Increased Radiation Intensity Found to Be Safe for the Treatment of Prostate Cancer

A new study examining radiation fractionation for the treatment of prostate cancer has found no increased toxicity when comparing ultrahypofractionated stereotactic body radiotherapy (SBRT) with conventionally fractionated or moderately hypofractionated radiotherapy (Lancet Oncol. 2019;20:1531-1543).

Known as PACE-B, it is one cohort of the Prostate Advances in Comparative Evidence study. The randomized, open-label, phase 3, noninferiority trial was conducted at 37 centers in the United Kingdom, Ireland, and Canada. “We believe this is the first study to show that 5 fractions of radiotherapy can be delivered without any detriment to acute toxicity, potentially changing clinical practice guidelines for prescribing radiotherapy,” says study author Nicholas John van As, MD, medical director at The Royal Marsden Hospital and The Institute of Cancer Research in London, United Kingdom.

**Study Details**

In the PACE-B trial, researchers selected men with low-risk and intermediate-risk, organ-confined prostate cancer (according to National Comprehensive Cancer Network criteria) between August 7, 2012, and January 4, 2018. The men were candidates for radical radiotherapy and were not willing to undergo or suitable for radical prostatectomy. Patients with a life expectancy of fewer than 5 years or those with a Gleason score of 4+3 were excluded.

These 874 subjects were randomly assigned to receive conventionally fractionated or moderately hypofractionated radiotherapy (441 men) or SBRT (433 men). Among these patients, 98% (432 men) of the conventionally fractionated or moderately hypofractionated radiotherapy subjects and 96% (415 men) of the SBRT subjects received at least 1 fraction of the allocated treatment.

The PACE-B trial ran concurrently with PACE-A, a randomized study in which patients received either laparoscopic prostatectomy or prostate SBRT delivered using 36.25 grays (Gy) in 5 fractions daily or on alternate days, plus a secondary clinical target volume dose target of 40 Gy. PACE-A and PACE-B share a common experimental SBRT arm. A future study, PACE-C, will evaluate patients at higher risk who all will receive androgen deprivation therapy.

In the PACE-B study, researchers measured toxicity using both the Radiation Therapy Oncology Group (RTOG) gastrointestinal (GI) and genitourinary (GU) scores and Common Terminology Criteria for Adverse Events (CTCAE; version 3). They measured toxicity at baseline and then after radiotherapy at 2, 4, 8, and 12 weeks after treatment.

**KEY POINTS**

- Ultrahypofractionated radiotherapy delivered over 5 fractions is tolerable, at least for the short term, in men with low-risk and intermediate-risk prostate adenocarcinoma.
- There now are several options for dose fractionation for the definitive treatment of patients with low-risk and intermediate-risk prostate cancer.
Study Results

GI toxic events of grade 2 or worse occurred in 53 of the 432 patients in the group receiving conventionally fractionated or moderately hypofractionated radiotherapy (12%) and 43 of the 415 patients in the SBRT group (10%). Similarly, 118 patients in the conventionally fractionated or moderately hypofractionated radiotherapy group (27%) and 96 patients in the SBRT group (23%) experienced grade 2 or worse GU toxicity. These small differences in GI and GU toxicity were not found to be statistically significant.

The researchers concluded that SBRT delivered in 5 fractions is tolerable, at least for the short term, in men with low-risk and intermediate-risk prostate adenocarcinoma. An earlier study, the Hypofractionated Radiotherapy of Intermediate Risk Localized Prostate Cancer (HYPO-RT-PC) trial had shown that 5-year biochemical progression-free survival outcomes were equivalent for doses delivered in 39 fractions and 7 fractions, but that short-term toxicity was worse with the shorter regimen. In contrast, the PACE-B trial demonstrated that 5 fractions, delivered with modern image-guided stereotactic techniques, can be delivered without higher short-term toxicity. “Our results suggest that substantially shortening treatment courses with stereotactic body radiotherapy does not increase either gastrointestinal or genitourinary acute toxicity,” says Dr. van As. “Overall, we found the toxicity in both arms was lower than we expected based on the literature, but most importantly, there was no significant difference between RTOG urinary deficiency and RTOG bowel toxicity for both arms of the study.”

According to Dr. van As, additional research will be needed to draw firmer conclusions regarding outcomes. “It is only acute toxicity so we can’t make any inference about the [other] outcomes of the study yet—we’re probably 2.5 to 3 years away from knowing the cancer outcomes and delayed toxicity,” he says “But it is very encouraging that these very large doses per day are given safely and without significant side effects as far as acute toxicity and, in fact, [are tolerated] better than we expected.”

The study authors write that increasing the dose per fraction above the conventional 2 Gy, meaning fewer total fractions, has a great deal of appeal. “The key advantages are 2-fold. First, the greater fraction size sensitivity of prostate cancer indicates by a lower ratio, relative to the relevant late gastrointestinal and genitourinary side effects, means that the therapeutic ratio might be improved by hypofractionation. Second, fewer fractions are needed with hypofractionation, allowing for quicker and more cost-effective EBRT [external beam radiotherapy] treatment courses.”

Study Implications

“This study is the first to provide randomized acute toxicity data for the common American SBRT fractionation of 36.25 Gy in 5 fractions,” says Peter A.S. Johnstone, MD, a vice chair of the radiation oncology department and a senior member of the Health Outcomes and Behavior Program at H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida. “We have had indications that PSA [prostate-specific antigen] control with this fractionation schema would be appropriate, but were lacking rigorous corresponding acute toxicity data.”

Dr. Johnstone says there still are some unanswered nuances that should be discussed with patients, such as the appropriateness of SBRT for patients with Gleason 4 + 3 disease, and how the size of the prostate gland affects the risk of SBRT toxicity. “For instance, in our experience, we have seen a single episode of nonhealing urethritis in our first approximately 100 SBRT patients; this has not previously been seen with external beam radiotherapy.”

Dr. Johnstone believes an important takeaway message should be that there now are several options for dose fractionation for the definitive treatment of patients with low-risk and intermediate-risk prostate cancer: standard fractionation over 8 to 9 weeks, moderate hypofractionation over 4 to 6 weeks, and ultrahypofractionation for approximately 2 weeks. He adds, “I do believe that fewer and fewer patients will agree to prolonged fractionation given equivalent outcomes and toxicity with shorter, cheaper, and more convenient courses. I await the PSA outcomes publication, and then the long-term toxicity data from this study.”

Study co-author Alison Tree, MD, a consultant clinical oncologist at The Royal Marsden NHS Foundation Trust in London, says this trial, among others, has shown that prostate cancer treatments can safely be made shorter and less arduous for patients, enabling them to return to a normal life and/or work sooner. “These trials have also improved efficiency in radiotherapy departments, expediting access to radiotherapy for all patients,” she says. However, she does caution that longer follow-up of the PACE-B trial is needed before definitive statements can be made regarding the equivalence of long-term survival and long-term toxicity.

doi: 10.3322/caac.21595