Personalizing the Duration of Androgen-Deprivation Therapy Use in the Management of Intermediate-Risk Prostate Cancer

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When considering a risk-based scheme for predicting outcomes following standards of practice for nonmetastatic, node-negative prostate cancer (PC), men experience recurrence either infrequently or commonly, depending on their risk group, and some who recur will go on to die as a result of PC. However, men with intermediate-risk PC have been shown to have 5-year prostate-specific antigen (PSA) progression-free rates that range from 30% (a high-risk outcome) to 98% (a low-risk outcome). As a result of this variation, investigators have sought to identify clinical factors in addition to those on which intermediate risk is based (PSA > 10 to 20 ng/mL, Gleason score 7, or clinical tumor category 2b or 2c) to stratify these men into low- and high-risk subgroups for PC-specific mortality (PCSM). Multiple studies exist to show that the percent of positive prostate biopsies (ppb) and the number of intermediate-risk factors, and primary versus secondary biopsy Gleason grade 4 in men with Gleason score 7 PC can aid in making this stratification. On the basis of these data, investigators from Memorial Sloan Kettering proposed two intermediate-risk subgroups as follows: (1) Favorable—Gleason 3 + 4 or less and ppb not exceeding 50% and only one intermediate-risk factor excluding 4 + 3; and (2) Unfavorable—Gleason 4 + 3 or at least two intermediate-risk factors or at least one intermediate risk factor and ppb greater than 50%.

The clinical significance of this subdivision relates to personalizing the use of androgen-deprivation therapy (ADT) for men with intermediate-risk PC. We know from prospective randomized controlled trials (RCTs) that when administering low-dose (approximately 70 Gy) external-beam radiation therapy (EBRT), the addition of 4 to 6 months of ADT as compared with no ADT prolongs overall survival in men with intermediate-risk PC. We do not know, however, which men with intermediate-risk PC benefited from the addition of ADT and whether that benefit would have existed if high-dose RT was administered. Specifically, several investigators have shown that using EBRT without ADT in men with favorable intermediate-risk PC results in low rates of PCSM after 10 years (< 2%), consistent with outcomes achieved for men with low-risk PC where ADT is not indicated because it has not been shown to prolong survival. Given that this is recent information, it was not incorporated into patient selection or prerandomization stratification schemes in RCTs such as in the RCT that accompanies this editorial, which creates difficulty in interpreting the results. Specifically, if men with favorable intermediate-risk PC are enrolled on RCTs evaluating the impact of the duration of hormone therapy on PCSM, the power of the trial to observe a difference in the PCSM outcome, if one exists, decreases because PCSM will not be impacted by differing durations of ADT in men with favorable-intermediate-risk PC. Therefore, while a significant reduction in PCSM may exist for longer- rather shorter-course ADT in men with unfavorable intermediate-risk PC, the overall study may be negative due to the dilution of any impact of the duration of ADT on PCSM from the inclusion of men with favorable intermediate-risk PC. This limitation is significant because data from nonrandomized institutional series show a significant association with a reduction in PCSM when 6 months of ADT are added to high-dose EBRT in men with unfavorable intermediate-risk PC. What has been lacking, however, are data from RCTs in which the potential for confounding is minimized so causality can be established.

In the article that accompanies this editorial, Pisansky et al present the initial results of Radiation Therapy Oncology Group (RTOG) 9910 [Clinical Trial Registry Number (NCT) 00005044], a randomized trial evaluating the impact on PCSM of adding 4 months versus 9 months of ADT to 70.2-Gy EBRT. The study cohort consisted of 1,489 eligible men (median age, 71 years) with 84% intermediate-, 15% high-, and less than 1% having very high–risk PC. After a median follow-up of 9.4 years, 450 (30.2%) men died; 54 (12%) of PC. The hazard ratio for PCSM, the primary end point was 0.81 (95% CI, 0.48 to 1.39; \( P = .45 \)) and cumulative incidence estimates of PCSM at 10 years was 4% and 5% in the 9- and 4-month ADT arms, respectively. The expected number of PC deaths on which the study was powered was 270 or five times the number observed.

Ideally, given the new information regarding the possible benefit of ADT in men with unfavorable but not favorable intermediate-risk PC, a postrandomization hypothesis generating analysis evaluating the impact of the duration of ADT in these subgroups would be helpful. Since this categorization requires knowing the ppb, these data may not have been prospectively

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collected. Therefore, we are left to wonder whether the study enrolled a sufficient number of men with favorable intermediate-risk PC to dilute out the potential benefit that may have been noted if only men with unfavorable intermediate-risk PC were enrolled. Certainly the PCSM event rate of 20% expected after a median follow-up approaching 10 years is suggestive that this may have occurred.

So, how do we decide whether to administer 4, 6, or 9 months of ADT to men with unfavorable intermediate-risk PC, and should any ADT be given to men with favorable intermediate-risk PC? First, the RTOG may be able to ascertain retrospectively the ppb data from RTOG 9910 and perform the postrandomization analyses described. However, we would still be left with the question of whether any benefit observed for the addition of 9 months versus 4 months of ADT would persist if high-dose RT, as practiced today, was employed. Fortunately, the RTOG has an ongoing study 0815 (NCT00936390) in which men receive high-dose RT (79.2 Gy or 45 to 50.4 Gy and a low- or high-dose rate brachytherapy boost) with or without 6 months of ADT. This RCT can be interrogated within intermediate-risk subgroups, if ppb data is available, to provide some guidance on whether 6 months of ADT reduces PCSM in men with unfavorable intermediate-risk PC undergoing high-dose RT and whether high-dose RT alone is sufficient to minimize PCSM in men with favorable intermediate-risk PC. Moreover, a recently reported Grupo de Investigación Clínica en Oncología Radioterápica (GICOR) sponsored RCT (NCT 02175212) of 28 months versus 4 months of ADT in the setting of high-dose RT (median dose: 78 Gy) observed a survival benefit after a median follow-up of 5.3 years. In that RCT men were stratified before random assignment by risk group (intermediate v high). In their initial report of overall survival, the group that appeared to benefit were men with high-risk PC. However, if ppb data is available then when the study matures, a postrandomization analysis by intermediate-risk subgroups could provide some insight into whether greater than 4 months of ADT is necessary in the setting of high-dose RT to reduce PCSM in men with unfavorable intermediate-risk PC.

Finally, if postrandomization analyses of GICOR and RTOG 0815 provide evidence to support a survival benefit for the addition of greater than 4 or 6 months of ADT respectively to high-dose RT in men with unfavorable intermediate-risk PC, then the only remaining question is whether high-dose RT is necessary in the setting of ADT. This would require having men with unfavorable intermediate-risk PC given short-course ADT and randomized to 79.2 Gy versus 70.2 Gy RT, but since such a trial has not been planned, it is unlikely to happen. What we do know from a randomized RT dose-escalation trial of 79.2 Gy versus 70.2 Gy and no ADT use performed by the RTOG in men with intermediate-risk PC is that after a median follow-up of 7 years, distant failure was significantly decreased (P = .026) with 10-year rates of 8% versus 5% but at the expense of a significant increase (P ≤ .001) in late 10-year actuarial grade 2 or higher GI (22% v 16%) and genitourinary toxicity (GI; 15% v 10%) with the use of three-dimensional conformal RT or intensity-modulated RT. Given the 5% to 6% increase in GU/GI toxicity and only a 3% decrease in distant metastasis by 10 years, one may consider using high-dose RT only in men without competing risks so that the small distant disease-free survival benefit observed at a median of 7 years after high-dose RT has the potential to translate into a reduction in PCSM. This is particularly relevant given that the major cause of death in men with intermediate-risk PC during the first decade following treatment is from non-PC causes as shown in the current study where only 12% of all deaths were from PC.

In conclusion, whether 4 months of ADT is sufficient or any ADT is necessary in men with unfavorable or favorable intermediate-risk PC, respectively, to minimize PCSM remains unanswered. While awaiting the postrandomization analyses of the RTOG 0815 and the GICOR RCTs within the intermediate-risk subgroups, withholding ADT in men with favorable intermediate-risk PC and adding 4 or 6 months of ADT to RT in men with unfavorable intermediate-risk PC are reasonable options based on the available evidence.

AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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