR 0.55; 95% CI 0.45-0.68). At IA2, 69% of placebo-treated and 40% of apalutamide-treated patients had received subsequent life-prolonging therapy for metastatic CRPC. No new safety signals were observed.

Conclusion: In men with nmCRPC, apalutamide was associated with a 25% reduction in risk of death compared with placebo. This OS benefit was observed despite crossover of placebo-treated men and higher rates of subsequent life-prolonging therapy for the placebo group.
Pembrolizumab for Treating Refractory Metastatic Castration-Resistant Prostate Cancer: Multicohort, Open-Label Phase II KEYNOTE-199 Study


J Clin Oncol 10 February 2020; Epub ahead of print

Purpose: Pembrolizumab has previously shown antitumor activity against programmed death ligand 1 (PD-L1)-positive metastatic castration-resistant prostate cancer (mCRPC). Here, we assessed the antitumor activity and safety of pembrolizumab in three parallel cohorts of a larger mCRPC population.

Methods: The phase II KEYNOTE-199 study included three cohorts of men with mCRPC treated with docetaxel and one or more targeted endocrine therapies. Cohorts 1 and 2 enrolled men with Response Evaluation Criteria in Solid Tumors (RECIST)-measurable PD-L1-positive and PD-L1-negative disease, respectively. Cohort 3 enrolled men with bone-predominant disease, regardless of PD-L1 expression. All patients received pembrolizumab 200 mg every three weeks for up to 35 cycles. The primary endpoint was objective response rate per RECIST v1.1 assessed by central review in cohorts 1 and 2. Secondary endpoints included disease control rate, duration of response, overall survival (OS), and safety.

Results: 258 men were enrolled: 133 in cohort 1, 66 in cohort 2, and 59 in cohort 3. Objective response rate was 5% (95% Confidence Interval [CI], 2 to 11%) in cohort 1 and 3% (95% CI, <1 to 11%) in cohort 2. Median response duration was not reached (range, 1.9 to ≥21.8 months) and 10.6 months (range, 4.4 to 16.8 months), respectively. Disease control rate was 10% in cohort 1, 9% in cohort 2, and 22% in cohort 3. Median OS was 9.5 months in cohort 1, 7.9 months in cohort 2, and 14.1 months in cohort 3. Treatment-related adverse events occurred in 60% of men, severity grade 3 to 5 in 15%, and led to discontinuation of treatment in 5%.

Conclusion: Pembrolizumab monotherapy shows antitumor activity with an acceptable safety profile in a subset of men with RECIST-measurable and bone-predominant mCRPC previously treated with docetaxel and targeted endocrine therapy. Observed responses seem to be durable, and OS estimates are encouraging.

Metastasis-Directed Therapy (Continued from page 1)

Belgium-based, multicenter STOMP trial involving men with metachronous oligo-recurrent PCa. The trial began in 2012, when the European Association of Urology (EAU) clinical guidelines dichotomized (split into two) recommended treatment for metastatic PCa into symptomatic and asymptomatic. Men with symptomatic disease received ADT, whereas asymptomatic men had the option of ADT or observation with ADT delayed until disease progression.

STOMP limited enrollment to men with asymptomatic or minimally symptomatic metastatic recurrence (one to three extracranial lesions identified by choline PET/CT). In keeping with EAU recommendations at the time, observation was chosen as standard care for the control arm. In the intervention arm, men received immediate MDT. In both groups, treatment continued until development of symptomatic local or polymetastatic progression, when ADT was initiated. The trial had a primary endpoint of time to begin ADT (ADT-free survival). The researchers defined statistical significance for the trial as P=0.20, but only results associated with a p-value <0.005 were considered definitive. The study included 62 men, with a median follow-up of 5.3 years. Baseline characteristics and other details of the trial design have been reported previously.

The primary analysis showed that immediate treatment led to a 43% reduction in the hazard for ADT-free survival (80% confidence interval [CI] 0.38-0.84, P=0.06). A per-protocol analysis yielded a hazard ratio (HR) of 0.53 (80% CI 0.35-0.79, P=0.04). Subgroup analyses yielded HRs of 0.41 for men with a PSA doubling time of less than three months, 0.65 for those with a PSA doubling time of three or more months, 0.42 for men with lymph-node involvement, and 0.74 for those without nodal involvement.

CRPC-free survival (post-ADT) favored the intervention arm (HR 0.62, 80% CI 0.35-1.09), but the difference did not achieve the trial-defined level of statistical significance. A per-protocol analysis showed a 49% reduction in the HR (80% CI 0.29-0.90, P=0.12). “Five-year OS was high in both groups, as was PCa-specific survival, as only six of 14 total deaths resulted from PCa,” said Ost.

The previously reported primary results of the STOMP trial showed a median ADT-free survival of 21 months with MDT vs. 13 months with AS. Vapiwala noted that metastatic progression was the principal reason for starting ADT in both treatment groups. Multiple trials of MDT with SABR are ongoing, including several randomized trials and trials of combination therapy.

“The value of MDT is really in the eyes of the beholder,” said Neha Vapiwala, MD, of the University of Pennsylvania during a review that preceded Ost’s presentation. “Whether the beholder is the patient, the provider, the insurer, or society is for us to answer as a group. We know that MDT is safe, feasible, and effective by a variety of important measures, but whether the outcomes – such as ADT-free survival – justify the intervention is an unanswered question.”

Presented at the 2020 Annual GuCS; Abstract 10.

MedPage Today
14 February 2020
PET Spots Prostate Cancer Metastases Missed on CT, MRI
Antigen-Targeted Tracer Highlighted Metastases in 27% of “Localized” Cases

More than a fourth of men with high-risk prostate cancer (PCa) had lymph node or distant metastases missed by CT or MRI, but detected by PET imaging targeting prostate-specific membrane antigen (PSMA), a prospective, multicenter study showed. Biopsy-confirmed results showed that 72 of 268 (27%) had disease that had spread beyond the prostate. Almost 15% had locally advanced disease, and 12% had distant metastases. At study entry, conventional pelvic CT or MRI showed no evidence of regional or distant metastases in 96-97% of the men.

On the basis of image interpretation by three readers blinded to all clinical results, $^{18}$F-DCFPyL PET/CT had sensitivity of 31-42% and specificity of 96-99%. Sensitivity increased to as high as 63% with no loss of specificity when small lymph nodes below the PET detection limit were excluded, as reported at the 2020 Genitourinary Cancers Symposium (GuCS).

“In men with high-risk PCa who are candidates for radical prostatectomy (RP) and pelvic lymph node dissection, PET/CT with $^{18}$F-DCFPyL improved clinical N (lymph node) and M (metastases) staging despite completely blinded image reads,” concluded Frédéric Pouliot, MD, of Laval University in Quebec City, Quebec. “Significant clinical information gained with $^{18}$F-DCFPyL PET imaging is likely to directly impact patient management.”

“PSMA-targeted imaging has a strong biological rationale in that it is overexpressed in 94% of PCas, including both primary and metastatic cancers,” Jeremy Calais, MD, of the University of California Los Angeles, said during a review of PSMA PET imaging. Several PSMA-targeting PET tracers have been developed and all demonstrated superiority to CT and MRI for evaluating PCa — and to other PET tracers, such as choline and fluorodihydrocholine.

Asked who should undergo PSMA imaging, Calais said, “For sure, the high-risk PCa patients and probably men with a high suspicion of PCa who have negative biopsies or equivocal MRI. PET-based imaging for PCa developed because conventional imaging modalities are suboptimal for staging or restaging high-risk PCa,” said Pouliot.

“Previous studies showed PSMA-targeting PET/CT had sensitivity and specificity of 33-100% and 80-100%, respectively,” Pouliot continued, “but most of the data came from retrospective analyses or prospective single-center studies without central image assessment.” DCFPyL (PyL) is one of several $^{18}$F-labeled low-molecular-weight PET tracers that exhibits selective, high-affinity binding to PSMA. The tracer was evaluated prospectively in the multicenter OSPREY trial, involving men with newly diagnosed high-risk PCa and those with recurrent or metastatic PCa. Pouliot reported findings from the men with high-risk PCa.

The phase II/III trial had three central, independent PSMA PET/CT readers and one central reader for conventional imaging, all blinded to clinical and imaging results. The cohort included 268 men with high-risk PCa, 252 of whom had evaluable DCFPyL PET/CT imaging results and evaluable pathologic findings from RP and pelvic lymph node dissection. The primary endpoint was specificity and sensitivity within the pelvic lymph nodes.

The 252 men with complete information had a median age of 64 and median PSA level of 9.3 ng/mL. A third of the men had T1 disease, 36.5% had T2 disease, and 26.6% had T3 cancers. Eight men had N1 disease and one had M1 disease. Almost half of cancers were Gleason 8 and a third were Gleason 9.

The primary analysis by central reader showed sensitivity and specificity for readers 1, 2, and 3 of 41.9, 97.9%; 30.6, 98.9%; and 40.3, 96.3%.

Positive and negative predictive values (PPV and NPV, secondary endpoints) ranged from 78.1 to 90.5% and 81.4 to 83.8%, respectively, across the three readers. Re-analysis that excluded 27 lymph nodes ≤5 mm yielded sensitivity of 62.9, 48.6, and 60.0% for the three independent readers and specificity of 97.9, 98.9, and 96.3%. PPV declined minimally and NPV increased by about 10 percentage points for each of the readers.

“At study entry, greater than 96% of men had no known regional or distant metastatic disease, based on conventional imaging,” said Pouliot. “A total of 72 of the 268 patients had [locally advanced or metastatic disease] detected on $^{18}$F-DCFPyL PET/CT.” The PET/CT results showed that 39 men had locally advanced disease and 33 had distant metastases.

Presented at the 2020 Annual GuCS; Abstract 9.

MedPage Today
14 February 2020

Modest Survival Gains Reported in Newly Diagnosed Metastatic Prostate Cancer
Survival of patients with newly diagnosed metastatic prostate cancer (PCa) has improved only slightly since the introduction of new agents shown to decrease death risk among men with advanced PCa, according to study data presented at the 2020 Genitourinary Cancers Symposium (GuCS).

Using the Surveillance, Epidemiology and End Results (SEER) database, investigators ran a real-world study of 34,034 men diagnosed with de novo metastatic PCa from 2000 to 2016.

They stratified men according to treatment eras: T1, 2000-03; T2, 2004-10, and T3, 2011-16. “In multivariable analyses adjusted for age and race, risk of death was only 8% lower among T3 patients vs. T1 and T2 patients,” reported Carlo Catrini, MD, and colleagues at the IRCCS Ospedale Policlinico San Martino in Genoa, Italy.

The median overall survival time was 29 months for the entire study population and 28, 28, and 31 months for the T1, T2, and T3 groups, respectively. Median cancer-specific survival (CSS) times were 36, 34, 34, and 38 months for these groups, respectively. Compared with T1 and T2 patients, T3 patients had a 7% and 8% decreased risk of cancer-specific death, respectively.

“Basically, this real-world analysis using the SEER database highlights that, despite the introduction of several new drugs in the treatment landscape of advanced PCa, only a slight survival improvement is evident in men with newly diagnosed meta-

(Continued on page 8)
Out-of-Pocket Costs (Continued from page 1)

$3,873 lower per RP, $29,641 lower per hysterectomy, $38,152 lower per partial colectomy, $33,394 lower per radical nephrectomy, and $9,163 lower per partial nephrectomy.

The robotic approach was associated with shorter length of stay for all procedures, ranging from 0.94 day shorter for RP to 3.18 days shorter for partial colectomy.

For the entire perioperative period (from 14 days before to 28 days after surgery), adjusted OOP costs were significantly lower for the robotic option for partial colectomy and radical nephrectomy, but not for the other procedures, and adjusted total payments were significantly lower for all robotic procedures except RP.

The authors caution that these analyses do not account for the costs of procuring and maintaining a robotic system (which can range from $0.5 million to $2.5 million), and that previous analyses have shown that robotic surgery could be more expensive perioperatively (during surgery) than open surgery when the costs of robotic maintenance and disposable instruments are included.

“These results highlight the complexity of economic factors that are associated with the rapid adoption and possible subsidization of the robotic approach for common surgically amenable conditions and lay a foundation for future work on this issue,” the authors conclude.

Reuters Health 25 January 2020

More Radium223 in mCRPC Means More Toxicity (Continued from page 1)

and 34%, respectively). This resulted in permanent treatment discontinuation in 16% and 17% of men in the high-dose and extended-schedule arms vs. 9% of men in the standard-dose arm.

Anemia was the most common adverse event, reported in 10% of men in the standard-dose arm, and 14% in both the high- and extended-schedule arms.

The multicenter, open-label study randomized 391 men at 63 centers in 16 countries 1:1:1 to either the standard 223Ra dose (55 kBq/kg) and schedule (every four weeks for six cycles), a high-dose arm (88 kBq/kg every four weeks for six cycles), or an extended-dose arm (standard dose every four weeks for 12 cycles).

“The current study supports six injections of standard-dose 223Ra as the optimal regimen for men with mCRPC and bone metastases.” The researchers noted that only 24% of men completed the planned 12 injections in the extended-schedule arm.

More than half the men in the trial received prior docetaxel. Also, about 22% of men were concurrently treated with abiraterone and about 14% with enzalutamide.

“This is in contrast to men treated in the ALSYMPCA study, where only symptomatic patients were recruited and abiraterone and enzalutamide were unavailable,” Sternberg and colleagues wrote. “However, the proportion of men who had received prior docetaxel in that study was 57 vs. 52% in the current study. Subsequent phase II studies of mCRPC and bone metastases reported improved disease control and pain relief using higher doses of 223Ra,” he and co-authors pointed out.

In an accompanying editorial, Oliver Sartor, MD, of Tulane Cancer Center in New Orleans, noted that the use of abiraterone and enzalutamide as both prior and concomitant treatments “may be important.” He also pointed to results from the ERA-223 trial showing that the addition of 223Ra to abiraterone plus prednisone did not improve SSE-free survival in men with mCRPC and bone metastases.

“Notably, the combination was associated with an increased frequency of bone fractures vs. placebo, which led investigators to unblind the study early,” he explained.

“The fact that [223Ra] at higher doses and longer schedules did not result in improved outcomes is potentially confounded by the fact that [223Ra] is ineffective when given concomitantly with abiraterone,” Sartor wrote.

“Additional trials are planned to explore concomitant therapies using [223Ra] and enzalutamide.”

MedPage Today 03 February 2020

Long-Term Outcomes of Gleason Grade Groups 2 and 3 Prostate Cancer Managed by Active Surveillance: Results from a Large Population Based Cohort


Can Urol Assoc J 20 January 2020; Epub

Active surveillance (AS) is an accepted management strategy for low-risk prostate cancer, but its role in the management of favorable intermediate-risk prostate cancer remains controversial. Most reports studying the role of AS for these men generally lack long-term followup and include small numbers of patients. Our objective was to report the outcomes of men diagnosed with Gleason grade groups (GGG) 2 and 3 prostate cancer who were managed expectantly.

Using administrative datasets and pathology reports, we identified all men who were diagnosed with GGG 2 and 3 prostate cancer and managed expectantly between 2002 and 2011 in Ontario, Canada. Outcomes and associated factors were estimated using cumulative incidence function methods and multivariable Cox regression models, respectively.

We identified 926 men who were managed expectantly (AS [n=374] or watchful waiting [n=552]). The eight-year cancer-specific survival was 94% and 89% for the AS and watchful waiting cohorts, respectively. Among AS men, 266 (71%) received treatment after a followup of approximately eight years. Cumulative AS discontinuation rates at one and five years were 30.5% and 65.1%, respectively.

Expectant management of GGG 2 and 3 PCs may be an option for certain men. Notably for AS patients, the cancer-specific mortality at eight years was 6%, and over 65% of men underwent treatment within five years. Further studies are required to evaluate which patients, based on disease-specific features and competing health risks, would benefit the most from a conservative strategy.
Guest Column: Staying Sexually Active After Prostate Cancer Treatment
by Daniela Wittmann, PhD, LMSW, Associate Professor of Urology, Certified Sex Therapist, University of Michigan

Men treated for prostate cancer can survive the disease for many years, especially if the cancer is discovered and treated early, while it is still located inside the prostate. Even if it is found later, many men live with it while under treatment.

Sexual dysfunction is a side-effect that can accompany prostate cancer treatment. Men treated with surgery can have immediate erectile dysfunction and penile shortening. They lose their ability to ejaculate. Approximately 20% recover erectile function in the course of 2 or more years; others cope with erectile dysfunction permanently. Men treated with radiation can experience a gradual softening of erections. Men on hormonal therapy can experience a loss of testosterone which leads to loss of desire, erectile dysfunction and genital shrinkage.

Research on men’s response to sexual dysfunction suggests that men are distressed, worry about their own function and about the impact of their sexual dysfunction on their relationships. Partners are also distressed: they worry about the man’s coping, they also worry about what will happen to their own sex lives. Partners often focus on supporting the man, making their own needs a lesser priority. We have learned from research that many couples don’t talk about sex, yet their sexual relationships can be fine. Once sexual problems arrive, they find it difficult to talk and find solutions. However, being able to talk about sex within the couple and with healthcare providers becomes important.

Not all sexuality is lost after prostate cancer treatment. While erectile function is generally affected, and there may be a loss of ejaculation and loss of libido, most men, even some men on hormonal therapy, can experience the pleasure of orgasm. This is due to the fact that the pudendal nerve, which is responsible for sexual sensation, is not affected by the treatment. Longer stimulation might be needed to arrive at orgasm. The Cowper’s gland that emists a clear, viscous fluid during arousal also remains active after prostate cancer treatment. Sensuality can help sustain the sexual connection with a partner.

Men can have penetrative sex after prostate cancer if they recognize and accept that they can learn to use sexual aids and incorporate them into their sexual relationships. Partners might have to make similar adjustments. Whether a man is straight or gay, he and his partner will likely go through a grief process in order to come to terms with the changes and their impact on sexual activity. A sex life may be different after prostate cancer treatment, but it can be pleasurable and close. Allowing oneself to have whatever feelings come up, being able to talk, trying out new things and having a sense of humor can help.

Aids for erectile function include pills, such as Sildenafil, Tadalafil, Vardenafil or Avanafil. They are most helpful to men who can have partial erections on their own. Men who do not benefit from these pills can try penile suppositories that contain Alprostadil. Or, some men prefer using penile injections. There are different types, some use Alprostadil, others a mixture of Phentolamine, Papaverine and Alprostadil. All medications require a prescription. Suppositories and injections require an in-office teaching. Men who do not want to take medications can learn to use a vacuum erection device - the penile pump. Aids to erections have associated costs and may be covered, at least in part, by insurance. There are also other ways of making one’s sex life more fun. Incorporating the use of vibrators encourages blood flow in erectile areas for both the man and the partner (penis, clitoris, the perineum) and leads to increased sexual pleasure. Giving each other a massage and spending more time on foreplay brings about relaxation and higher arousal as well as emotional intimacy.

The new way of being sexually intimate might no longer rely on having a hard penis. Confidence in one’s ability to satisfy a partner in a variety of ways is key and it is attainable. Most men and partners, if they were honest, recognize that spontaneity is rarely available in adulthood when life is filled with responsibility for children, grandchildren, elderly parents, households and jobs. Those, who have come to terms with the new sexual blueprint, have learned to schedule sexual activity and anticipate it with pleasure, even excitement. Having a date for love making means that one can spice things up and look forward to a special time together. Couples who have worked towards a new way of being sexual have said that the hard work of keeping their sex life alive has made them closer. For some, sex is better because it is emotionally more connected and pleasurable. There is, potentially, a silver lining to an experience that one would never have chosen.

Some men and couples may wish to have expert support. Talking to a certified sex therapist can help work towards attaining sexual goals in prostate cancer survivorship. Local resource information is available on the website of the American Association of Certified Sexuality Educators, Counselors and Therapists (aasect.org). Researchers in the US, funded by the Movember Foundation, an Australian charity devoted to men’s health, have worked on developing a TrueNTH Sexual Recovery support program after prostate cancer which will become available online soon.
Earlier Cabazitaxel Use in Metastatic CRPC Possibly Beneficial

Chemotherapy-naïve patients with metastatic castration-resistant prostate cancer (mCRPC) may benefit from earlier use of cabazitaxel, according to study findings presented at the 2020 Genitourinary Cancers Symposium (GuCS).

In a multicenter phase 2 trial, a team led by Susan F. Slovin, MD, PhD, of Memorial Sloan Kettering Cancer Center in New York, randomly assigned 81 men with mCRPC (median age 68 years) to receive a combination of abiraterone acetate plus prednisone (AAP) and cabazitaxel (39 men) or AAP alone (42 men) with crossover to cabazitaxel upon AAP failure. None of the men previously had received chemotherapy. The primary endpoint was radiographic progression-free survival (rPFS), defined as the time from randomization to radiographic progression or death, whichever occurred first.

“Compared with the monotherapy arm, the combination arm had a longer median time to rPFS 14.4 vs. 7.9 months) and PSA progression (13.8 vs. 9 months),” Dr. Slovin and her colleagues reported in a poster presentation. Median overall survival time was 20.7 months in the combination arm and 16.4 months in the monotherapy arm. The proportion of men who experienced a 50% or greater decline in PSA from baseline was 87.2% in the combination arm and 52.4% in the monotherapy arm. “Treatments were well tolerated,” said the investigators.

“Trial results support further study of the combination of AAP and cabazitaxel in men with mCRPC,” the authors concluded.

Presented at the 2020 Annual GuCS; abstract 84 Cancer Therapy Advisor 14 February 2020

Survival in Newly Diagnosed Metastatic PCa (Continued from page 5)

stat PCa from 2000 to 2016,” Dr. Cattrini told Renal & Urology News.

The small improvement in survival is “quite disappointing,” he said, but might be due to limited access to expensive drugs, insurance issues, and intrinsic aggressiveness of de novo PCa.

“Recent approvals of novel oral androgens for use in metastatic castration-sensitive PCa could lead to a more significant overall survival benefit,” he said.

FDA approved abiraterone in 2018 and the androgen-receptor inhibitors enzalutamide and apalutamide in 2019 for use in this phase of the disease.

Dr. Cattrini and his colleagues acknowledged that confounding factors not available in the SEER database, such as disease volume, number of metastatic sites, and type of treatment, were not included in their multivariable analysis.

Presented at the 2020 Annual GuCS; poster B14 Renal & Urology News 13 February 2020

A Prostate Cancer Forum for Gay Men and Their Partners Us TOO Call-In Support Group

A Prostate Cancer Forum for Gay Men and Their Partners is an ongoing conference call series which provides gay men and their partners with important peer-to-peer support. Usually, both the man living with prostate cancer and his husband or partner are deeply impacted, and each is subject to his own physical and emotional concerns. It can be helpful to address these concerns by speaking with others in a similar situation.

Contact Terri Likowski at terril@ustoo.org or 336-842-3578

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**Between the Sheets...**

This column provides the platform for experts in the field to help men and women by providing answers to questions about sexual health and intimacy challenges that can result from prostate cancer treatment.

This column was compiled with the help of Dr. Jeffrey Albaugh, Director of Sexual Health at NorthShore University HealthSystem and at Jesse Brown VA Medical Center in Chicago, IL. Dr. Albaugh is a funded researcher, a board certified advanced practice urology clinical nurse specialist, and a board certified sexuality counselor. In addition to his many publications in peer reviewed journals and chapters in books on sexual dysfunction, Dr. Albaugh published *Reclaiming Sex and Intimacy After Prostate Cancer Treatment*. He has been quoted in media and publications as an expert in the treatment of sexual dysfunction, and is a member of the Us TOO Board of Directors.

**QUESTION FROM PROSTATE CANCER SURVIVOR:**
*The cost of Viagra and Cialis has gotten so expensive. My friend said he is using generic Viagra and it is working well and much cheaper. Is that true?*

**RESPONSE FROM DR. JEFFREY ALBAUGH:**

*One of the most frustrating things for men treated for prostate cancer is the cost of the oral medications (phosphodiesterase type 5 inhibitors – PDE-5 inhibitors). In the last few years costs spiraled to over $60 per pill for some of the medications! The good news is that there are now generic equivalents for several of the medications and they are an incredibly small fraction of the cost of the branded medications. The generic sildenafil and tadalafil are the same chemicals as the branded medications of Viagra and Cialis. You will still need a prescription for these medications as they remain FDA approved prescription medications. There are many counterfeit versions of these medications, so beware of where you get the prescription filled. If anyone is giving you these medications without a prescription, you are not getting the approved medications from a reputable pharmacy. Be very careful because everyone wants your money and it is important to use a legitimate US pharmacy if you want a medication that is compliant with FDA standards. Generic sildenafil and tadalafil can be obtained for two dollars or less per pill with a goodrx.com coupon from your local pharmacy and may be as low as 30 cents per tablet at some local reliable pharmacies. The goodrx.com website helps you find the medication at a pharmacy near you and shows you the comparative prices at many of your local pharmacies. Many people use this website for a multitude of different medications including the PDE-5 inhibitors. The prices can vary by more than 100% difference between pharmacies! The app can be downloaded for free to your phone or you can simply go on the internet to access the website. On the website, you don’t have to reveal any personal or identifying information to get the coupons. Most of these medications are not covered by insurance plans, but if your medication is covered, you can get it at the pharmacy you get your other covered prescription medications.*

You can access the new edition of my book or download a free copy of my original book at [www.drjeffalbaugh.com](http://www.drjeffalbaugh.com).

Watch Dr. Albaugh’s presentation on sexual health and intimacy from the *Prostate Cancer Pathways for Patients and Caregivers* event recorded at NorthShore University HealthSystem in Skokie, IL on November 3, 2018 at [https://www.youtube.com/watch?v=Hiq0dDeb1l0&t=4483s](https://www.youtube.com/watch?v=Hiq0dDeb1l0&t=4483s).

Read previous issues of Between the Sheets at [www.ustoo.org/BTS](http://www.ustoo.org/BTS).

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:**
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Progress on Prostate Cancer Research

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).

Focus on STAMPEDE: A Uniquely Designed Clinical Trial is Delivering Practice-Changing Findings to Patients (Part 2)

Last month, we discussed the design of the STAMPEDE phase 3 clinical trial, which uses a multi-arm, multi-stage approach to simultaneously test multiple interventions against a single control arm. Patients in this trial have node-positive or metastatic prostate cancer, are newly diagnosed or relapsing after previous primary treatment with surgery or radiation, and are starting ADT. Here, we describe results in three key areas.

Addition of Docetaxel to ADT

STAMPEDE demonstrated that the addition of docetaxel in men with hormone-naïve prostate cancer who are starting ADT improves overall survival, with a reduction in risk of death representing 22%. Docetaxel also improved failure-free survival by 39% and reduced the risk of skeletal events by 40%. While the phase 3 CHARITY trial found that the addition of docetaxel in this setting only benefitted men with high-burden metastatic disease, STAMPEDE found that adding docetaxel to the standard of care (ADT +/- radiotherapy) improves overall and failure-free survival in newly diagnosed metastatic hormone-naïve prostate cancer regardless of metastatic burden. In STAMPEDE, docetaxel reduced the risk of death by 34% in patients with low-burden metastatic disease and by 19% in patients with high-burden metastatic disease. These results have contributed to recommendations that docetaxel should now be considered as an option for patients newly diagnosed with metastatic hormone-naïve prostate cancer who are starting ADT.

Abiraterone

The STAMPEDE trial found that the addition of abiraterone in men with hormone-naïve prostate cancer who are starting ADT improves overall survival, with a reduction in risk of death representing 37% (see Figure). Abiraterone was beneficial in patients with both high-risk and low-risk disease (reduction in risk of death representing 46% and 34%). Abiraterone also improved failure-free survival by 71% and reduced the risk of skeletal events in patients with metastatic disease by 64%. A head-to-head comparison performed using 566 patients who were treated contemporaneously on the abiraterone and docetaxel arms found no significant difference in overall survival between the two regimens. However, slightly more men in the abiraterone arm died from non-prostate cancer causes such as cardiovascular disease and fractures, suggesting that overtreatment with abiraterone may have increased the risk of death in some men. Based on the results from STAMPEDE and a second phase 3 trial, LATITUDE, abiraterone is now FDA-approved for the treatment of men with hormone-sensitive metastatic prostate cancer who are starting ADT.

Radiation Therapy

The STAMPEDE trial found that the addition of radiotherapy to the primary tumor improves survival in men with newly-diagnosed low burden metastatic prostate cancer who are starting ADT +/- docetaxel (reduction in risk of death representing 32%; reduction in failure-free survival of 41%). No statistical benefit was seen for the addition of radiotherapy in patients with high-burden metastatic disease. Based on the results from STAMPEDE, NCCN guidelines now include radiation therapy to the prostate as an option in patients with low-volume hormone-naïve metastatic prostate cancer.

Approximately 4,000 men have already experienced a gain in survival on the completed arms in this trial. Correlative studies are being conducted using samples from patients on the trial to evaluate questions such as whether patients with certain hereditary cancer risk genes or tumor mutations have different treatment responses, and to evaluate the relationships between tumor biology, pathology, and molecular imaging. Altogether, STAMPEDE has demonstrated that a trial of this design can rapidly test numerous treatment regimens in a multi-center phase 3 randomized setting, and has resulted in several new standard-of-care regimens for men with advanced prostate cancer.

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