New Prostate Cancer Staging System May Improve Pretreatment Prognostication

A pretreatment, predictive staging system for nonmetastatic prostate cancer (PCa), based on data analysis rather than expert consensus, promises to improve on existing risk-stratification systems, according to an international group of researchers.

“For over a decade, PCa remains one of the few cancer types that do not routinely utilize the common stage-1-to-4 groupings that almost every cancer type uses to describe prognosis,” Dr. Daniel E. Spratt of the University of Michigan School of Medicine, who worked on the study, told Reuters Health.

“Prostate cancer,” he added, “has both national American Joint Committee on Cancer system (AJCC) and international Union for International Cancer Control (UICC) staging systems, but they fail to meet criteria put forth by staging committees to truly be valid. Furthermore, the prognostic systems we use in our national guidelines, e.g., National Comprehensive Cancer Network (NCCN) risk groups, have suboptimal performance.”

The new analysis was published online ahead of print 10/27/2020 in JAMA Oncology. The report included data on more than 19,000 men with clinical stage cT1-c4 (tumor stage)-N0-1 (no measurable lymph node involvement) - M0 (no metastases) PCa treated between 1992 and 2013.

Overall, 12,421 men underwent radical prostatectomy and the remaining 7,263 received radiotherapy with or without androgen-deprivation therapy. Median follow-up was almost 6 years but more than 20% of men were followed for at least 10 years.

For men with localized prostate cancer (PCa) undergoing radiotherapy (RT), adjuvant androgen deprivation therapy (ADT) may yield superior oncologic outcomes compared with neoadjuvant ADT, pooled data from two phase III trials suggested.

“In the analysis of over 1,000 men receiving RT to the prostate, progression-free survival (PFS) was significantly improved in men receiving adjuvant ADT, with an estimated 15-year PFS rate of 36% vs. 29% with neoadjuvant ADT [Hazard Ratio [HR] 1.25, 95% Confidence Interval [CI] 1.07-1.47, P=0.01],” reported Daniel Spratt, MD, of the University of Michigan.

For men with localized PCa undergoing RT, adjuvant androgen deprivation therapy (ADT) may yield superior oncologic outcomes compared with neoadjuvant ADT, pooled data from two phase III trials suggested.

“The hypothesis of this study was that sequencing of ADT with RT – independent of ADT duration – will have a clinically meaningful impact on oncologic outcomes, just as it does in other disease settings,” said Spratt during the virtual American Society for Radiation Oncology (ASTRO) annual meeting.

With a median follow-up of 14.9 years, biochemical recurrence (BCR) was lower in the adjuvant group, with 15-year rates of 33 vs. 43% in the neoadjuvant group (HR 1.37, 95% CI 1.12-1.68).

(Continued on page 4)
Focal RT Boost in High-Risk Prostate Cancer Cuts PSA Relapse

Rates of Biochemical Relapse Cut in Half with Boost to 95 Gy

An integrated focal boost of radiation (RT) improved biochemical disease-free survival (bDFS) without increasing toxicity in prostate cancer (PCa) patients with mostly high-risk disease, a Dutch randomized trial showed.

“With a median follow-up of 71 months, the 5-year bDFS rate significantly improved from 86% in the external-beam RT (EBRT) arm, to 93% with a focal boost, meeting the study’s primary endpoint,” reported Linda Kerkmeijer, MD, PhD, of Radboud University Medical Center Nijmegen, The Netherlands.

“FLAME is the first phase III trial to show that focal boosting improves 5-year bDFS, with relapse rates reducing from 14 to 7%,” Kerkmeijer said during the 2020 virtual American Society for Radiation Oncology (ASTRO) meeting. “This was achieved without impacting toxicity or quality of life (QoL).

“Local recurrences in PCa most often occur at the primary tumor,” she said, “and while control of PSA levels improves with increasing doses of RT, EBRT trials have shown that whole-gland dose escalation increases toxicity. A potential solution may be focal-dose escalation, increasing the dose to the microscopic intraprostatic lesion without raising the dose to at-risk organs.”

In the study, no differences were seen in late gastrointestinal (GI) grade ≥2 adverse events with rates of 12 and 13% in the standard and dose-escalation arms. Late GI grade ≥3 AEs were 1% in each arm. Late genitourinary (GU) grade ≥3 AEs were elevated in the dose-escalation arm (6 vs. 4%), but this finding was not significant.

“For patient-reported outcomes assessed using the EORTC QLQ-PR25 questionnaire, GU and GI QoL were comparable in both groups, decreasing from baseline by 12 and 5 points, respectively, with both returning to normal within the first year,” said Kerkmeijer. Among men not taking hormonal therapy, sexual activity and functioning were also similar between arms, decreasing by fewer than 5 points.

Kerkmeijer noted that more than half of men in the focal-boost group did not reach the target 95 Gy, as organs at risk were prioritized. “This is important in interpreting the toxicity results,” she said.

“Focal boosting will become the new standard of care for RT for intermediate- and especially high-risk PCa,” Kerkmeijer said, but cautioned that the FLAME trial used a conventional fractionation scheme. “Results of hypofractionated focal boost studies should be awaited first before routinely implementing this.”

ASTRO discussant Alison Tree, MD, of the Royal Marsden and the Institute of Cancer Research in London, highlighted that bDFS has not been shown to be a surrogate for overall survival in PCa. To date, only metastasis-free survival has been proven to predict overall survival.

“The endpoints that we should use in our trials, in my opinion, is not a solved problem,” she said. “It depends on the cost of the intervention. Biochemical relapse-free survival may be a sensible endpoint if you are looking at something that doesn’t come with a toxicity penalty. Endpoints also have to be pragmatic. If it takes you 15 years to find your overall survival advantage, then technology would have moved on and your trial will have become obsolete.”

Tree called the 93% bDFS rate “remarkable” considering the high-risk cohort included – a third of men had a Gleason score of 8 or above and 84% were high risk as classified by the European Association of Urology.

“Is this enough to change practice? Well certainly I think we’re going to be moving in that direction,” said Tree.

“But as Dr. Kerkmeijer pointed out, this trial is only relevant to conventional fractionations, which most of us – certainly in Europe – are not giving any longer.

“If you have an intervention like this which can improve bDFS with no toxicity penalty, I would say the bar for actually doing it is low,” she continued. “So is this a ‘no penalty’ way to improve bDFS? Does this return the PSA control endpoint? Let’s watch this space.”

FLAME was a phase III trial that randomized 571 men with intermediate- and high-risk PCa from 2009 to 2015 to either standard EBRT (77 Gy over 35 fractions) or EBRT with a focal boost up to 95 Gy. In the boost arm, gross tumor volume contouring was performed on multiparametric MRI. Baseline characteristics were well balanced, with 82% having International Society of Urological Pathology (ISUP) grade ≥2 tumors and two-thirds received adjuvant hormonal therapy.

“Details on the primary endpoint will be presented later this year at the 2020 European Society for Radiotherapy & Oncology (ESTRO) online congress,” said Kerkmeijer.
I love Kiwi! Yeah, I said it, and I will say it once again...“I LOVE KIWI!” I am not kidding, and I am not just talking about my love for my New Zealand sisters and brothers, but also my love for this amazing fruit. Like last month, I’m talking about another unsung hero of the nutrition world. Yeah, I could talk about a lot of other things, but at the end of the year, we need to reflect on some of the dietary blessings in life, including the humble, tiny, yet formidable, kiwi. It is super low in calories (40 calories per kiwi), and it is starting to get the attention it has deserved for some time. Past and recent clinical studies continue to suggest it could even prevent constipation with minimal-to-no side effects, compared to other products that get all the commercials on TV.1-3

Over-the-counter high-profile fiber powders, pills, capsules, and wafers are costly. But more importantly, they cause some folks to rely on them as a fiber source without countless other healthy nutrients (aka “nutrient dense/diverse” food-based sources). For example, each Kiwi contains 2-3 grams of beautiful dietary (dare I use the word “natural” — ok I just did) fiber in such a small low-calorie space. Kiwi contains approximately 100% of the RDA (recommended daily allowance) of vitamin C, and it is loaded with potassium and little sodium. Tell me more! Okay, I will! I like the kiwi because it can easily fit in the palm of your hand and, when cut in half, reveals that rich hue (green, or actually gold in another type) along with beautiful dark seeds. You take a tiny spoon and start scooping out the fleshy fruit and it is yummy time! Some folks get really adventurous and consume the skin for even more fiber and nutrients. There is so much beauty in such a small space. But wait, there is more!

I know I sound like a bad commercial trying to sell you a bunch of exotic steak knives. Kiwi contains a tiny bit of serotonin.4,5 You know, the happy mood and sleep compound or neurotransmitter! Now, I cannot promise that you will eat this fruit and become happier and sleep better, but it is a nice bonus, and some studies do suggest it may improve your sleep, thus your mood a bit more. If kiwi were a pill, most folks would consider buying some right now, and that is actually my point here...it is an amazing gift from nature and all you have to do is open this present to enjoy the inside. Now, you know why KIWI RULES, which is just ‘young-person’ vernacular suggesting something is “awesome” and worth an immediate try! I can see the commercial now...“Kiwi the movie”—“coming to a spoon near you!”

References:

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### Evaluation of Fall and Fracture Risk Among Men with Prostate Cancer Treated with Androgen Receptor Inhibitors, a Systematic Review and Meta-analysis

Myint ZW, Momo H, Otto DE, et al.

JAMA Netw Open. 2020; 3(11): e2025826

**Importance:** A high incidence of fall and fracture in a subset of men treated with androgen receptor inhibitors (ARIs) has been reported, although the relative risk (RR) of fall and fracture for men who receive ARI treatment is unknown.

**Objective:** To evaluate whether treatment with ARIs is associated with an elevated relative risk for fall and fracture in men with prostate cancer (PCa).

**Data Sources:** Cochrane, Scopus, and MedlinePlus were searched from inception through August 2019.

**Study Selection:** Randomized clinical trials comparing men with PCa treated with any ARI or placebo.

**Data Extraction and Synthesis:** Two independent reviewers used a standardized data extraction and quality assessment form. A mixed effects model was used to estimate the effects of ARI on RR, with included studies treated as random effects and study groups treated as fixed effects in the pooled analysis. Sample size for each study was used to weight the mixed model. Statistical analysis was performed from August to October 2019.

**Main Outcome Measures:** The primary outcome was RR of fall and fractures for men receiving ARI treatment.

**Results:** Eleven studies met this study’s inclusion criteria. The total population was 11,382 men (median [range] age: 72 [43-97] years), with 6,536 in the ARI group and 4,846 in the control group. Participants in the ARI group could have received enzalutamide, apalutamide, or darolutamide in combination with androgen deprivation therapy or other enzalutamide combinations; men in the control group could have received placebo, bicalutamide, or abiraterone. The reported incidence of fall was 525 (8%) in the ARI group and 221 (5%) in the control group. The incidence of fracture was 242 (4%) in the ARI group and 107 (2%) in the control group. Use of an ARI was associated with a statistically significant increased risk of falls and fractures: all-grade falls (RR, 1.8; 95% confidence interval [CI], 1.42-2.24; P < 0.001); grade 3 or greater fracture (RR, 1.59; 95% CI, 1.27-2.08; P < 0.001); all-grade fracture (RR, 1.59; 95% CI, 1.35-1.89; P < 0.001), and likely grade 3 or greater fracture (RR, 1.71; 95% CI, 1.12-2.63; P = 0.01).

**Conclusions and Relevance:** ARI use was associated with increased falls and fractures in men with PCa as assessed by a retrospective systematic review and meta-analysis. Additional studies are needed to identify and understand potential mechanisms and develop strategies to decrease falls and fractures associated with ARI use.
Adjuvant ADT in Localized PCa (Continued from page 1)

P=0.002, and point estimates for secondary end-points favored adjuvant ADT:
- Distant metastasis: HR 1.40, 95% CI 1.00-1.95
- Metastasis-free survival: HR 1.17, 95% CI 1.00-1.37
- Prostate cancer-specific mortality (PCSM): HR 1.29, 95% CI 0.95-1.75
- Overall survival (OS): HR 1.11, 95% CI 0.95-1.30

“Late grade ≥3 genitourinary toxicity was no different between the 2 groups, with a cumulative incidence of 5% in each. For late grade ≥3 gastrointestinal toxicity, 15-year rates were 3% with neoadjuvant ADT and 2% with adjuvant treatment. There was also no difference in patient-reported quality of life,” said Spratt.

“We believe this analysis currently serves as the highest level evidence to support the importance of sequenc- ing ADT with RT,” he said.

Spratt pointed out that numerous trials testing different durations of neoadjuvant ADT have failed to show improvements in metastasis, PCSM, or OS. “But when you look at trials that either used adjuvant ADT, or those extending the duration of adjuvant ADT, all of them were positive for either metastasis, PCSM, or OS,” he said.

ASTRO discussant Alejandro Berlin, MD, MSc, of Princess Margaret Cancer Centre in Toronto, called the study “thought-provoking” and said it resurfaces the longstanding need “to better understand the biological underpinnings” behind the improved outcomes seen in PCA patients treated with ADT and RT.

“It’s important to remember that studies exploring different durations of neoadjuvant ADT have not shown benefit of extending its duration, unlike what we have seen in the adjuvant setting,” he said. “When men are referred to us with an already-started ADT regimen, it poses a challenge to determine the optimal total duration of that therapy.”

But Berlin also cautioned that the takeaway message should not be to avoid neoadjuvant ADT.

“In fact, most studies exploring the use of adjuvant hormonal therapy have had a component of neoadjuvant treatment,” he said. “What I think is relevant here is that, in the future, we should move beyond exploring solely the RT local treatment effect because there are impacts of what we do before, during, and after treatment, and this seems to be a dynamic field.”

The pooled analysis from Spratt and colleagues used patient-level data from two randomized trials – Ottawa 0101 and RTOG 9413 – to compare use of prostate-only RT plus ADT delivered either in the concurrent/neoadjuvant setting (n=531) or concurrent/adjuvant setting (n=534). All patients in Ottawa 0101 were included, while in RTOG 9413, those in the whole-pelvis arm RT were excluded to “harmonize” the datasets.

Men had a median age of 70 years. Median PSA was 14.1 ng/mL, with more than a third with a PSA >20 ng/mL. A majority (58%) of men had Gleasonscore 7 tumors, 25% had a score <7, and 17% had a score of 8-10. For tumor stage, 42% had T1-T2a tumors, 38% had T2b-T2c, and 20% had T3-T4 tumors.

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AS for Blacks vs. Whites (Continued from page 1)

black men with PCa were about 30% more likely to have disease progression (subdistribution hazard ratio [SHR] 1.3, 95% Confidence Interval [CI] 1.2-1.4, P<0.001) and receive definitive treatment (SHR 1.3, 95% CI 1.2-1.4, P<0.001) compared with white men.

Despite this increased risk, however, the rates of metastatic disease were similar between the 2 groups: cumulative incidence at 10 years of 1.5% for black men and 1.4% for white men. Additionally, PCa-specific and all-cause mortality rates were similar between the 2 patient populations, with Black men having no increased risk on multivariable competing risk regression analyses, the researchers reported.

They cautioned, though, that longer-term follow-up is needed to better assess the mortality risk.

“Hopefully, these results encourage African American men with low-risk PCa to consider AS,” Rose said.

“Additionally, these findings may support higher rates of PSA screening and early detection if men know that they may not need treatment if they find a low-risk cancer. This will help us to identify the aggressive cancers that do need to be treated in order to reduce the disparity in PCa outcomes for African American men.”

Writing in an accompanying editorial, Xinglei Shen, MD, MS, of the University of Kansas Medical Center in Kansas City, and colleagues acknowledged the dearth of data about whether AS – the use of which is increasing, they note – is as safe for black PCa patients as it is for white men with the disease.

“This is because prior studies have shown that among black patients, compared with white patients, the onset of PCa is earlier and tumor volumes are greater even among men with low-risk disease,” the editorialists wrote. “Further, existing data show that black patients with low-risk PCa who underwent radical prostatectomy were more likely to harbor more aggressive disease on surgical pathology compared with white patients.”

“Because black patients have more biologically aggressive PCa and higher progression rates during AS compared with white men, there is a greater need for black men in the general population to have access to high-quality and timely care to avoid delays in diagnosing cancer progression and receiving definitive treatment,” the editorialists emphasized.

“Indeed,” Rose said, “it will be important that black men who decide to undergo AS receive the frequent PSA testing, repeat biopsies and, in some cases, imaging that is required. Barriers that prevent African American men from receiving appropriate surveillance could put them at risk for missing the early signs of progression and delay treatment in those that need it.”

“Additionally,” Shen and colleagues wrote, “how well AS is being implemented into routine practice – for all men – has not been well studied. In the study by Rose and colleagues, all men had undergone at least one sur-

(Continued on page 8)
New Staging System
(Continued from page 1)

Among factors considered when developing the scoring system were age, T category, N category, Gleason grade, pretreatment serum PSA level, and proportion of positive core biopsies. The system performed well across validation cohorts. In one validation set, predicted 10-year PCA-specific mortalitry ranged from 0.3% to 40.0%. The 10-year C index of the Score staging system (0.796) exceeded that of the AJCC 8th edition (0.757) – [1.0 is 100% correlation]. This improved performance was evident across age, race, and treatment subgroups. In a second validation set, the Score system also showed superior performance “Thus, an international consortium of over 60 practices created the first staging system for PCa that not only is valid and meets all criteria to be used as a formal staging system, but it outperforms NCCN risk groups, Cancer of the Prostate Risk Assessment (CAPRA), and the expert opinion derived AJCC 8th edition of staging. This will help physicians better communicate and personalize their treatment recommendations” concluded Dr. Spratt.

Dr. Yaw A. Nyame of the University of Washington, co-author of an accompanying editorial, told Reuters Health, “The strength of this study is that it provides an easy-to-use clinical decision aid that was developed using contemporary data and evaluates a meaningful clinical endpoint in death from PCa.”

Hood Technique Can Facilitate Swift Return to Urinary Continence After Radical Prostatectomy

The “hood” technique for robot-assisted radical prostatectomy (RARP) returned continence within 4 months, without compromising surgical margins, in a single-center, single-surgeon study. “The clinical findings show that early urinary continence is possible and the novel hood technique helped to speed up this process,” Dr. Ashutosh (Ash) Tewari of the Icahn School of Medicine at Mount Sinai in New York City told Reuters Health by email. “Ninety-five percent of men were able to achieve urinary continence within days to a week rather than waiting weeks when the more standard technique is used.

“Hundreds of thousands of men have undergone one or another transperineal anterior or RP technique, so most surgeons are already familiar with this approach,” he said. “The hood technique was a minimalistic change in an existing and familiar approach for many surgeons.” After RP, the new technique preserves tissues that together have the appearance of a hood – namely, “the detrusor apron, arcus tendineus, puboprostatic ligament, anterior vesicles, and some fibers of the detrusor muscle,” Dr. Tewari explained. The strategy “spared musculofascial structures anterior to the urethral sphincter complex, with early return of continence after surgery without compromising surgical margins.” As reported in European Urology, the researchers studied outcomes of 300 men (median age, 64) treated by Dr. Tewari using the RARP hood technique from 2018-2019. Fifty-one percent had stage T1 cancer; 35% had T2; and 14% had T3.

Catheter removal was performed on post-op day 7. The continence rate – defined as completely pad-free at 1, 2, 4, 6, 12, 24, and 48 weeks after catheter removal were 21, 36, 83, 88, 91, 94, and 95%, respectively. Fourteen men (5%) were not continent at the end of 1-year follow-up: 9 were occasional using 1 pad per day (PPD); 3 were using 2 PPDs; and one was using 4 PPDs. The overall positive surgical margin rate was 6%.

Thirty men (9.7%) experienced complications after RARP: 17 (5.7%) had Clavien-Dindo grade I complications; 11 (3.6%), grade II; and 1 (0.4%), grade III.

Despite the technique’s success, “guidelines should not be changed as comparative trials are still needed,” Dr. Tewari said. “This is not the only technical refinement happening in this field. There are, and will be, many other approaches and techniques that will impact the guidelines. We need to tailor the surgery towards the patient, rather than applying one surgery to every patient.”

Dr. Ali Zhumkhawala, a urologic oncology surgeon at City of Hope in Duarte, CA commented, “Many studies have shown the importance of preserving or reconstructing anterior support in post-operative continence. The ‘hood’ technique appears to be a feasible modification on more traditional techniques with low complication rates and low positive margin rates.”

That said, like Dr. Tewari, he noted that while the technique is “very promising,” comparative studies are needed. “In addition,” he said, “surgeons with less experience may not see the continence rates and low positive margin rates presented by Dr. Tewari’s group.”

Reuters Health Information
27 October 2020

The Clinical Significance of Multiple Negative Surveillance Prostate Biopsies for Men on Active Surveillance — Does Cancer Vanish or Simply Hide?

Chu CE, Cowan JE, Fasulo V, et al.

J Urol. 17 November 2020; E-Pub ahead of print

Purpose: Men with low-risk prostate cancer (PCa) on active surveillance (AS) undergo multiple prostate biopsies over time. The long-term clinical significance of consecutively negative biopsies is not known.

Materials and Methods: Men with low-risk PCa prospectively enrolled in an AS database with at least 4 biopsies were included in the study. Exposure variables were 0, 1 or 2 consecutively negative biopsies after diagnosis. Other variables included age, PSA, PSA density, Gleason grade group, percent positive cores and magnetic resonance imaging (MRI) findings. Outcome variables were the detection of any cancer at fourth biopsy and active treatment.

Results: A total of 514 men were included, with 112 (22%) men having 1 negative biopsy and 78 (15%) with consecutively negative biopsies. Median PSA density was

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Could Ipilimumab Have Benefit in Metastatic Prostate Cancer After All?
Long-Term Analysis of Post-Radiotherapy Data Suggests the Answer is Yes
Karin Fizazi, Charles G. Drake, et al.

Goal:
The goal of this study was to evaluate radiotherapy (RT) to bone metastases followed by ipilimumab or placebo in men with metastatic castration-resistant prostate cancer (mCRPC) who had received previous docetaxel.

Question Addressed:
Did long-term follow-up show that men with mCRPC survive longer with RT plus ipilimumab vs. placebo?

Synopsis and Perspective:
Although immune checkpoint inhibitors have shown limited clinical benefit in prostate cancer (PCa) PCa treatment, the reality is that these agents appear to work best against so-called “hot” tumors, i.e., cancers invaded by T cells, which often have a high mutational load.

PCa is regarded as an immunologically “cold” tumor, but emerging evidence indicates that a subset of cold tumors could be converted into hot tumors. Final results from a randomized phase III trial were recently published online in *European Urology* comparing RT for bone metastases plus ipilimumab or placebo in men who had already received docetaxel treatment for mCRPC.

The primary analysis, conducted after a median follow-up of 9-10 months, showed a median overall survival (OS) of 10-11 months in the 2 treatment arms, as opposed to a hypothesized 5-month improvement with the addition of ipilimumab (15 vs. 10 months). Progression-free survival (PFS) and response were significantly higher in the ipilimumab arm.

Although OS was not improved in the initial analysis, the current intent-to-treat analysis with long-term follow-up showed a 2-3 fold improvement at 2, 3, 4, and 5 years in the ipilimumab arm. A piecewise hazard model showed a changing survival hazard ratio (HR) over time in favor of ipilimumab, ranging from 1.49 at 0 to 5 months to 0.66 beyond 12 months.

“Long-term analyses of survival are rarely reported in mCRPC studies, although this is of even greater importance for immunotherapy trials, because a delayed effect on the immune system is expected,” wrote Karim Fizazi, MD, of Gustave Roussy Institute in Villejuif, France, and colleagues. “This global study was the first phase III trial testing ipilimumab in men with mCRPC that included long-term follow-up and the primary endpoint of OS was not improved at the initial analysis.”

The trial enrolled almost 800 men from 2009 to 2012—a notable period of time when there was a dearth of effective treatments for mCRPC, except for docetaxel.

Initially, there was no significant improvement in OS in the 399 men randomized to RT followed by ipilimumab compared with the 400 men randomized to placebo (HR 0.85, 95% Confidence Interval [CI] 0.72-1.00, P=0.053). However, Kaplan-Meier analysis of OS showed crossing of the curves at 7-8 months, followed by persistent separation of the curves, favoring the ipilimumab arm beyond that point.

While the 1-year OS rate did not differ significantly between men receiving ipilimumab vs. placebo (47 vs. 41%), the between-group differences became significant thereafter:
- 2 years: 25 vs. 17% (8.6-point absolute difference, 95% Confidence Interval [CI] 3.0-14)
- 3 years: 15 vs. 7.9% (7.4, 95 CI 3.0-12.0)
- 4 years: 10 vs. 3.3% (6.8, 95 CI 3.4-10)
- 5 years: 7.9 vs. 2.7% (5.2, 95 CI 2.1-8.3)

Seven men died due to study drug toxicity in the ipilimumab arm compared to 1 man in the placebo arm. Overall, the safety profile for ipilimumab was similar to that reported previously, with immune-related adverse events most commonly occurring in the gastrointestinal tract and skin, and in the liver and endocrine organs to a lesser extent. The researchers did not identify any long-term safety signals.

Study limitations included the use of subsequent therapy beyond the primary analysis cutoff in 41% of ipilimumab-treated men vs. 47% of placebo-treated men.

Study Highlights and Explanation of Findings:
Long-term results of a randomized phase III trial show that OS was improved with RT for bone metastases followed by ipilimumab compared with placebo in men with mCRPC who had previously received docetaxel.

Fizazi and team emphasized that the data were collected after the primary OS analysis and should therefore be considered hypothesis generating, rather than definitive. They noted that patients in the ipilimumab arm initially had worse outcomes in the first 7 months of treatment. Following crossover of the Kaplan-Meier survival curves, the ipilimumab group appeared to have improved OS compared with the placebo group.

“Of note, hyperprogression of cancer has been described with these immunotherapies, and they may explain this phenomenon, at least in part,” the researchers wrote. Another possible explanation was an excess of side effects noted in the ipilimumab arm during the initial weeks of the trial that might have been associated with the excess of early deaths in this arm.

“It finally is plausible that men with more indolent cancers and those with a lower burden of cancer may also be more sensitive to immunotherapy, which may account for the delayed effect on survival,” they added.

In an accompanying editorial, Russell Pachynski, MD, of the Washington University School of Medicine in St. Louis, noted the observed disconnect between PFS and OS seen in several immunotherapy trials might be due to complex reasons, including issues of drug-mediated toxicity and delayed onset and/or effect of antitumor responses in the setting of progressive disease.

Pachynski said that the initial (Continued on page 8)
A 2-day course of high-dose stereotactic body radiotherapy (SBRT) doubles the complete pain response for patients with painful spinal metastases vs. conventional palliative RT. It is also safe and non-stabilizing, conclude researchers reporting a phase 3 Canadian trial.

“Conventional RT has historically not achieved high rates of complete response to pain or long-term local control,” commented lead author Arjun Sahgal, MD. “So many years ago, we started building on the idea of using high-dose SBRT for the spine.”

Sahgal, who is professor and deputy chief of radiation oncology at Sunnybrook Health Sciences Center, the University of Toronto, Ontario, Canada, explained that his team devised a plan to use SBRT with 24 Gy in 2 fractions. This involves only 2 consecutive treatments, which is very convenient for patients. Conventional RT requires 5 or more sessions.

“Now we have shown a doubling of the complete response rate to pain at 3 and 6 months compared with conventional palliative RT, and patients appreciate fewer treatment sessions, too, so we are helping our patients financially,” Sahgal told Medscape Medical News.

He presented the new results during the 2020 virtual annual meeting of the American Society for Radiation Oncology (ASTRO).

Patients enrolled in this trial had de novo (recent onset) painful spinal metastases with metastatic involvement in 3 or fewer consecutive spinal segments arising from a primary tumor causing pain that was scored at least 2 on the Brief Pain Inventory.

“The median baseline worst pain score was 5 in a range of 2 to 10. The median total spinal instability and neoplasia score (SINS) was 7 in a range of 3 to 12,” Sahgal noted. “The primary endpoint was complete pain response rate at 3 months,” Sahgal told a press briefing held within the context of the virtual meeting.

Patients were randomly assigned to receive either SBRT with 24 Gy delivered in 2 fractions over 2 consecutive days or conventional palliative RT with 20 Gy delivered in 5 fractions.

“The trial was launched as a phase 2 study initially, but once investigators could demonstrate that patient accrual was possible, they converted the trial into a phase 3 study,” Sahgal noted.

A total of 114 and 115 patients were enrolled in the SBRT and conventional RT arms, respectively. All were included in the intent-to-treat analysis. “We found that at 3 months, the complete response rate was 35 vs. 14% in the SBRT and conventional RT arms, and the difference was statistically significant,” Sahgal reported.

The complete response rate was sustained at 6 months. It remained at 32% in the SBRT arm and 16% in the conventional RT arm. There was also a reduction in the total SINS score at 6 months that favored the SBRT arm.

Adjusted for age, sex, performance status, primary cancer, and total baseline SINS, SBRT was almost 3.5-fold more likely to result in a complete pain response rate at 3 months and was about 2.5-fold more likely to yield the same response at 6 months compared with conventional RT – “which was highly significant at both endpoints,” Sahgal noted.

However, there was no difference between treatment groups in either radiation-site-specific progression free survival (PFS) or overall survival (OS). After 3 months, 92 and 86% of patients in the SBRT and conventional RT arms, respectively, were cancer free at the treated site, and at 6 months, 75 and 69%, respectively, were cancer free at the treated site.

As for adverse events, 17% of patients who received conventional palliative RT developed a vertebral compression fracture following treatment, compared with 11% of SBRT-treated patients, but the risk for adverse events of grade 2 or higher was essentially the same in both treatment arms.

Importantly, those treated with SBRT reported a better quality of life (QoL) than those treated with conventional RT. “Patients are dealing with metastatic disease. Now they have to come to the hospital for another treatment, and the financial burden of coming to the hospital is not inconsiderable,” Sahgal said.

“So patients appreciate fewer treatment sessions and, even if it costs our department more, because treatment with SBRT needs so much more planning and resources, we are helping our patients financially, and this will push our departments to say, even if it costs more to do, SBRT is better for our patients,” he said.

**Special Advantage**

Commenting on the study, session moderator Sue Yom, MD, PhD, professor of radiation oncology, otolaryngology-head and neck surgery, University of California, San Francisco, reminded the press that with SBRT, very high doses can be delivered very safely to precise areas of the body with a small number of treatments. “This has obvious advantages over conventional RT,” she noted, “and may be especially an advantage now in the midst of the COVID pandemic, as it reduces the risk [for viral exposure] to patients and hospital personnel.

“With this study, the additional resources and expense involved in offering SBRT in comparison with conventional RT appear to be justified,” Yom said. “The increased dose that was given in only 2 fractions of SBRT produced results that allowed significantly more patients to achieve complete pain relief than patients who got conventional treatment with 5 fractions to the same site,” Yom reaffirmed.

“And the complete resolution rate of the spinal tumors at 6 months was also superior with SBRT, so the oncologic benefits with SBRT vs. conventional RT are also better,” she said. Yom also felt that the QoL surveys that were filled out by patients during the study – not reported during the press briefing, but alluded to by Sahgal during his interview with Medscape Medical News – were also quite revealing.

“‘It’s easy to dismiss any difference between 2 and 5 treatments as not being significant, but there was a real quantifiable difference between 2 and 5 treatments in terms of patients’ QoL,’” she noted.

“So being able to have fewer treatments is significant to patients, and that significance buttresses this study’s importance,” she said.

Presented at the ASTRO 2020 Annual Meeting, Abstract LBA-2, on 26 October 2020

Medscape Medical News 29 October 2020
Iopilimumab
(Continued from page 6)

analysis suggested ipilimumab might provide the most benefit in men with favorable prognostic features. Immuno-
therapy might be used in metastatic PCa at a point of lower tumor burden in which tumor-induced immunosup-
pression is lower.

Citing metastatic hormone-sensitive PCa as a prime example, he noted that different immune checkpoint inhibitor-
based therapies are in trials or are about to be tested in this space, i.e., (NCT03532217, NCT04191096, NCT04477512).

“While much remains unknown and unstudied in the field, outcomes from this and ongoing trials and studies will help to expand our understanding of how best to increase and extend the ‘tail’ of immunotherapy in prostate cancer,” Pachynski concluded. 

MedPage Today
27 October 2020

Comparing Active Surveillance for Blacks vs. Whites (Continued from page 4)

veillance biopsy and had a median of 12 PSA tests. In contrast, a study reported at the 2019 American Society of Clinical Oncology annual meeting using data from a North Carolina cancer registry showed that only 58% of men received routine PSA tests within the first 2 years of AS, and only 45% had a surveillance biopsy.

“Further reassurance [about AS] would be gained from research showing similar outcomes in broader general population settings outside of the VHA context,” Shen and co-authors concluded. “Until such evidence is available, concerns about biologic differences in PCa between black and white men and potential disparities in receiving timely AS monitoring and treatment on cancer progression may continue to drive lower rates of AS use among black patients.”

MedPage Today
3 November 2020

Multiple Negative Surveillance Biopsies – Does Cancer Hide? (Continued from page 5)

lower for men with 1 negative biopsy (0.11) and consecutively negative biopsies (0.10) compared to men who never had a negative biopsy (0.13, p < 0.01, a statistically significant difference). On univariable logistic regression higher PSAD density (Odds ratio [OR] 1.68, 95% confidence interval [CI] 1.16-2.45) and suspicious magnetic resonance imaging lesions (OR 2.00, 95% CI 1.16-3.42) were associated with a higher likelihood of detecting cancer on fourth biopsy. On multivariable logistic regression 1 negative biopsy (OR 0.22, 95% CI 0.12–0.41) and consecutively negative biopsies (OR 0.12, 95% CI 0.06–0.24) were associated with a lower likelihood of detecting cancer subsequently. Unadjusted 10-year treatment-free survival was highest for men with consecutively negative biopsies (84%) and 1 negative biopsy (74%) than those who had none (66%) (log rank p=0.02).

Conclusions: Consecutively negative surveillance biopsies are correlated with favorable clinical risk factors and independently associated with subsequent negative biopsy and lower risks of active treatment.

SEA Blue 2020 Video!
Video is now available from our SEA Blue 2020 National, Virtual Prostate Cancer Walk, Run, and More!
https://youtu.be/LHE_zMmu7Hg

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PAGE 8
QUESTION FROM PROSTATE CANCER SURVIVOR:
I can’t get the answers I need for my questions or problems but I am really frustrated at the length of time it is taking for things to return to normal for me. I had radiation (36 treatments) that ended about 9 months ago, as well as hormone therapy with my last injection 3 months ago. I am still having hot flashes and I have not seen any return of erections, never mind sexual interest. I’m 74 years old and I feel like my life is over. I thought that once my treatment was done I would see improvements in all areas but, so far, things are as bad as they ever were. Am I alone in this? What do other men experience?

RESPONSE FROM DR. ANNE KATZ:
Firstly, you are NOT alone. This is a question that I am frequently asked, always by men who are frustrated about the length of time it is taking for things to return to normal. Every man has his own idea of what normal is, but the three issues that seem to be most common are hot flashes, return of sexual interest (libido), and ongoing lack of erections.

The quick answer to this is “It depends.” There are many factors that go into when any of the above will improve. This depends, in part, on the return of testosterone levels to the normal range or to baseline for the individual man. A recent study (Nascimento et al., 2019) of men who had from 3 to 42 months of androgen deprivation therapy found that two years after the end of the treatment, 8% did not see any increase in their testosterone levels, 76% returned to testosterone in the normal range, and 51% had testosterone levels at their baseline (before treatment) level. Those with lower levels of testosterone at the start of treatment and those who received more than 6 months of androgen deprivation therapy were less likely to see a return to normal levels, and those who were older than 65 years and who had also received more than 6 months of androgen deprivation therapy were more likely to see a slower recovery of testosterone levels. This all means that you can hope for, or expect, changes in all your symptoms with time – although this may not be fast enough for you.

But testosterone is not the only issue. You have had radiation, in addition, and you are now a year older than you were when you started treatment. You do not say if radiation was your first treatment; did you have surgery before that and when? And age is not a friend to the penis! As men age their ability to both achieve and maintain an erection declines. This is related to changes in the cardiovascular system (arteries and nerves) as well as other conditions they may have (for example, diabetes) and any medications they are taking to treat these conditions.

The hot flashes may often persist for many months and this can be distressing, as this may affect your sleep and can also be embarrassing. Hopefully you were advised about some measures that can help – fan in the bedroom, light cotton clothing etc. when you started treatment. You can also talk to your primary care provider about possibly taking medication that may help. ‘It depends’ as an answer is frustrating for most men, but this is all we have to offer. Everyone is different, and how your body reacts to the medication – as well as how quickly things return to whatever you define as normal – is variable.


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 at: https://www.youtube.com/watch?v=A2ZdDHw2WGY&t=8542s.

Read previous issues of Between the Sheets at 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: ustopBTS@ustoo.org

Or mail your letter to:
Us TOO International
Between the Sheets
2720 S. River Road, Suite 112
Des Plaines, IL 0018
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).

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.

Our holidays may look different, but we’ll probably have the chance to sample some less-than-healthy foods – perhaps a box of homemade cookies left on the doorstep by a neighbor. It’s a time enjoy some treats, while keeping the “big picture” of healthy eating in mind. Janet Farrar Worthington consulted experts about the relationship between food and prostate cancer.

Your Best Life Before, During, and After Prostate Cancer: Focus on Diet

By Janet Farrar Worthington

Eating the right diet can boost your spirits, your energy level, and just generally make you feel better. Most importantly for prostate cancer, certain foods can help lower chronic inflammation (https://pubmed.ncbi.nlm.nih.gov/32546840) and insulin (https://www.pcf.org/c/prostate-cancers-sweet-tooth) that fuel prostate cancer growth, and, in addition, can help your body fight or prevent any number of chronic diseases that are also driven by chronic inflammation. The good news is that it goes both ways: there is growing evidence that the lifestyle choices that keep you safe from other diseases – such as eating low sugar for diabetes, or exercising for your heart – can also help prevent or curtail prostate cancer.

First, Why Studying Diet is Hard

Research on food as medicine is one of the hardest areas in which to do controlled, rigorous research. PCF-funded epidemiologists June Chan, Sc.D., of UCSF and Lorelei Mucci, M.P.H., Sc.D., of Harvard both study lifestyle factors and their effect on prostate cancer. Even though many late-night TV ads might try to tell you otherwise, there are no single magic bullet diet prescriptions for disease.

In many studies over the years, scientists have tried to isolate specific foods to see if they promote or prevent cancer; they do that by asking people to recall what they ate over certain periods of time or keep a food journal. Such studies take a long time, and are not without their share of problems. For example, even if you isolate certain foods that seem promising, there is still a lot of variation! Let’s say, hypothetically, you notice that people who eat apples are less likely to get cancer. But what about the kind of apples, how many were eaten, whether people who eat apples are also more likely to exercise and take better care of their health in general? – it’s not that simple. This is why you might notice that science around nutrition takes time; or you might see it evolve over time as scientists “factor out” more variables.

Broad Strokes are Better

There are a confusing number of variables in food science, so researchers don’t yet have a Paint-by-Number approach, with every single food accounted for. Instead, today’s food science is painting with some broad – but definitive – strokes.

Chan and Mucci both cite work led by Harvard scientists Fred Tabung, Ph.D., M.S.P.H., and Edward Giovannucci, M.D., Sc.D., that look at the relationship (https://pubmed.ncbi.nlm.nih.gov/29897561) between diet and inflammation. In the study, the scientists tracked inflammatory markers in the blood and whether inflammation was raised or lowered by what people ate, based on data from thousands of participants in the Nurses’ Health Study and the Health Professionals Follow-Up Study. The key lies in the foods they found that significantly reduce chronic inflammation: dark yellow vegetables (carrots, winter squash, sweet potatoes, etc.); leafy green vegetables (like spinach, broccoli, kale, etc.), coffee, and wine. Beer (one bottle, glass, or can) was in this category, too. So was tea, but its effect was not very strong.

The pro-inflammatory (aka, bad) category included: processed meats (hot dogs, bacon, pepperoni, lunch meat, etc.), red meat, refined grains, high-energy beverages (with additives and sweeteners), and “other vegetables,” like potatoes and corn. Interestingly, not all fish is equal: canned tuna, shrimp, lobster, scallops, and “other” fish were more inflammatory than “dark-meat” fish like salmon or red snapper.

But if you love canned tuna, and if you love a baked potato or corn on the cob, don’t freak out: remember, broad strokes! The key seems to be to make sure you DO eat the anti-inflammatory foods. For example, the anti-inflammatory effects of leafy green vegetables, dark yellow vegetables, wine and coffee are more powerful than the very mild, pro-inflammatory effect of “other fish” or “other vegetables.” If you feel like you just can’t give up meat entirely, that’s okay too: just aim for small portions of meat, surrounded by a rainbow of anti-inflammatory vegetables.

For more information visit www.pcf.org, email info@pcf.org, or call 1-800-757-2873.
This Season, Give the Gift of Hope...

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There are nearly three million men in the U.S. living with a prostate cancer diagnosis. That number is estimated to climb to four million by 2024 as men in the baby boom 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. Your donation helps Us TOO International raise the awareness of prostate cancer, encourage more men to get screened, and provide life changing medical information to men and their families.

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Us TOO International’s educational website has been visited more than 1.8 million times over the past three years. More than 1,640 people seeking information about prostate cancer visit our website every day! Us TOO International facilitates more than 200 prostate cancer support groups in 40 states and five countries! We send a monthly newsletter to more than 23,000 subscribers, with helpful information about prostate cancer. Your donation dollars mean thousands of people have access to up-to-date information on prostate cancer, diagnosis information, scientific breakthroughs, and information on treatment options and side effects!

How You Can Help
As the year comes to a close, please consider a gift to Us TOO International to help more families like Kathie and Dave Houchens to fight this disease.

THANK YOU FOR YOUR SUPPORT!

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On behalf of the board, staff and volunteers at Us TOO International, those we have helped in their battle with prostate cancer, and those we will help... THANK YOU for your donation!

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