Absolute versus Relative Benefit of Androgen Deprivation Therapy for Prostate Cancer: Moving Beyond the Hazard Ratio to Personalize Therapy

Daniel E. Spratt, MD,* and Jonathan D. Tward, MD

*Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan; and †Department of Radiation Oncology, Huntsman Cancer Center, Salt Lake City, Utah

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Introduction

Multiple phase 3 randomized trials of men with localized prostate cancer have proven that androgen deprivation therapy (ADT) improves metastasis-free survival, prostate cancer-specific survival, and overall survival when added to conventionally fractionated radiation therapy (RT).¹ Post hoc subset analyses of these trials demonstrate that these clinically meaningful endpoints are improved predominately in men with National Comprehensive Cancer Network (NCCN) intermediate- and high-risk disease. This level 1 evidence forms the basis of the current guidelines, which recommend ADT with RT for intermediate- and high-risk disease.²

Although ADT may increase the probability of tumor control, the absolute risk reduction of metastasis seen in trial populations ranges from 2% to 12% by 10 years (Fig. 1A). This range of absolute risk reduction reflects the heterogeneity of these individual trial populations. Nearly all men who receive ADT experience variable side effects and decrements in their quality of life, notwithstanding the financial cost of ADT.³ Thus, it is important for a patient to understand the therapeutic ratio of this intervention (ie, an individual’s potential benefit of ADT against morbidity), given that treatment guidelines recommend the use of ADT for all men with unfavorable intermediate- and high-risk prostate cancer, despite heterogeneity in the risk—benefit ratio at the individual level.

We propose that practitioners use the most precise and accurate prognostic biomarkers, whether that be clinicopathologic models, molecular gene expression biomarkers, or imaging biomarkers, to better estimate the absolute benefit of treatment intensification rather than a one-size-fits-all approach. This requires moving beyond the relative benefit derived from a hazard ratio and thinking in terms of absolute benefit.

Importance of Prognostic Biomarkers to Provide Personalized Risk Estimates

By definition, a prognostic biomarker provides information of prognosis that is independent of treatment. For example, men with higher Gleason scores are more likely on average to develop metastases, irrespective of treatment with surgery or RT, than those with lower Gleason scores on average. Risk stratification systems that combine multiple prognostic variables, such as NCCN risk groups, are no different. They serve as prognostic rather than predictive biomarkers. This was demonstrated specifically in the Radiation Therapy Oncology Group (RTOG) study 9408 randomized trial, in which the relative benefit of ADT was similar across risk groups and there was no significant statistical interaction of treatment and outcome by NCCN risk group.

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risk group. In other words, the hazard ratio (HR), or relative benefit, from ADT was similar across risk groups. However, the absolute benefit was different because it is dependent on the baseline risk of the groups.

The Limitation of the Hazard Ratio

Nearly all clinical trials are designed to detect a relative difference between 2 or more groups. This relative benefit is expressed as the HR. The HR consistently seen across trials assessing the benefit of ADT when added to RT is approximately 0.5 to 0.65 for most endpoints. Although an HR of 0.5 is a large 50% relative reduction of events from the addition of ADT, the HR itself cannot determine whether this is clinically meaningful. If the probability of an event of interest is rare (eg, 1 in 100 at 10 years), a 50% risk reduction would alter this risk to 1 in 200 at 10 years. If ADT was used in a population with that baseline risk, 200 men would be exposed to all of the ADT side effects and cost to prevent only 1 additional metastasis in this time-frame. This is also known as the number needed to treat (NNT). Most would argue that this therapeutic ratio is not clinically justifiable. It is for that reason that the addition of ADT is not routinely recommended for patients with low-risk and favorable-intermediate risk disease, despite a similar relative benefit to those with unfavorable-intermediate and high-risk prostate cancer.

When Absolute Benefit is More Important Than Relative Benefit

The NCCN prostate cancer guideline was revised recently to state that men with favorable intermediate risk disease may omit ADT, whereas other guidelines, such as those of the European Association of Urology, still do not subclassify intermediate-risk disease and recommend ADT for all intermediate-risk men receiving external beam radiation. The subclassification of intermediate risk was not based on level 1 evidence, but rather level 3 evidence initiated by a single center’s retrospective study. Since then, multiple studies of thousands of men have consistently demonstrated that men with favorable intermediate-risk disease typically have low rates of metastasis and thus would be less likely to derive a meaningful benefit from ADT. However, given that clinical trials show that approximately 90% or more of men with unfavorable intermediate-risk cancer do not derive a measurable risk reduction of metastasis from ADT by 10 years, it is imperative that providers and patients work together to understand the patient’s goals and to determine what absolute risk reduction is clinically meaningful to them specifically. This type of shared decision-making regarding the benefits versus risks of ADT is strengthened by using and communicating the most accurate risk estimators as they become available.

What is a Meaningful Reduction in Risk of Metastasis to Warrant ADT?

The authors emailed a core group of members of the NRG Oncology Genitourinary Committee to determine what would constitute a meaningful improvement in metastasis to add ADT if they themselves had prostate cancer. This group was chosen for their expertise and familiarity with national guidelines, clinical trial data, and the harms associated with ADT from the literature and their own patients. The following question was originally posed to this group via a blind carbon copy e-mail on November 13, 2019, and the answers were gathered so that only the original sender (J.T.) could see the responses.

Pretend you were personally diagnosed with an intermediate- or high-risk localized prostate cancer and have decided to get treated with radiation therapy. You are also considering receiving ADT for at least 6 months along with the radiation
therapy. At which absolute risk reduction threshold for metastasis at (10 years) would you consider doing the combined ADT/radiation over radiation therapy alone?

A) <1% risk reduction (NNT >100)
B) 1% risk reduction (NNT of 100)
C) 2.5% risk reduction (NNT of 40)
D) 5% risk reduction (NNT of 20)
E) 10% risk reduction (NNT of 10)
F) 25% risk reduction (NNT of 4)
G) ≥50% risk reduction (NNT of ≥2)

Sixteen of the 33 individuals contacted responded (48.5%). Follow-up requests were not performed. Given that no respondents chose options A, F, or G, we posed the question to a more generalized audience on social media (Twitter) of providers who prescribe ADT (n = 181 respondents) to include only option B through E. The results are shown in Figure 1B, with substantial heterogeneity in the interpretation of what constitutes a clinically meaningful benefit (range, 1%-10% absolute benefit).

Interestingly, the benefit in 10-year metastasis from ADT across all RT ± short-term ADT trials was heterogeneous, with the high-risk trials demonstrating the largest absolute benefit from ADT (RTOG 8610 and TROG 96.01; Fig. 1A). In fact, of the trials that included intermediate-risk disease (RTOG 9408 and EORTC 22991), neither trial demonstrated more than a 6% absolute benefit in metastasis at 10 years. Thus, approximately 30% of respondents would not have deemed the benefit from ADT in intermediate-risk trials to be clinically meaningful enough to choose the therapy for themselves, given that they would not consider ADT until a 10% absolute benefit was achieved. However, these trial estimates are exactly that: trial-level estimates that are individualized only to the extent of the trial population and/or NCCN risk group.

The Current Challenge of Using NCCN Risk Groups to Personalize Treatment

If NCCN risk groups were homogenous and could consistently prognosticate accurate outcomes, they would suffice to determine a patient’s probability of developing metastasis. Unfortunately, it has now been repeatedly demonstrated that the prognostic factors that comprise NCCN risk groups (Gleason score, T-stage, prostate-specific antigen, and percent positive cores), and the risk model itself, have only a modest ability to discriminate which men will or will not develop metastasis. This is often measured using a concordance index, or area under the receiver operating characteristic curve (synonymously referred to as C-index, AUC, or ROC), in which a value of 0.5 indicates that the prognostic indicator or model is no better than a coin toss and values closer to 1 indicate a nearly perfect risk estimator. Values of 0.7 or more are generally accepted as good predictive models. For NCCN risk groups, the C-index is approximately 0.65. This means that many men are misclassified as having either more indolent or aggressive disease. This poses a challenge when trying to personalize the decision of whether or not one should use ADT with RT.

The Role of Prognostic Biomarkers to Help Establish Absolute Risk to Personalize Treatment

It can be useful to think of prognostic biomarkers in terms of precision and accuracy. The precision of a risk-stratification system is dependent on the number of risk groups defined by the system, and accuracy is measured by the concordance index. The NCCN risk stratification system uses 6 discrete risk groups for localized disease.

Various genomic molecular tests based on the expression pattern of an individual’s tumor are now commercially available that also prognosticate outcomes. Rather than discrete risk groups, these tests produce a score that effectively acts as a continuum of risk, resulting in a very precise risk estimate for any individual. These tests also have C-indices that are typically reported at ≥0.8 for metastasis endpoints, meaning they are also highly accurate. This allows a better estimation of the absolute risk of metastasis. If the combined clinical-genomic model estimates one’s risk of metastasis at 10 years as 6% after RT alone, the absolute 10-year absolute risk reduction from the addition of ADT would be approximately 2% to 3%. Patients can therefore better decide, with the appropriate guidance of their physicians, what is best for them. Some may believe this is a clinically meaningful benefit, but most others (based on our survey results) would choose to omit ADT.

Although we focused on metastasis as the endpoint, the same logic can be applied to other endpoints as well (biochemical recurrence, prostate cancer-specific mortality, and overall survival). Additionally, this logic could be used for other treatment decisions, such as intensification through the use of long-term ADT or a brachytherapy boost. It is important to recognize that what matters most to a patient is highly individual. A consequence of withholding ADT based on a low risk of developing metastasis over a 10-year period may be detrimental to the goals of a patient who prioritizes avoiding a biochemical recurrence over metastasis. Because these are different endpoints of interest, one should not be cavalier in altering management based on one prognosticator without understanding the effect on others. Fortunately, several genomic classifiers can simultaneously prognosticate different endpoints, such as biochemical recurrence, metastasis, and prostate.
cancer–specific survival, so that the clinician and the patient can make an extremely informed decision.

The cost to a payer for running a genomic molecular-based test is typically $3000 to $4000. Companies offering a US Food and Drug Administration–approved genomic test on tumor biopsy specimens are widely available in the United States, and there are programs in which the out-of-pocket cost to a patient is usually <$350 if their insurer denies the payment. Because these tests are typically used to deescalate therapy, testing may reduce costs to the health care system overall. Of note, in the United States, the billed amount of molecular positron emission tomography imaging can exceed $10,000 and the median price of prostate magnetic resonance imaging is approximately $2500, neither of which has comparable data to prognosticate long-term outcomes, such as metastasis or overall survival.

Fortunately, prognostic markers are now being integrated into study designs of randomized trials and used in secondary analyses of randomized trials in which the tissue and outcome data are available. By estimating the absolute benefit of treatment intensification using prognostic tools, patients and providers can better personalize their recommendations. Furthermore, clinical trialists can power their studies appropriately by avoiding a population with very low event rates. Because these biomarkers would be used as inclusion criteria, they would also ultimately be tested in the trial as potential predictive biomarkers of benefit for the various trial arms.

Conclusions

What constitutes a clinical benefit to an individual is highly variable, even among experts. In early stage breast, prostate, rectal, and human papillomavirus–positive head and neck cancer, where the majority of patients die of other causes, we should use highly precise and accurate biomarkers that can identify patients with indolent biology to avoid overtreatment, and likewise identify patients with aggressive biology who may require therapeutic escalation.

Currently, in prostate cancer, the combination of genomic information with clinicopathologic data consistently demonstrates the greatest ability to accurately discriminate which patients harbor biologically aggressive disease. Use of these biomarkers will allow clinicians to refocus from trial-level relative benefit derived from HRs to calculating individual absolute benefit from treatment intensification. This will usher in a new era of truly individualized shared decision making.

References