Too Much Radiotherapy Still Being Used for Bone Metastases

One third of physicians are still treating patients who have cancer and bone metastases with extended-fraction radiotherapy (RT), even though a single eight-Gy fraction for this purpose has been strongly recommended since 2013.

Indeed, the new analysis of more than 12,000 patients treated for bone metastases found that only 9% received the recommended single-fraction treatment. The study was published online April 13th in JCO Oncology Practice.

“In this era of COVID-19, we are trying to minimize contact with the healthcare system as much as possible, so coming into the hospital 20 times over four weeks when you could come in once is extraordinarily important,” lead author Arjun Gupta, MD, Johns Hopkins University told Medscape Medical News.

“While I am not suggesting that every patient can be successfully treated with a single fraction, since patients can have complicated bone metastases,” he added, this finding that only 9% of patients received a single fraction is “shockingly low.”

The study authors used Medicare fee-for-service carrier claims to estimate the use of single vs. extended-fraction RT to treat bone metastasis. “We identified 12,221 Medicare beneficiaries who underwent RT for bone metastases between 2016 and 2018,” they note. The median age of the cohort was 75.6 years, and almost 41% of the group were women. Over 1,400 physicians were included in the analysis.

RT episodes were categorized as nonextended if they involved one to 10 fractions; they were categorized as extended if they (Continued on page 5)

10-Year Update of a Randomized, Prospective Trial of Conventional Fractionated Versus Moderate Hypofractionated Radiation Therapy for Localized Prostate Cancer

J Clin Oncol 38: 1676-1684, 2020

Purpose: The previously published single institution randomized prospective trial failed to show superiority in the five-year biochemical and/or clinical disease failure (BCDF) rate with moderate hypofractionated intensity-modulated radiation therapy (H-IMRT) vs. conventionally fractionated IMRT (C-IMRT). We now present 10-year disease outcomes using updated risk groups and definitions of biochemical failure.

Methods: Men with protocol-defined intermediate- and high-risk prostate adenocarcinoma were randomly assigned to receive C-IMRT (76 Gy in 38 fractions) or H-IMRT (70.2 Gy in 26 fractions). Men with high-risk disease were all prescribed 24 months of androgen deprivation therapy (ADT) and had lymph node irradiation. Men with intermediate-risk disease were prescribed four months of ADT at the discretion of the treating physician. The primary endpoint was cumulative incidence of BCDF. We compared disease outcomes and overall mortality by treatment arm, with sensitivity analyses for National Comprehensive Cancer (Continued on page 8)
Shared Decision Making and Prostate-Specific Antigen Based Prostate Cancer Screening Following the 2018 Update of USPSTF Screening Guideline

Jiang C, Fedewa SA, Wen Y, Jemal A, Han X

Prostate Cancer Prostatic Dis 15 April 2020 [Epub ahead of print]

Previous studies reported shared decision making was underused in PSA-based prostate cancer (PCa) screening. In mid-2018, the US Preventive Service Task Force recommended shared decision making (SDM) before PSA-based PCa screening among men aged 55-69 years while it remained against PSA testing in men aged 70 or older. The objective of this study is to examine recent changes in SDM and PCa screening following recent USPSTF recommendations. A retrospective cross-sectional study among men aged 50 years or older was conducted using 2015 and 2018 National Health Interview Survey data (n 10,926). Outcomes included self-reported PSA testing for PCa screening last year and whether the respondent ever had a discussion with the healthcare provider about its advantages and disadvantages. Analyses were stratified by age (50-54 vs. 55-69 vs. 70+). Routine PSA screening rates remained stable from 34.3% in 2015 to 35.4% in the first half of 2018, and 36.0% in the second half of 2018 (p trend = 0.57, not a statistically significant trend). A similar pattern was found in men ≥70 years (p trend = 0.98). Receipt of SDM increased in men aged ≥50 years from 30.5% in 2015 to 33.6% in the first half of 2018, and 36.7% in the second half of 2018 (p trend = 0.002, a statistically significant trend).

The increase was most prominent in men aged 55 to 69 years (31.6, 36.9, and 40.2% in 2015, the first half of 2018 and the second half of 2018 respectively; p trend = 0.001). Between 2015 and 2018, there was no significant increase in the PSA-based PCa screening. However, a significant increasing trend in SDM was observed, especially in men aged 55-69 years.

17-Gene Genomic Prostate Score Test Results in the Canary Prostate Active Surveillance Study (PASS) Cohort


J Clin Oncol 38: 1549-1557, 2020

Purpose: The 17-gene Oncotype DX Genomic Prostate Score (GPS) test predicts adverse pathology (AP) in men with low-risk prostate cancer treated with immediate surgery. We evaluated the GPS test as a predictor of outcomes in a multicenter active surveillance (AS) cohort.

Materials and Methods: Diagnostic biopsy tissue was obtained from men enrolled at eight sites in the Canary Prostate Active Surveillance Study. The primary endpoint was AP (Gleason Grade Group [GG] ≥ 3, pathologic stage ≥ pT3a) in men who underwent radical prostatectomy (RP) after initial AS. Multivariable regression models for interval-censored data were used to evaluate the association between AP and GPS. Inverse probability of censoring weighting was applied to adjust for informative censoring. Predictiveness curves were used to evaluate how models stratified risk of AP. Association between GPS and time to upgrade on AS biopsy was evaluated using Cox proportional hazards models.

Results: GPS results were obtained for 432 men (median follow-up, 4.6 years); 101 underwent RP after a median 2.1 years of AS, and 52 had AP. A total of 167 men (39%) upgraded at a subsequent biopsy. GPS was significantly associated with AP when adjusted for diagnostic GG (hazards ratios [HR]/5 GPS units, 1.18; 95% Confidence Interval [CI], 1.04 to 1.44; p = 0.030), but not when also adjusted for prostate-specific antigen density (PSAD; HR, 1.85; 95% CI, 0.99 to 4.19; p = 0.066). Models containing PSAD and GG, or PSAD, GG, and GPS may stratify risk better than a model with GPS and GG. No association was observed between GPS and subsequent biopsy upgrade (p = 0.48).

Conclusion: In our study, the independent association of GPS with AP after initial AS was not statistically significant, and there was no association with upgrading in surveillance biopsy. Adding GPS to a model containing PSAD and diagnostic GG did not significantly improve stratification of risk for AP over the clinical variables alone.
Doc Moyad’s What Works & What is Worthless Column — Also Known as “No Bogus Science” Column
“Intrusive Thought Awareness During a Pandemic?!?”

Mark A. Moyad, MD, MPH, University of Michigan Medical Center, Department of Urology

Editor’s Note: Us TOO invites certain physicians and others to provide information and commentary for the Hot SHEET to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and are not necessarily those of Us TOO International.

Everyone loves to preach about the importance of mental health and cancer. Perhaps it has become PC to simply mention it, but not to elaborate on it. This is partially or slightly analogous to the how past and sometimes current utilization of the words “diet” or “exercise” or “lifestyle changes” are “critical” declarations and then the sound of silence after that... It is so much easier to review or comment on more traditionally tangible items or outcomes such as imaging, pathology, PSA, cholesterol, newest drugs or procedures, blah blah blah, you get the idea. Look, I am just as guilty here, so why not pivot toward changing this poor track record throughout cancer on mental health, and in this column.

A beautiful study of over 4,000 men receiving a radical prostatectomy (RP) involved collecting data pre-surgically, and three, 12, and 24 months post-RP. The unique goal of this investigation was to capture the impact of intrusive thoughts on patients, which are “unintentional recurrent and distressing thoughts about things one does not intend to think about” (also known as unwanted intrusive thoughts or negative self-talk). Researchers found an association between these thoughts and reduced quality of life, depression and “waking up with anxiety.” Pre-RP, approximately one-third of men had this experience and after two years it was about 20%. Thus, one of the conclusions was there is a strong need to address and then potentially treat these issues, if needed.

Past studies from some of these same researchers found that preoperative binge drinking, less optimal physical health, not being prepared for some of the side effects of surgery, and other observations were associated with an increased risk of intrusive thoughts. Thus, attempting to take better care of yourself, reducing self-medication behaviors (excessive alcohol), and better upfront objective education as to the pros and cons of cancer treatment could potentially reduce the risk of intrusive thoughts. However, the psychological impact of cancer, in some individuals, goes well beyond what can be self-controlled or within your immediate personal empowerment milieu. It could be a signal of greater psychological distress, as suggested by these researchers, and could or should be an indicator of the need to seek other forms of support or psychological care.

Whether you get a suggestion from a spouse, support group member, your health care team, or wherever, it is entirely possible that within your specific circle you might need to broach the subject. People are more inundated than ever before in the medical field and COVID-19 awareness and guidelines are taking this to another level. Health care professionals have become incredibly sensitive, in general, to the importance of mental health, but their own mental health is also being tested in this new normal of a pandemic world.

References:

Radical Prostatectomy Without Pelvic Lymph Node Dissection is Widely Practiced in High-Risk Patients Despite Poorer Survival

Kodiyan J, Guirguis A, Ashamalia H
Clin Genitourin Cancer, 13 Match 2020; [Epub ahead of print]

Radical prostatectomy (RP) with pelvic lymph node dissection (PLND) is the standard of care for unfavorable-risk prostate cancer. We investigated dissection practice patterns and their impact on overall survival using a large national database.

Men with prostate adenocarcinoma diagnosed between 2004 and 2013 were identified from the National Cancer Data Base. Disease was classified as either favorable or unfavorable on the basis of National Comprehensive Cancer Network guidelines. Minimum follow-up was four years. All patients received risk-appropriate surgery: RP with or without PLND. RP alone and RP with PLND was propensity score matched within each risk cohort. Survival analysis included Kaplan-Meier statistics, Cox proportional hazards model, and multivariate logistic regression.

A total of 66,469 men met the inclusion criteria. Median (range) age was 63 (27-90) years. Median (range) follow-up was 59.53 (48-143.54) months. Within the cohort of men with favorable risk disease, 51% did not undergo nodal dissection. Matched analysis demonstrated no difference in survival (p=0.926). Within the cohort of men with unfavorable risk disease, 39.2% did not receive nodal dissection. Matched analysis demonstrated that nodal dissection had superior survival (log-rank p=0.002; hazard ratio = 0.624; 95% confidence interval, 0.466-0.835; p=0.002, a statistically significant difference). Greater odds of receiving nodal dissection included an open or robot-assisted approach vs. a laparoscopic approach, academic/research programs, and higher risk groups.

Although PLND is associated with a significant survival benefit in men with unfavorable-risk prostate cancer, nearly 40% of patients with unfavorable risk disease did not receive PLND.

Get the Latest on COVID-19 and Prostate Cancer

Including resources, tips on holding virtual meetings, and an ongoing series of informational articles with some important comments regarding the coronavirus, cancer patients, and safety from Dr. Mark A. Moyad at www.ustoo.org/covid
Urinary incontinence, or the loss of ability to control urination, is a well-known consequence of prostate cancer treatment (surgery or radiation). It is a highly distressful situation for both the patient as well as their loved ones. Incontinence can affect many aspects of life, such as avoidance of activities, fear of intimacy, financial burden, and mental well-being.

There are two main types of urinary incontinence—stress incontinence and urge incontinence. Stress incontinence is urine leakage that occurs with changes in intra-abdominal pressure, like sneezing, coughing, or heavy lifting. Urge incontinence refers to urine leakage that occurs with a sudden strong desire to urinate that is unable to be suppressed. Stress incontinence is more common after prostate surgery and will be the main focus in this article. However, urge incontinence can also occur after prostate cancer treatment and this should be discussed with a physician as this may change the treatment options.

If you suffer from incontinence after prostate cancer treatment, you are not alone. Incontinence rates after prostate cancer treatment vary in studies, but it has been shown that a majority of men improve in the first six months following treatment.

Initially after surgery, the first step to becoming dry is beginning pelvic floor muscle exercises or therapy. This promotes muscle awareness and strengthens the urinary sphincter (the muscle that controls continence). It’s also an opportunity for a man to have some control over his outcomes. The exercises improve the time to recovery, but it is important to remember that this takes time and effort to complete.

After six to 12 months, only a minority of men will show further improvement in urine leakage. Therefore, if urinary leakage persists at this point, you should discuss your symptoms and level of bother with a urologist to determine your options.

Non-Surgical Management

Non-surgical management can be a way to manage the incontinence in the recovery period, but can also be used as a long-term management option. Treatment that falls under this category include:

- Pads/briefs
- Penile clamps/occlusive devices (Cunningham Clamp). During the day, it is important to remove this device every two hours to allow blood flow to the area. Men with decreased sensation in the genital area should not use penile clamps as they will not be able to sense any pressure wounds forming from the device. These devices are not to be worn overnight.
- Condom catheters. A condom catheter is an external device in which a condom is connected to a small urine collection bag. It is different from the catheter that is used after prostate surgery. This is ideal for men with severe incontinence.
- Indwelling catheters. This is usually a last resort for severe incontinence. Leaving an indwelling catheter in place is only an option if all others have been exhausted and/or are not possible.

Surgical Management

In a recent study, less than 4% of men who had their prostate removed pursued surgery for incontinence, even though reported rates of incontinence after prostate removal are much higher. In addition, they pursue surgery on average two years after their prostate removal, even though recommendations state that it is ok to have surgery for urinary incontinence as early as six months after prostate surgery. The reasons for this are many, but education is the first step!

Prior to any surgical intervention, it is important that the urologist evaluates if you are a good candidate for any of the therapies. They should also discuss what to expect during and after surgery and the risks/benefits of each procedure prior to moving forward. The goal of these therapies is to improve the incontinence, but the degree of improvement may vary from patient to patient depending on the severity of incontinence, radiation history, and more.

Currently available surgical therapies include the male urethral sling, artificial urinary sphincter and adjustable balloon devices. The descriptions below are brief overviews of the treatment and are not comprehensive by any means. Other therapies are considered investigational and not listed here. It is important to discuss with your urologist the specific details of each therapy.

Male Urethral Sling (Advance XP or Virtue Sling)

- Description: A sling is a synthetic material that is placed on the urethra to help support the urethra when you have increases in abdominal pressure, like with coughing and sneezing, to minimize leakage. The sling works right away. This is a passive therapy meaning the patient does not have to actively do anything to urinate.

- Surgical Expectations: The surgery can be performed as an outpatient surgery or the patient can be observed overnight depending on the urologist.

- Possible Complications: Urinary retention or inability to urinate, lack of improvement in incontinence, infection, and very rarely erosion.

- Comments: If this surgery is not effective, other options are still possible. This is often used in patients with mild stress incontinence and no history of radiation treatment.

Artificial Urinary Sphincter (AMS 800)

- Description: This is considered the gold standard for stress urinary incontinence in men. This has been in use since the 1970s. It is a three-piece device with a cuff, pump and a balloon. Everything is implanted and there are no external devices. The cuff sits around the urethra and provides compression of the urethra. To urinate, the patient presses the pump in the scrotum, which then opens the cuff for the patient to urinate. The cuff then closes on its own.

- Surgical Expectations: During the recovery period, men are advised not to perform any heavy lifting or any straddle activities. The device is then activa-

(Continued on page 6)
involved 11 to 20 fractions. For all comers, “the overall use of extended-fraction RT was 23.4%,” the authors report.

“However, we also looked just at patients who died within six months [of receiving RT for bone metastases], and in this group, one in six patients (16%) died within six months of getting extended-fraction RT,” Gupta added. “This means that patients are coming in for a whole month of 20 fractions when they are living six months or less,” he emphasized.

The American Society for Radiation Oncology’s Choosing Wisely guidelines, first issued in 2013, in particular emphasize that “strong consideration” be given to the use of single-fraction RT for the treatment of bone metastases for patients who have a poor prognosis and for whom durable local control may not be required, as well as for patients who have difficulty with transportation.

To identify practice patterns, the authors analyzed a subgroup of 382 physicians who had treated more than 10 patients. They found that 13.9% of this subgroup of providers had never used extended-fraction RT. Another 39% of this group used extended-fraction RT between 0% and 10% of the time. However, over half (55%) of the physicians in this subgroup used extended-fraction RT between 0% and 20% of the time.

Furthermore, for one third (33.2%) of these physicians, the extended-fraction RT use rate was 30% or higher. This was the threshold set by expert consensus for the study; use of extended-fraction RT at rates higher than 30% was considered excessive.

On multivariate analysis, men who were aged 85 years or older were less likely to be treated with extended-fraction RT compared with younger patients. This is reassuring, the authors suggest, inasmuch as physicians are clearly considering remaining survival time in their treatment decisions when treating elderly patients.

One of the predictors of use of extended-fraction RT in the study was the length of time since physicians had graduated from medical school. The analysis indicated that older physicians – those who had graduated 30 years ago or longer – were more likely to use extended-fraction RT vs. those graduating 10 or 20 years ago.

“What we speculate is that these practitioners have not potentially kept up with the evidence – they did not undergo training when this evidence was being carried out – so perhaps they are just entrenched in their ways,” Gupta suggested. “This finding raises the question as to whether targeting continuing medical education to these individuals would be helpful,” he added.

“Physicians who practiced in the South were more likely to use extended-fraction RT than those who practiced in the Northeast and the Midwest,” the authors also report. This is particularly troubling, the investigators suggest, because median travel time to any cancer care center is higher in the South than in other parts of the country.

The Choosing Wisely authors acknowledge that single-fraction RT is associated with higher retreatment rates. However, Gupta and colleagues argue that balanced against this are the drawbacks of multiple fractions.

“Unnecessary protracted RT causes financial toxicity and prolonged time spent in treatment and in travel, resulting in decrements in quality of life,” they note.

Moreover, Gupta pointed out, coming to the hospital for RT can be difficult for patients. “When you have painful bone metastases – they may be in your spine, in your arm, or in your leg – you have to get up, get into your car, drive an hour, get out of the car, wait an hour, get RT for an hour, drive back home, so your whole day is gone,” he emphasized. “It’s very intense,” Gupta said.

The authors suggest that their data highlight “actionable targets” for intervening in instances such of this that involve high-cost, low-value healthcare.

*Medscape Medical News*

1 May 2020

**Improvement in Overall Survival in Men with Non-Metastatic Castration-Resistant Prostate Cancer Treated with Darolutamide and Androgen Deprivation Therapy vs. Androgen Deprivation Therapy Alone**

NUBEQA® (darolutamide) plus androgen deprivation therapy (ADT) is shown to significantly improve overall survival (OS) compared to ADT alone, in men with non-metastatic castration-resistant prostate cancer (nmCRPC). These data from the pre-specified final OS analysis of the Phase III ARAMIS trial was presented at the American Society of Clinical Oncology (ASCO) 2020 Virtual Scientific Program, held from May 29-31, 2020. Previously published results in 1,509 men from the Phase III ARAMIS trial (N Engl J Med 380: 1235-1246, 2019) demonstrated a highly significant improvement in the primary efficacy endpoint of metastasis-free survival (MFS), with a median of 40.4 months (n=955) with darolutamide plus ADT, compared to 18.4 months (n=554) for placebo plus ADT (p =0.001, a statistically significant difference); however OS data were not yet mature at the time of the MFS analysis.

MFS is defined as time from randomization to the time of first evidence of blinded independent central review (BICR)-confirmed distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first. Darolutamide was approved by FDA in July 2019 for the treatment of men with nmCRPC based on data that was previously reported in the ARAMIS trial.

Adverse reactions occurring more frequently in the darolutamide arm (≥2% over placebo) were fatigue (16 vs. 11%), pain in extremity (6 vs. 3%) and rash (3 vs. 1%).

**ARAMIS OS Analysis**

Men receiving darolutamide plus ADT showed a statistically significant improvement in the secondary endpoint of OS vs. ADT alone, with a 31% reduction in risk of death (Hazard Ratio [HR] 0.69, 95% Confidence Interval [CI] 0.53–0.88; p=0.003).

With extended follow-up, any grade of treatment-emergent adverse events (AEs) at final analysis were generally consistent with the primary analysis of the Phase III ARAMIS trial. Previously, in (Continued on page 8)
95 out of every 100 men with low or intermediate-risk localized PCs do not die of PCs within 10 years, irrespective of whether treatment is by means of AS, RP, or RT.

The results are consistent with those of a previous report that focused on outcomes in the randomized cohort and showed an overall PCa-specific survival rate of 98.8% at 10 years in the ProtecT study. The updated analysis showed more separation between the AS and upfront-treatment groups, and the analysis of the men who declined randomization and chose their own treatment showed an even greater survival difference in favor of definitive treatment.

The new data prompted authors of an accompanying editorial to question whether “the pendulum has swung too far towards surveillance.” “While we note that such comparisons of PCa mortality should be considered exploratory, as they were not in the original randomization protocol, these data still represent relatively high-quality evidence and underscore the small but increased risk of PCa mortality for men on AS vs. treatment,” wrote Vidit Sharma, MD, and R. Jeffrey Karnes, MD, both of the Mayo Clinic in Rochester, MN. “This necessitates a thorough discussion of the risks of AS, particularly for patients with intermediate- or high-risk PCs.”

“Despite limitations of the study – relatively ‘loose’ monitoring in the AS arm and potential for selection bias in the selected-treatment arm – the data provide reason to reconsider the role of AS in men with favorable intermediate-risk PCs,” they added.

“In our decision analytic cost-effectiveness modeling of the original ProtecT data, initial treatment was the preferred option for patients with more than a 2.4% 10-year risk of metastasis on AS. On this basis, AS is probably the right choice for most men with low-risk PCa and select men with favorable intermediate-risk PCa. However, incorporation of the newfound PCa mortality and metastasis estimates into such models would cause AS to be suitable for even fewer men with intermediate-risk PCa.”

The primary objective of ProtecT was PCSM after a median follow-up of 10 years in the randomized arm of the study population. Secondary outcomes included rates of disease progression and distant metastasis and all-cause mortality. Overall, 17 men in the randomized cohort died of PCa, as did 14 in the treatment-choice arm.

In the updated analysis, Neal and colleagues analyzed outcomes by actual treatment received, including both the randomized and treatment-choice cohorts. In the treatment-choice group, 507 (51%) men opted for AS, 262 chose RP, and 189 (19%) chose RT. For the exploratory analyses, authors combined men treated with RP or RT.

In the randomized cohort, the combined active-treatment arm had a 66% lower hazard for PCa death as compared with the AS arm (95% Confidence Interval [CI] 0.13-0.94). In the treatment-choice arm, upfront definitive therapy reduced the hazard for PCa death by 73% vs. AS (95% CI 0.08-0.91). A pooled analysis of the randomized and treatment-choice data yielded a 69% reduction in the hazard for PCa death in favor of active treatment (95% CI 0.14-0.67, P=0.003, a statistically significant difference). Because of the relatively small number of PCa deaths, the difference represented a modest absolute risk reduction, the authors acknowledged.

Analysis of the treatment-choice group showed the rate of distant metastasis in the AS patients (5.6%) was twice that of the men who opted for RP (2.4%) or RT (2.7%). Disease progression occurred more than three times as often with AS (20.35%) as with surgery (5.87%) or RT (6.62%).

As expected, treatment-related side effects occurred more often in men who chose radical therapy. Sexual dysfunction at six months was reported by 95% after RP and urinary incontinence by 55%. Among men who chose RT, 88% reported sexual dysfunction at six months and 5% reported bowel dysfunction.

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Options for Urinary Incontinence After Prostate Cancer Treatment (Continued from page 4)

ed at six weeks and the patient can start to use the device. This means that for the first six weeks after surgery, the leakage will be the same as it was before surgery.

- Possible Complications: Infection requiring removal of the device, urethral erosion, device malfunction, and very rarely urinary retention. After 10 years with the device, 50% of patients had a failure of the device and revisions or replacements can be pursued.

Adjustable Balloon Device (ProACT)

- Description: ProAct has been commercially available in the USA since 2017. This device consists of two silicone balloons that are placed next to the urethra where it joins the bladder. The balloons are inflated to compress the urethra on either side. These balloons are attached to thin tubing with ports that are in the scrotum. This also is a passive therapy as there are no actions a patient needs to take to urinate.

- Surgical Expectations: This is usually an outpatient surgery with effects seen immediately after surgery. In follow-up, the urologist can access the ports in the scrotum and adjust the balloon volume in clinic to get an optimal compression on the urethra.

- Possible Complications: Device erosion, infection, lack of efficacy, urinary retention

- Comments: Studies have shown a higher rate of failure and complications in men with a history of radiation. In addition, only certain centers provide this procedure. Having this procedure does not exclude other treatment options in the future.

Urologists recognize the importance of quality of life after prostate cancer treatment and can discuss these options with you in further detail.
Prostate SBRT Shows Positive Outcomes in the Treatment of Low- and Intermediate-Risk Disease
Sponsored Column Brought to You by Accuray

There are several options for treating localized prostate cancer with the most common being active surveillance, hormone therapy, radiotherapy and surgery. It’s important for each man to have an open conversation with his physician about his specific diagnosis, lifestyle and the potential benefits and risks associated with each treatment option so that the patient can select the most appropriate for their unique situation. This process is often referred to as “shared decision making” or “informed decision making.” In either case, the patient has the power and responsibility to make the ultimate choice. It’s their life and their choice.

If the patient selects radiotherapy as the most appropriate treatment option, he will generally work with a radiation oncologist. (Urologists and medical oncologists also manage prostate cancer). The patient and physician will then discuss how to proceed, whether to use external beam radiotherapy (EBRT) in one of several different treatment duration regimens, internal radiation (brachytherapy), or a combination of the two.

Technological innovations have significantly advanced the field of radiotherapy over the past few decades and many physicians now use a form of EBRT called stereotactic body radiotherapy (SBRT) to treat localized prostate cancer. SBRT has been used worldwide since the early 2000s and couples a high degree of targeting accuracy with high doses of extremely precise, externally delivered radiation to maximize the cell-killing effect on the tumor(s) and minimize radiation-related injury to healthy tissues. Treatment is generally administered in 4 or 5 sessions over 1 to 2 weeks, compared to conventional EBRT that is typically delivered in 40 to 45 sessions over 8 to 9 weeks.

Clinical data report on the outcomes of prostate SBRT, with studies evaluating effectiveness, safety and impact of treatment on quality of life. Below is a summary of a few of these studies.

In one SBRT study, a prospective, phase II study, physicians at 18 institutions analyzed 259 prostate cancer patients; 112 low-risk and 147 intermediate-risk who received a dosing regimen similar to what is delivered with HDR brachytherapy. A much greater amount of radiation was delivered to the peripheral zone of the prostate, where prostate cancer is typically located, while less radiation was given centrally to spare the urethra. The entire course of treatment, delivered using a machine called the CyberKnife® System, was completed in 4 visits.

At 5 years, the disease-free survival rate for low-risk prostate cancer patients treated with SBRT was 100% and for intermediate-risk patients was 88.5%. These results were maintained by patients followed for 7 years. The 5-year median PSA was 0.1 ng/mL for low- and intermediate-risk prostate cancer patients and the median PSA value subsequently decreased to 0.035 ng/mL at the 7-year mark for patients followed to this time point. The lower the PSA value and the longer it continues to decline, the greater the patient’s likelihood of achieving long-term disease free survival. Patients experienced low toxicity rates despite the high SBRT dosage and heterogeneous dose distribution, with higher dosage in the prostate peripheral zone.

In a prospective SBRT study, 21 centers evaluated 172 low-risk and 137 intermediate-risk patients. Radiation was administered with the CyberKnife System to the prostate gland itself, with a 3 to 5 millimeter margin of radiation around the outside edge of the prostate to eradicate any microscopic cancer that could reside just outside the gland. The 5-year cancer control rate was 97.3% for low-risk prostate cancer patients and 97.1% for intermediate-risk patients. As with the 4 treatment session study, the 5-year median PSA was 0.1 ng/mL for all patients. After more than 5 years of follow-up, serious side effects were uncommon (less than 2%), an incidence that compares favorably to other radiotherapy techniques based on results from other studies. There were 2 low-risk patients (1.2%) and 2 intermediate-risk patients (1.5%) who experienced grade 3 genitourinary toxicities (GI) including urinary retention, hematuria, urinary tract infection and ureteral stenosis: there were no grade 3 gastrointestinal toxicities (GI) or grade 4-5 GU or GI toxicities.

A study analyzed 10 single institution phase 2 trials and 2 multi-center prospective phase 2 trials of prostate SBRT in the treatment of 2,142 men with low- or intermediate-risk disease. SBRT was delivered using either the CyberKnife System or a conventional linear accelerator. Treatment was associated with high rates of disease control and low rates of severe toxicity in the long term. The 7-year incidence of biochemical recurrence was 4.5% for men with low-risk prostate cancer and 10.2% for men with intermediate-risk disease. The 7-year cumulative incidence of severe late GI was 0.4% and severe late GU was 2.4%.

These studies demonstrate that prostate SBRT provides high rates of disease control with low risks of severe toxicity, while providing a convenient treatment option for men diagnosed with low- or intermediate-risk prostate cancer.

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


10-Year Randomized Trial of Conventional IMRT vs. Moderate Hypofractionated IMRT
(Continued from page 1)

Network (NCCN) risk group adjustment.

Results: Overall, 303 assessable men were randomly assigned to C-IMRT or H-IMRT. The median follow-up was 122.9 months. Per updated NCCN risk classification, there were 28 men (9.2%) with low-risk, 189 (62.4%) with intermediate-risk, and 86 (28.4%) with high-risk prostate cancer. The arms were equally balanced for clinicopathologic factors, except that there were significantly more black men in the C-IMRT arm (17.8 vs. 7.3%; p=0.02). There was no difference in ADT use (p=0.56). The 10-year cumulative incidence of BCDF was 25.9% in the C-IMRT arm and was 30.6% in the H-IMRT arm (hazard ratio, 1.31; 95% CI, 0.82 to 2.11). The two arms also had similar cumulative 10-year rates of biochemical failure, prostate cancer-specific mortality, and overall mortality; however, the 10-year cumulative incidence of distant metastases was higher in the H-IMRT arm (rate difference, 7.8%; 95% CI, 0.7 to 15.1%).

Conclusion: H-IMRT failed to demonstrate superiority compared with C-IMRT in long-term disease outcomes.

Darolutamide plus ADT showed statistical significance in delaying time to pain progression (HR 0.65, 95% CI 0.53-0.79; p <0.001), time to first initiation of cytotoxic chemotherapy (HR 0.58, 95% CI 0.44-0.76; p <0.001) and time to first symptomatic skeletal event (SSE) (HR 0.48, 95% CI 0.29-0.82; p=0.005) vs. ADT alone, all p-values indicate a statistically significant difference. In the final analysis of the ARAMIS trial, the addition of darolutamide led to a 31% reduction in the risk of death (HR, 0.69; 95% CI, 0.53-0.88; p=0.003) vs. placebo. Further, extended follow-up showed durability of the tolerability of treatment with darolutamide plus ADT.

Men with nmCRPC typically do not have cancer symptoms. In selecting a treatment for these patients, my goal as a clinician is to improve their overall survival while limiting side effects and drug interactions,” investigator Karim Fizazi, MD, PhD, professor of medicine at the Institut Gustave Roussy, Villejuif, France, said in a statement. “These data add to the growing evidence for darolutamide as an effective treatment option with proven tolerability that extends patients’ lives and delays cancer symptoms.”

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US TOO INTERNATIONAL, 2720 S. RIVER ROAD, SUITE 112, DES PLAINES, IL 60018
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. Anne Katz, Certified Sexuality Counselor and Clinical Nurse Specialist at CancerCare Manitoba. She has educated thousands of healthcare providers and cancer survivors about cancer, sexuality and survivorship. She is the editor of the Oncology Nursing Forum, an avid blogger for ASCO Connections, and the author of 13 books on the topics of illness, sexuality and cancer survivorship. (www.drannekatz.com)

QUESTION FROM PROSTATE CANCER SURVIVOR:
I got a prescription from my family doctor for Viagra but it doesn’t work at all. I had my prostate removed about six months ago and I sailed through the surgery. I’m 60 years old and I was assured that everything would work as normal after the surgery. Is it me or am I missing something here?

RESPONSE FROM DR. ANNE KATZ:
You are not missing anything here, other than education and support! When I see men in a very similar situation I ask some important questions:

1. How are you taking the medication (Viagra)?
This sounds like a really stupid question I know and many men look at me and state “By mouth of course!” But that is not what I am asking. What I want to know is if the man is taking the medication correctly as in:
   • Waiting one hour before attempting to get an erection
   • Using genital stimulation to get blood into the penis
   This is important because (a) the medication needs time to be absorbed into the circulation and (b) there needs to be genital stimulation. Viagra and other medications like this do NOT cause an erection; they merely prevent blood from leaving the penis by contracting the veins that allow blood to leave the penis.

2. What were your erections like BEFORE the surgery?
Men who were having problems before surgery are not going to see improvements in their erectile functioning. If the man had some degree of erectile problems before surgery, surgery is going to make things worse.

3. What other medications and/or recreational drugs are you taking?
Many medications commonly prescribed to men in their 50s and 60s and beyond cause erectile difficulties. These include medications for high blood pressure, depression and/or anxiety, diabetes, anti-histamines, anti-inflammatoryatories, muscle relaxants and others used for more rare diseases. For a complete list see: https://www.webmd.com/erectile-dysfunction/guide/drugs-linked-erectile-dysfunction. Cannabis, Ecstasy, cocaine, opiates and alcohol also affect erections.

4. How anxious are you about regaining erections?
The answer to this is often “highly anxious” for any number of reasons! The more anxious the man is about getting back to “normal,” the more likely he is to have performance anxiety. The man has lost confidence in his ability to either achieve or maintain even a partial erection and this leads to a vicious cycle of self-doubt and failure. It is very difficult, however, to stop that little voice in his head that tells him that things are not going to work again...

It can take up to two years for erectile function to return so patience and practice is needed. A man has to take any of the erectile medications on five to eight separate occasions before we can say that it’s the medication that is not working. And he should then try one of the other similar medications. If the oral medications don’t work, there are other options including penile self-injection that is highly effective.

Watch Dr. Katz’ presentation on sexual health and intimacy from the Prostate Cancer Pathways for Patients and Caregivers event recorded at Englewood Health in Englewood, NJ on September 29, 2018.
https://www.youtube.com/watch?v=A2ZdDHw2WGY&t=8542s.

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: ustooBTS@ustoo.org

Or mail your letter to:
Us TOO International
Between the Sheets
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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.

Promising Results of Phase 1b Trial Lead to Upcoming Phase 3 Trial in mCRPC

At the GU-ASCO meeting held earlier this year, Dr. Neeraj Agarwal of the Huntsman Cancer Center at the University of Utah presented results of a Phase 1b trial of combination therapy with two drugs (cabozantinib + atezolizumab) in metastatic castration resistant prostate cancer (mCRPC).

Many treatments for mCRPC exist, but the cancer progresses in almost all men despite therapy, and more options are needed. Cabozantinib is an inhibitor of multiple proteins called tyrosine kinases that are involved in cancer processes (tumor growth, angiogenesis, and immune cell regulation). Atezolizumab is an immune checkpoint inhibitor that targets the immune-suppressive protein PD-L1 – in other words, the drug prevents the cancer from blocking the body’s immune response, allowing the immune system to kill the cancer cells.

These drugs had not been effective on their own, but data suggested that the combination might be beneficial, leading to a multinational phase 1b trial across many cancer types. Dr. Agarwal presented the results of one specific cohort of 44 patients: men with mCRPC who had cancer in soft tissues that progressed while on treatment with abiraterone or enzalutamide or both. These men had significant disease: 82% were classified as “high risk” mCRPC based on the extent and location of the metastases.

The overall response rate was 32% among all 44 CRPC patients and an additional 48% of patients experienced stable disease. Thus, the clinical benefit rate (response or stabilization of disease) was seen in 80% of patients. The median duration of treatment was 6.3 months, and the median duration of response was 8.3 months. This waterfall plot shows changes in tumor burden for each patient. Most patients showed a decrease in the amount of tumor as measured on scans.

The side effect profile of the combination was primarily associated with known effects of cabozantinib. 59% of patients had a Grade 3 or 4 treatment-related adverse event (AE) and 9.1% of patients had an immune-related Grade 3 AE. One grade 4 AE of diverticular perforation was reported. One patient had a Grade 5 AE (dehydration).

The overall response rate of 32% was highly promising. These results have led to the initiation of an international phase 3 trial to test the combination of cabozantinib + atezolizumab in men with mCRPC. The trial has already been approved by the FDA and is opening at several sites. The investigators hope to enroll the first patient within months.

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