



The Long and Short of It: New Lessons on the Optimal Duration of Androgen Deprivation Therapy for High-Risk Prostate Cancer and Where We Need to Go From Here

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Recently in the *International Journal of Radiation Oncology, Biology, Physics*, we have seen 3 articles providing updates or reanalyses from landmark trials testing the optimal duration of androgen deprivation therapy (ADT) with radiation in high-risk prostate cancer. Although it was started more than 25 years ago by Dr Gerald Hanks, the pioneering radiation oncology leader and former American Society for Radiation Oncology president who sadly passed away on December 20, 2017, the Radiation Therapy Oncology Group (RTOG) protocol 92-02 continues to provide valuable insights through its updates, as does the more recent DART 01/05 trial, and I will highlight them both in this month's Oncology Scan.

Lawton et al. Duration of androgen deprivation in locally advanced prostate cancer: Long-term update of NRG Oncology RTOG 9202. *Int J Radiat Oncol Biol Phys* 2017. (1)

Summary: This trial randomized 1554 patients with cT2c-T4N0/NX and prostate-specific antigen (PSA) < 150 ng/mL (essentially higher risk than the typical "high risk" patient we see in the PSA screening era) to radiation to the pelvis (44-46 Gy) and prostate (65-70 Gy to isocenter) with either 4 months of neoadjuvant and concurrent goserelin and flutamide, or the same plus an additional 24 months of adjuvant goserelin (for a total of 28 months of ADT in the long-course arm). The previous report of this study by Dr Eric Horwitz in 2008 in the *Journal of Clinical Oncology* had 10 years of follow-up and reported a nearly 5% disease-specific survival benefit (88.7% vs 83.9%) at 10 years favoring long-term androgen

deprivation (LTAD), but there was no difference in overall survival ($P = .36$) (2).

Now with nearly double the follow-up at 19.2 years, the long-term update shows that although the univariable analysis of overall survival still was not quite statistically significant with a P value of .12 (29.8% vs 27.1% at 15 years favoring LTAD), a post hoc multivariable analysis adjusting for PSA, T stage, Gleason, and age found that the LTAD arm was associated with significantly improved overall survival (hazard ratio [HR] 0.88 [95% confidence interval (CI) 0.79-0.98], $P = .03$) (1).

Notably in this study, the LTAD was not associated with increased noncancer deaths (48.7% vs 45.3% at 15 years for short-term androgen deprivation [STAD] vs LTAD, $P = .95$). As in the prior update, LTAD significantly improved metastasis-free survival (82.6% vs 74.0% at 15 years, $P < .001$).

Mirhadi et al. Effect of long-term hormonal therapy (vs short-term hormonal therapy): A secondary analysis of intermediate-risk prostate cancer patients treated on NRG Oncology RTOG 9202. *Int J Radiat Oncol Biol Phys* 2017. (3)

Summary: In this secondary analysis of the RTOG 92-02 trial using locked data with approximately 11 years of follow-up, Mirhadi et al identified 133 men from RTOG 92-02 who fit National Comprehensive Cancer Network intermediate risk criteria. Because this was a post hoc analysis and risk group had not been a stratification factor, the arms were not quite balanced, with 74 randomized to STAD and 59 randomized to LTAD. The authors sought to

determine whether the subgroup of patients in the trial with intermediate-risk disease had a benefit from extending the duration of ADT from the standard STAD to LTAD. They found that through the follow-up, there was no difference in any clinical endpoint, including overall survival (10-year estimates, 61% STAD vs 65% LTAD; $P = .53$), disease-specific survival, (10-year disease-specific survival, 96% vs 97%; $P = .72$), or even PSA failure (10-year PSA failure, 53% vs 55%; $P = .99$) (3).

Zapatero et al. Late radiation and cardiovascular adverse effects after androgen deprivation and high-dose radiation therapy in prostate cancer: Results from the DART 01/05 randomized phase 3 Trial. *Int J Radiat Oncol Biol Phys* 2016. (4)

Summary: The Spanish DART 01/05 trial launched in 2005, a full 13 years after the launch of RTOG 92-02. It randomized only 355 patients with cT1c-T3bN0, National Comprehensive Cancer Network intermediate- and high-risk disease, to the same schema as RTOG 92-02, namely radiation with 4 months of neoadjuvant/concurrent goserelin and flutamide (although bicalutamide was allowed) with or without an additional 2 years of adjuvant goserelin (5). The notable differences between the trials were that the DART 01/05 contained a more modern, lower-risk population than RTOG 92-02. Additionally, it had a higher minimum dose (76 Gy to isocenter) and median dose (78 Gy) than the RTOG trial, which used only 65-70 Gy, and unlike in the RTOG trial, in which pelvic nodal irradiation was mandated, only 14% received pelvic nodal radiation in the DART 01/05 trial.

The primary endpoint was overall survival, and with a median follow-up of only 5 years the initial publication found that the use of long-term ADT seemed to significantly improve overall survival (95% vs 86%, HR 2.48 [95% CI 1.31-4.68], $P = .009$), as well as metastasis-free survival and biochemical recurrence-free survival. Unlike RTOG 92-02, this trial was actually stratified by intermediate- versus high-risk disease. On subgroup analysis, the overall survival benefit seemed to be demonstrable for the high-risk patients (HR 3.43, $P = .015$) but not intermediate-risk (HR 1.67, $P = .381$).

In the secondary analysis published in 2016, the authors focus on the long-term side effects of choosing the longer- versus shorter-duration ADT in terms of rectal and bladder irritation and also cardiovascular events (4). They found that LTAD was not associated with any increase in late grade 2+ bladder or bowel toxicity, but there was a significant increase in cardiovascular events in the LTAD arm (adjusted HR 2.09 [95% CI 1.17-3.72], $P = .012$).

Comments: More than 25 years after Dr Hanks launched RTOG 92-02; its update and the related DART 01/05 reanalysis allow us to conclude the following.

First, LTAD improves overall survival for high-risk prostate cancer. Overall survival is of course the holy grail for randomized cancer trials, and RTOG 92-02 (at least on multivariable analysis) now joins DART 01/05 and European Organization for Research and Treatment of Cancer (EORTC) 22961 (6) in proclaiming that radiation and long-term ADT (28-36 months) improves overall survival compared with radiation and short-term ADT (4-6 months).

Second, intermediate-risk disease does not seem to benefit from LTAD. The post hoc subgroup analysis of the intermediate-risk patients from RTOG 92-02 showed nearly identical 10-year PSA failure-free survival for STAD and LTAD. These results reinforce the prestratified finding from DART 01/05 that intermediate-risk disease does not seem to benefit from LTAD.

Third, high dose does not overcome the need for LTAD in aggressive prostate cancer. One of the underlying questions about many of the trials originally showing the benefit of ADT versus no ADT or LTAD versus STAD is whether higher, more modern doses of 76 to 80 Gy rather than the 66 to 70 Gy used in the landmark studies would reduce the benefit of ADT. On the basis of the DART 01/05 trial with its median dose of 78 Gy (albeit to isocenter), dose does not seem to overcome the need for LTAD in high-risk prostate cancer. Whether extreme dose, such as what is provided by the 46 Gy plus a low-dose-rate brachytherapy boost to 115 Gy in the ASCENDE-RT trial, would allow for a reduction of duration of ADT to only 12 months, as was done in ASCENDE-RT, remains unknown, but certainly the DART 01/05 trial provides no reason to think that brachytherapy boost would allow for a shortening of ADT duration (7).

Fourth, radiating the pelvic nodes may not be needed to obtain the benefits of LTAD. When the 2007 update of RTOG 94-13 no longer showed a progression-free survival benefit to adding pelvic nodal radiation to 4 months of ADT, possible explanations were raised, including that an interaction with the timing of ADT in that 2×2 trial could have obscured the ability to discern the impact of pelvic nodal radiation (8-11). At the time, one of the arguments raised to continue using pelvic nodal radiation in high-risk disease was that RTOG 92-02 used pelvic nodal radiation (as did EORTC 22961), and those who hope to obtain the benefit of LTAD should also follow the radiation scheme used in those trials. However, 86% of the patients in DART 01/05 did not have pelvic nodal radiation, suggesting that radiating the pelvis is not necessarily needed to obtain the benefits of LTAD over STAD (5). Ultimately, this question will be answered definitively in the large RTOG 09-26 trial.

Fifth, compared with STAD, LTAD increases cardiovascular events but not cardiovascular deaths. The DART 01-05 reanalysis is the first evidence from any randomized trial to suggest that LTAD can increase the risk of cardiovascular events compared with STAD. Of note, neither the reanalysis of RTOG 92-02 by Efsthathiou et al

(12) nor the original publication of EORTC 22961 found any evidence that LTAD increased cardiovascular *deaths* compared with STAD. This concept of ADT possibly increasing cardiovascular events but not cardiovascular deaths is echoed in the literature on studies of any ADT duration versus no ADT: a large meta-analysis of observational studies has suggested that ADT increases the risk of nonfatal cardiac events, but a meta-analysis of randomized trials suggests that ADT does not increase cardiovascular death (13).

Last, whether all high-risk patients need LTAD remains the next big question to answer from these trials. These trials collectively show us that LTAD has a potential survival benefit for high- and not intermediate-risk patients, but there is a real and quantifiable cardiac event risk to receiving LTAD, in addition to all of the other known side effects of ADT. The key question now is whether *all* high-risk patients truly need LTAD, especially given the known harms of longer therapy. One study has found that nearly 50% of high-risk patients who were intended to receive 2 or more years of ADT at an academic center stopped their ADT before the original goal duration, suggesting that either clinicians or patients are already dialing down the duration on the basis of their perception of benefit and risk (14). A look at the RTOG 92-02 survival curves reveals that more than 70% of patients who received just 4 months of ADT were free from metastases at 20 years of follow-up, suggesting that at least by that measure, those patients did not seem to need LTAD. But who are those patients?

One way to parse this out rationally could be based on the clinical aggressiveness of the disease. For example, high-risk disease is a heterogeneous group, with some “favorable high risk” patients (cT1c, Gleason 8, PSA < 10 ng/mL; or cT1c, Gleason 6, PSA > 20 ng/mL) having a risk of prostate cancer death as low as in intermediate-risk patients, and perhaps these patients are the ones who can safely be spared the side effects of LTAD (14). This conjecture remains to be proven, however. In addition, a recent study by Spratt et al (15) has suggested that the clinical variables alone do not tell the full story of a tumor’s aggressiveness and that by incorporating tumor genomic information, risk can be determined more accurately. Perhaps then it is the clinically high-risk patients with lower-risk genomic features who can safely receive STAD, but this will also need to be proven.

Thankfully, Dr Hanks and colleagues in 1992 had the great vision and foresight to build tissue-banking into the RTOG 92-02 protocol, even though it was not exactly clear at the time what could be done with that tissue. Because of that vision, a study can now be undertaken to attempt to determine whether a tumor genomic signature can be developed that identifies the high-risk patients who would benefit the most from LTAD and who can get by with just STAD. Further work is also needed to help identify exactly which patients are most susceptible to the excess cardiac events that may be caused by LTAD, and one hypothesis is

that it is the patients with prior cardiac events who are most at risk. Between a better understanding of which tumors are least likely to need LTAD and which patients are most likely to be cardio-metabolically harmed by LTAD, we will be able to move much closer to true personalization. Until then, the standard of care for most high-risk patients should remain LTAD, as outlined by the landmark trials above; and a special thanks should be given to Dr Gerald Hanks, whose leadership and vision more than 25 years ago led to a trial that established a treatment paradigm that has now prevented many men worldwide from dying from prostate cancer, and that will continue to serve as a valuable resource for generating new knowledge about personalization of therapy for many years to come.

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