Editorial Commentary

Androgen deprivation therapy and Gleason grade: unravelling implications on survival

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The efficacy of concurrent androgen deprivation therapy (ADT) with radiation therapy among patients with high-risk prostate cancer is well documented. A meta-analysis by Kishan *et al.* (1) compared the effect of ADT duration on survival in patients with Gleason grade group (GGG) 4 and GGG 5 prostate cancer receiving radiation therapy by performing an individual patient-level network meta-analysis with data from six randomized controlled trials. Due to the significant adverse effects of ADT, efforts have been made to assess the efficacy of shorter ADT durations. The present study investigated if the effect of ADT duration on survival differed between patients with GGG 4 and GGG 5 disease.

The study compared overall survival (OS), cancer specific survival (CSS), and distant metastasis free survival (DMFS) among GGG 4 (n=593) and GGG 5 (n=399) patients who received radiation therapy alone, short-term ADT, long-term ADT, and lifelong ADT.

Both short-term ADT (HR 0.43; 95% CI, 0.26–0.70; P=0.03) and long-term ADT (HR 0.59; 95% CI, 0.38–0.93; P=0.03) improved OS as compared to radiation therapy alone in GGG 4 patients. However, lifelong ADT showed no difference in OS compared to radiation therapy alone in GGG 4 patients (HR 0.84; 95% CI, 0.54–1.30; P=0.44). The trend in these effects (with a diminishing benefit to ADT with increasing duration), suggests that while the concurrent administration of ADT with radiotherapy provides significant benefit, the harms of ADT may outweigh its advantages while administered for long durations in this patient population.

In contrast, among GGG 5 patients, there was an improvement in OS for patients that received lifelong ADT (HR 0.48; 95% CI, 0.31–0.76; P=0.04) but not among those receiving long-term (HR 0.80; 95% CI, 0.45–1.44; P=0.45) or short-term ADT (HR 1.13; 95% CI, 0.69–1.87; P=0.64). This suggests that, even among patients with apparently localized disease, patients with GGG5 disease benefit from treatment approaches more in keeping with men with disseminated disease.

In patients who received short-term ADT and in all patients studied, GGG 5 patients exhibited worse OS compared to GGG 4 patients (HR 1.40; 95% CI, 1.05–1.88; P=0.05 and HR 1.25; 95% CI, 1.07–1.47; P=0.04, respectively). Among patients who received long-term or lifelong ADT, there was no difference in OS between GGG 5 and GGG 4 patients (HR 1.21; 95% CI, 0.89–1.65; P=0.23 and HR 0.85; 95% CI, 0.53–1.37; P=0.52, respectively) (1).

Management of prostate cancer has changed significantly since the studies included in this meta-analysis were published. The NCCN guidelines for treatment of prostate cancer recommend radiation dosages of up to 75.2–81.0 Gy for treatment of high-risk disease (2). Among the included studies, only one utilized radiation dosages in this range with a subset of patients in EORTC 22991 trial receiving dosages up to 78 Gy (3). The other studies included did not

exceed dosages of 72 Gy, with most using a maximum of 70 Gy (4-8). Giving lower radiation dosages than suggested by current guidelines may affect the relationship between the administration of ADT and OS due to less effective local radiation therapy. With greater efficacy of radiation therapy protocols today, it is possible that patients with GGG 5 disease would have greater survival benefit with short and long-term ADT. Alternatively, more effective local therapy may obviate the benefit of systemic ADT.

In addition to changes in radiation treatment, there have been significant advances in imaging technologies that have improved the ability to diagnose and stage advanced prostate cancer. ^{68}Ga-PSMA positron emission tomography/computed tomography (PET/CT) offers significantly increased sensitivity in detecting nodal and distant metastases compared to other imaging modalities (9). Additionally, ^{68}Ga-PSMA PET/CT has improved the ability to detect recurrent prostate cancer, especially at lower PSA levels (10). As the authors note, the less sensitive staging modalities available at the time of the included trials introduces the possibility of unknown metastatic burden among the study patients that may have impacted the greater benefit of lifelong ADT (*vs.* shorter regimens) in GGG 5 patients. Today, the ability to more accurately stage high-risk prostate cancer using more sensitive modalities provides better patient selection and validity to results of clinical trials.

When evaluating the application of these results to clinical practice, it is important to consider the adverse effects of ADT and their impact on patient quality of life (11,12). Known toxicities of ADT include fatigue, osteoporosis, decreased sexual function, hot flashes, depression, alterations in blood lipid levels, cognitive dysfunction, and metabolic effects (13,14). Additionally, longer duration of ADT has been associated with greater risk of these adverse effects in a dose-dependent fashion (13). Awareness of ADT side effects is especially important when weighing the increased survival associated with lifelong ADT in patients with GGG 5 disease, as these patients should be counseled on these adverse effects prior to starting treatment. Furthermore, intermittent ADT, which was not mainstream during accrual for these trials, as noninferior to continuous ADT has significant implications on the application of these results. Intermittent ADT offers improved quality of life and similar overall survival to continuous ADT (15). The use of intermittent ADT in GGG 5 patients may improve survival with less negative impact on quality of life and minimize the deleterious, cumulative effects of prolonged ADT.

The data reported by Kishan *et al.* suggesting differential survival among GGG 4 and GGG 5 for patients receiving short-term, long-term, and lifelong ADT has treatment implications for high-risk patients. Despite limitations, these data suggest that these high-risk patients should not be considered equivalent and that nuanced prescribing of ADT may improve outcomes for patients with high grade prostate cancer undergoing radiotherapy.

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Footnote

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