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EDITORIAL

Long-Term Benefits of Dose-Escalation in Localized Prostate Cancer

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Before we have the honor of contextualizing the importance of this paper, the authors should first be congratulated for not simply conducting and completing a randomized controlled trial (RCT), but for following patients for nearly 2 decades and reporting the long-term results from their work.

Radiotherapeutic dose-escalation by the addition of fractions of conventional radiation therapy was the principle method to improve oncologic outcomes in radiation oncology for decades. The general hypothesis was that improved local control would translate into a reduction in metastasis, thereby reducing death from cancer while not affecting other-cause mortality, leading to improved overall survival (OS). Unfortunately, although many RCTs across numerous disease types have shown improved local control, near uniformly they have been unable to demonstrate that dose-escalation will improve OS.[1-3] Theories behind these findings include that primary drivers of death are pre-existing micrometastasis and not local recurrence, that prolonging treatment time with more fractions counteracts dose-escalation through accelerated repopulation, or that the incremental improvement of local control is not large enough to measure a reduction in metastatic disease in the context of competing risks of other-cause mortality. In contrast, these trials have consistently demonstrated increased toxicity, increased inconvenience, and presumed increased costs, thus calling into question the true clinical benefit of simply adding more fractions of radiation therapy to all-comers.

In prostate cancer, more than 10 RCTs have attempted to demonstrate the benefits of dose escalation, nearly all with the primary endpoint of biochemical control. Meta-analyses clearly demonstrate that dose escalation improves biochemical control.[4] Until the present study by Pasalic et al no other trial or meta-analysis has demonstrated a reduction in prostate cancer–specific mortality (PCSM), and none demonstrated an improvement in OS. So, we must ask: What are the benefits of dose escalation, what is unique about the current trial, and how should we interpret the results?

There are numerous strengths to this landmark study—it is an RCT (comparing 70 Gy vs 78 Gy) and thus eliminates most of the potential biases present in observational or retrospective study designs. Second, it has very long-term follow-up (median 14.3 years), allowing for analysis of endpoints such as PCSM, which occur relatively late. Third, it included low-, intermediate-, and high-risk patients, making it generalizable across risk groups. Fourth, androgen deprivation therapy (ADT) was not allowed, which provides a nonconfounded interpretation of the benefit of dose escalation. Fifth, the authors have reported previously detailed toxicity outcomes and now present prespecified outcomes of biochemical control, local control, and OS. In contrast, what are some of the limitations? It is a single-institution trial at a center of excellence, which may decrease its generalizability.[5] Additionally, the authors did not prespecify to report or longitudinally capture endpoints such as distant metastasis or PCSM; thus, these are post hoc unplanned analyses. Finally, the treatment

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techniques are antiquated, so the therapeutic ratio of tumor control versus their previously reported toxicity from dose escalation is less applicable today with modern treatment methods.[6]

The primary endpoint of this trial, as stated in the protocol, was freedom from prostate-specific antigen failure (not combined with clinical failure). The authors demonstrate that there was a borderline significant difference in biochemical failure ($P = .051$) favoring the 78 Gy arm, with an absolute improvement of 5.2% at 15 years. Twenty of the 69 biochemical failures were, in fact, biopsy proven. The authors also demonstrated in their preplanned secondary endpoints that local failure was not significantly reduced ($P = .33$), but there was a 2.9% absolute reduction in local failure from dose escalation. OS was also not significantly different ($P = .47$), with numerically worse OS by 4.5% in the 78 Gy arm. What is very impressive is how low the biochemical failure rate was at 15 years, with only 12.3% and 7.1% of patients experiencing a recurrence in the low- and high-dose arms, respectively. Remember, 80% of this cohort had intermediate- or high-risk disease, and ADT was not allowed for these patients. Comparing the outcomes from this trial to Radiation Therapy Oncology Group (RTOG) 0126, which had an overall more favorable population of predominately favorable intermediate-risk disease, Michalski et al reported 8-year rates of biochemical recurrence of 35% and 20% for the low- and high-dose arms, respectively (~3-fold higher than the MD Anderson Cancer Center results despite 50% shorter follow-up). This raises the questions of either ascertainment bias (how closely and for how long were prostate-specific antigens followed?) or generalizability of the study results.

Pasalic et al also report on multiple unplanned secondary endpoints. They found a significant improvement in metastatic failure ($P = .018$) with an absolute reduction in metastasis of 2.3% from dose escalation. They also found a significant reduction in PCSM ($P = .045$) with a 3% absolute reduction from dose escalation. Finally, they demonstrated a borderline significant 9.9% increase in death from other causes ($P = .061$), the largest absolute difference of any endpoint in the trial. Importantly, on multivariable analysis there was no significant difference in biochemical control, distant metastasis, PCSM, or other-cause mortality between arms. Given the unplanned nature of the reporting of metastasis and death from prostate cancer or other causes, how does one interpret these findings? One could simply state they are all hypothesis generating, as they were unplanned and were not significant on multivariable analysis, or we can try to contextualize them in the context of other RCTs.

First, they show an amazingly low 3.4% incidence of metastasis with low-dose external beam radiation therapy alone at 15 years posttreatment. Furthermore, in their intermediate-risk subset there were no metastatic events in either arm. In contrast, RTOG 9408 recently reported its 18-year outcomes and found that ~12% of patients developed metastasis with low-dose radiation therapy alone.[7] Similarly, RTOG 0126 demonstrated that at 8 years the low-dose radiation therapy alone arm had a 6% incidence of metastasis, or 2 fold higher than what is reported with half the follow-up of the MD Anderson Cancer Center trial.[3] Given the unplanned nature of the metastatic endpoint and the exceptionally low event rates of metastasis, this raises the possibility of ascertainment bias; how rigorously were computed tomography and bone scans obtained serially over the study duration of the trial? Or is this simply a reflection of these patients being treated at a center of excellence under the management of expert radiation oncologists? Can we expect only 1.1% of patients with localized prostate cancer (~80% of whom were intermediate and high risk) treated with 78 Gy without ADT to develop metastasis within 15 years? If so, this would call into question the benefit of further dose or systemic intensification beyond 78 Gy.

Next, how does one explain that this trial uniquely has shown a reduction in PCSM but a large and borderline significant increase in other-cause mortality? Is this simply due to the long-term follow-up? Perhaps this may be from attribution bias, in that some patients who died of other causes actually died of prostate cancer or vice versa. This can be appreciated in that there were more PCSM events than metastatic events, meaning that some patients were counted as having a PCSM event who simply died in the setting of a biochemical recurrence while on treatment and were unlikely to have truly died from prostate cancer. In fact, 9 of 41 PCSM events (22%) were in patients that had no evidence of metastasis. The alternative, less plausible explanation for reduced PCSM and increased other-cause mortality with dose escalation is that dose escalation somehow directly led to increased deaths unrelated to prostate cancer. It is challenging to understand how this would occur, especially considering there were no differences in secondary malignancy rates between arms. Although exciting to see a difference in PCSM, we are cautiously optimistic when interpreting these results given the potential for misattribution of this unplanned analysis. This trial does have the longest follow-up of any dose-escalation trial, and we hope to see the results validated by other trials as they mature in follow-up.

To summarize, the authors have shown that dose escalation with long-term follow-up leads to a small improvement in biochemical control, which did not translate into an improvement in OS (although the study was not powered to detect this difference). This is consistent with every prior dose-escalation trial and meta-analysis. So, could the 8 Gy of dose escalation lead to the 5% improvement in biochemical control? Yes. Could this then lead to a 2% improvement in clinically assessed local control? Definitely. Could this 2% improvement in local control translate to a 3% reduction in death from prostate cancer? This is harder to understand, and further validation from longer follow-up of RTOG 0126 will be critical to understand in a large, multi-institutional

cooperative group setting if such a relationship exists. Regardless of the answer, radiotherapeutic dose escalation is an accepted standard of care, and with modern image guidance, intensity modulation, and use of rectal spacers, it has exceptionally low rates of severe side effects. Ongoing and future important work must determine if we can genomically identify pretreatment the ~90% of patients in this trial who did not have recurrence after low-dose radiation therapy and could be spared the increased side effects of therapeutic intensifications. We have been successful in intensifying treatment for our patients, and it appears we have reached the crossroads where we need to biologically classify which men will benefit from less intense treatment.

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