



## Androgen deprivation therapy in high risk prostate cancer

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We thank Dr. Kim and colleagues for their interest in our study (1,2). The authors mention some limitations of our study, all of which were discussed in our initial report, but can be discussed further. First, however, it is worth noting that the central conclusion of the study is not necessarily that patients with Gleason grade group (GG) 5 tumors need lifelong androgen deprivation therapy (ADT), but rather that GG 5 tumors are not inherently resistant to ADT, as had been previously suggested (3). If they were truly resistant, then lifelong ADT would have no impact on endpoints such as distant metastasis or prostate cancer-specific mortality, let alone overall survival, particularly given the known adverse sequelae of ADT that Kim *et al.* mention (2). Instead, it is entirely possible that GG 5 tumors require more potent androgen inhibition to achieve the level of control that is seen with GG 4 tumors with less intensive/shorter duration ADT—consistent with a Gleason grade-dependent effect of ADT, in the context of definitive radiotherapy (RT). Thus, we support ongoing efforts to determine strategies that seek to maximize the efficacy of ADT while limiting its duration. This is the same conclusion that Kim *et al.* propose in their own Summary and Conclusions (2).

Second, although there was a lack of central pathologic review across all patients in this meta-analysis, only two of the six trials in the analysis did not include central pathologic review within the trial comprising approximately 27% of the total analyzed cohort (4,5). Although this lack of central review between studies does present a limitation with respect to concordance between the cohorts as well as changes to the Gleason grading

system over time, the vast majority of patients analyzed in this study had their pathology centrally reviewed which allows for reliable comparison of treatment effect within each cohort. A more general problem regarding determination of ADT duration with definitive RT is the demonstration of discordance between biopsy Gleason grade and surgical Gleason grade as seen after radical prostatectomy (6). Although this discordance remains worrisome with respect to accurate risk classification of patients and additional work is needed to improve accuracy and concordance of biopsy Gleason grade, all prior investigations of prostate cancer treatment response to definitive RT with or without ADT—including the six studies included in this meta-analysis—rely on biopsy Gleason grade. Thus, this is not a limitation of our study, but a limitation of all trials and in fact a limitation of definitive RT for prostate cancer in general. Further, discordances between biopsy Gleason grade and “ground truth” surgical Gleason grade (had these patients undergone prostatectomy) would be unexpected to lead to the consistent result of worse outcomes (including OS) between GG 5 and GG 4 tumors.

Finally, the use of substandard radiation doses and the high enrichment of tumors with locally advanced lesions is again a valid point. However, these six trials are routinely used to justify the current standard of care for the management of high-risk prostate cancer with definitive RT. Therefore, those limitations apply not only to this meta-analysis, but to the data foundation used to drive current treatment guidelines. Within this context, our conclusions are relevant to modern practice.

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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