Editorial Commentary

Effects of androgen deprivation therapy duration and Gleason grade on survival outcomes of high risk prostate cancer

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Introduction

Prostate cancer (PCa) is the most frequently diagnosed malignancy in men worldwide. There are various types of PCa treatments like as surgery, radiotherapy, and hormone therapy. Many PCa patients receive androgen deprivation therapy (ADT) based on the hormone dependence of PCa. Recently, several studies have been conducted to establish the relationship between ADT and various complications (e.g., cardiovascular disease, stroke, Alzheimer's disease, and osteoporosis). Most of them have reported a correlation between ADT and these complications, leading to an interest in proper duration of ADT. Consequently, several trials have been conducted to confirm this.

Kishan *et al.* (1) focused on identifying the difference in association of ADT duration with clinical outcomes of patients with Gleason grade group (GG) 4 (formerly Gleason score 8) *vs.* GG 5 (formerly Gleason score 9–10) disease. Meta-analysis using individual patient-level data of 6 randomized clinical trials was done to compare the different treatment methods [RT alone, lifelong ADT, short term ADT (STADT), and long-term ADT (LTADT)]. The hypothesis of the study indicated that longer durations of ADT offered significant survival chances in both groups (GG 4 and 5).

The objective of the meta-analysis was to consolidate the results of several similar studies to verify the validity of the conclusions and to enhance evidence in actual practice or to make a substantial change in practice. Network meta-analyses combine a networks of direct and indirect comparisons of interventions which allows researchers to simultaneously evaluate the impact of two or more interventions on the same condition (2). The term "individual patient data" refers to the data recorded for each participant in a study. Meta-analysis of individual participant data has potential statistical and clinical advantages over meta-analysis of aggregate data such as: (I) more standardization of analyses across studies; (II) direct induction of desired information; (III) a longer follow-up time; and (IV) more participants and outcomes than were considered in the original study publication (3).

Interpretation of meta-analysis results

This study finally included 6 randomized trials comparing various treatment methods (RT alone, lifelong ADT, STADT, and LTADT). There was full access to all individual patient data of 992 patients who had enrolled in 6 randomized clinical trials. Individual patient data included a total of 593 male patients (mean age, 70 years; range, 43–88 years) with GG 4 and 399 patients with GG 5, having a median follow-up age of 6.4 years. The analysis defined STADT as 4 to 6 months and LTADT as 28 to 36 months.

Trials involving outdated therapies such as interferon alfa were excluded, while clinically current and relevant therapies such as targeted therapies and immune therapies were included. The selection bias inherent to any meta-analysis is that the study selection is geared towards positive result trials. Negative results trials are less likely to be

published and hence they are frequently not captured in meta-analyses.

The main conclusions of this study were: (I) prolonged durations of ADT improve overall survival (OS) in both GG 4 disease and GG 5 disease, but in other ways; (II) use of STADT and LTADT offer OS improvements in GG4 disease, but not in GG5 disease; the opposite is true for lifelong ADT.

Brief history and prognostic features of Gleason grade group (GG)

In 1966, Donald Floyd Gleason proposed a grading system of a prostate adenocarcinoma for reproducible classification in place of the existing subjective grading system. Among the nine patterns, four patterns that showed similar prognosis were removed (4). In 1974, as prostate cancer showed two histological patterns, the primary and secondary patterns were added to achieve a representative score. Henceforth, the Gleason score became a category 1 prognostic parameter by the College of American Pathologists.

After collection of more clinical information and outcomes of prostate cancer, the grading system was modified by International Society of Urological Pathology (ISUP) in 2005 and 2014. Cribriform and glomeruloid are refined to Gleason pattern 4 regardless of the size and shape of margin (5).

In order to have a classification that would represent the relationship between treatment and outcome of disease, different grading methods were proposed and the use of three-tiered grouping (6-10) was found to be the most reliable.

However, as an example, among the seven Gleason scores (Gleason 3+4=7), and (Gleason 4+3=7), had limitations in defining the treatment method and predicting the outcome. Jonathan, I Epstein suggested a new grading system composed of 5 grade groups and had accuracy, simplicity and effectiveness to treatment even though the classification failed to reflect the tertiary and minor pattern (6).

According to the new Gleason grade group, Grade group 4 is composed of three types of Gleason score namely; 4+4/3+5/5+3. The histologic features were only poorly formed, fused, cribriform glands/ well-formed glands in major with focal lacking glands/predominantly lacking glands with focal well-formed glands, respectively. Through numerous verification studies, Gleason grade group 1 (Gleason score 6=3+3) revealed excellent prognosis, while the grade group 5 [Gleason score 9 (4+5 or 5+4) and 10 (5+5)] showed poor prognosis.

Application of results

This meta-analysis assessed the duration of ADT to improve survival compared to RT alone in patients with GG 4 and 5. A new PCa grading system based on the data from Johns Hopkins Hospital in 2013 has been proposed to address the confusion inherent to the Gleason system (7). There was a proposal to adopt a new prostate cancer grade system during a discussion at the 2014 Chicago grading meeting. The new grading system and the terminology "Grade Groups 1–5" had already been approved in the 2016 edition of Pathology and Genetics: Tumors of the Urinary System and Male Genital Organs by the World Health Organization (5). The new PCa grading system had the following advantages: (I) more precise grade stratification compared to the current Gleason system; (II) a simplified grading system of 5; and (III) A higher probability of reducing overtreatment of indolent PCa using the lowest grade of 1 (8).

The two studies validated new Grade Group system for patients treated for PCa using either radical prostatectomy or radiation (6,9). Both studies found that Grade Groups were associated with a recurrence risk after primary therapy. The 5-year biochemical non-recurrence progression probabilities after radical prostatectomy decreased with increasing Grade Group. Particularly, those of GG4 and GG5 were 48% (95% CI, 95–96%) and 26% (95% CI, 23–30%), respectively (6). In another study, all-cause mortality and PCa-specific mortality were higher in patients with GG5 than in GG4 patients (10).

The National Comprehensive Care Network (NCCN) has defined PCa as a high-risk disease characterized by having at least one of the following features: locally advanced disease (T3 disease or greater), GG ≥4, or a serum prostate specific antigen (PSA) >20 ng/mL. The standard treatment for the high-risk disease is external-beam radiation therapy (RT) coupled with ADT (11).

How long is the most appropriate ADT duration? Zapatero *et al.* (12) presented powerful data for answering this question using the first report of the DART01/05 GICOR study. Phase 3 trial compared 4 months of neoadjuvant and concurrent ADT plus dose-escalated RT with similar treatment in addition to 24 months of ADT. They reported that LTADT improved the outcomes of biochemical progression-free survival, metastasis-

Table 1 Interpretation of meta-analysis

Endpoint	Preferred duration of ADT (compared to RT alone)
OS in Gleason grade group 4	STADT (HR, 0.59; 95% CI, 0.38–0.93; P=0.02); LTADT (HR, 0.43; 95% CI, 0.26–0.72; P=0.02)
OS in Gleason grade group 5	Lifelong ADT (HR, 0.48; 95% CI, 0.31–0.76; P=0.01)

ADT, androgen deprivation therapy; LTADT, long term androgen deprivation therapy; OS, overall survival; RT, radiotherapy; STADT, short term androgen deprivation therapy.

Table 2 Limitations likely to impact conclusions of this study

None of the trials that specifically powered or designed to evaluate differences in outcome based on GG
Lack of centralized pathology review
Use of radiation that would be considered substandard today
High enrichment of patients with locally advanced lesions compared with modern

GG, Gleason grade group.

free survival, and overall survival. When classified by a risk group, the effects were more prominent in high-risk patients than in those with an intermediate-risk disease.

The value of this meta-analysis could be that as the duration of ADT increases, the survival outcome of high-risk disease may become better. However, the optimal ADT duration depends on GG4 and GG5 (*Table 1*). The safely shortening of the long-term ADT is crucial due of its effects the quality of life. However, long-term ADT should remain the standard of care for high-risk patients, depending on the results of this meta-analysis incorporating their results as well as the results of previous trials. Furthermore, following the results of this meta-analysis, it is more efficient to use RT together with LTADT in GG4 patients and RT coupled with lifelong ADT in GG5 patients.

There are the various limitations likely to impact the conclusions of this study (*Table 2*). This meta-analysis was performed by assessing the individual patient data of several randomized controlled trials and classifying them into unplanned subgroups. Therefore, interpretation of the results must be cautiously done, owing to the fact that any trials have not been specifically designed or driven to assess the difference in results based on the GG. The definition of LTADT is a minimum of 28 months and a maximum of 36 months. The difference between the two is 8 months, which is too broad compared to the 2 months in STADT. It is possible that this further highlights the effects of LTADT.

Summary and conclusions

The meta-analysis has enhanced the evidence for using a longer duration of ADT in a high-risk patient with PCa. However, it could be difficult to apply these results to actual practice due to the various limitations of this study. A high-quality study should be conducted to determine the difference in survival outcome due to the differences in ADT duration according to Gleason group. In conclusion, new anti-androgen or strategies of treatments for maximizing the efficacy of ADT while minimizing its duration should be explored.

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Footnote

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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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