Editorial

Quality of life after ultra-hypofractionated radiotherapy for prostate cancer: the challenge of RTOG 0938 trial

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In the *Red Journal*, Lukka and colleagues reported optimal quality of life (QoL) outcomes of the NRG Oncology RTOG 0938 trial (1). This trial randomly compared two short radiation schedules of 5 and 12 fractions of 7.25 and 4.3 Gy each, respectively, for the treatment of localized, low risk prostate cancer. The primary endpoint was the proportion of patients with a change in bowel and urinary EPIC-50 score at 1-year. They found that both these regimens were well tolerated and comparable to conventionally fractionated radiotherapy (RT), thus confirming that a course of RT with fewer daily treatments can be as safe as the traditional schedule—at least at short/medium time interval—with clear advantages in terms of patients' convenience and health economics.

The authors should be commended for having used patient-reported outcomes (PROs) as a valuable tool to report on symptomatic toxicities that might be missed by clinicians, even when data are prospectively collected within clinical trials.

Although more robust proofs of tolerability and efficacy of ultra-hypofractionation are currently being investigated in ongoing clinical trials, accumulating data that supports its use in daily clinical practice are rapidly growing and have matured to such an extent that current AUA/ASCO/ASTRO guidelines (2) recommend it as an alternative to conventional fractionation for low-intermediate risk prostate cancer, in spite of the moderate quality of evidence.

To strengthen this issue, the excellent outcomes herein reported, irrespective of the inclusion of patients with different age and ethnicity and the use of different treatment techniques (IMRT/VMAT, Cyberknife) and dosimetric parameters, add further insights on the safety and appropriateness of this approach. Furthermore, the authors' findings are in keeping with other large series reporting on PROs using prostate stereotactic body radiotherapy (SBRT) (3-11), which must be considered the most important endpoint when treating non-threatening cancers. Notably, the most significant changes at 1- and 2-year, involved the EPIC urinary domain regardless of which schedule has been used. This data adds to a large body of literature showing that the introduction of extreme hypofractionation for prostate cancer has resulted in a paradigm shift in considering the urinary (instead of the gastrointestinal) toxicity as the most bothersome. Indeed, a change >2 points in EPIC urinary score of 45.7% and 42.2% of the patients at 1-year and of 47.3% and 43.2% at 2-year, respectively, occurred when daily fractional doses >4 Gy have been employed. Interestingly, these outcomes are even better than those that have resulted from brachytherapy (BT), as emerged from two studies (7,12) that have compared QoL after SBRT, intensity modulated radiotherapy (IMRT), and BT using the EPIC questionnaire. As a matter of fact, both have found that external beam RT, and namely SBRT (7), was associated with a statistically significantly lower urinary toxicity at 2 years. Similarly, Shaverdian *et al.* (13) have launched a survey to obtain patients' feedback about their experience with different RT techniques: those who underwent SBRT manifested less treatment regret and less toxicity than expected (5% versus 18% and 19% in the BT and IMRT groups, respectively).

Despite several strengths, this study is not devoid of limitations that might prevent a widely adoption of ultra-hypofractionation in the current daily practice: the median follows up of 3.8 years is not long enough to see most of the possible treatment-related adverse effects; a radiation-induced toxicity might indeed occur late and negatively impact patients' QoL, especially of those who are frail and elderly. Coupled with the typical behaviour of low risk prostate cancers that would likely relapse later in the course of follow-up because of a slow tumor growth, these observations suggest that a longer follow-up is required to show more reliable outcomes. Ultimately, PROs gathered from conventional or moderately hypofractionated RT should be used as a benchmark to provide a meaningful comparison with ultra-hypofractionated schedules. To this end, a pooled analysis of multiple prospective studies (14) that have focused on changes in PRO QoL after moderate hypofractionation or extreme hypofractionation for prostate cancer, showed that there was no statistically significant difference between the groups in bowel and sexual toxicity, but the former was associated with a more pronounced worsening of urinary symptoms at 2-years. Randomized trials comparing these regimens are currently ongoing (NCT01584258, ISRCTN45905321, NCT01794403, NCT01230866), and their mature results are eagerly awaited to resolve the scientific dispute. Some of them (15,16) have already released preliminary data: in the HYPO-RT-PC trial (15), patients who received extremely hypofractionated RT in 7 sessions experienced similar side effects two years following treatment as those who received conventional RT in 39 sessions. Likewise, the interim analysis of the PCG GU 002 trial (16) showed no difference regarding the EPIC urinary, bowel, or sexual function scores at 3, 6, 12, 18, or 24 months after treatment between low-risk prostate cancer patients who underwent either standard fractionation or hypofractionated proton-beam therapy.

Long-term results of the present study (1) are warranted to provide further evidence that ultra-hypofractionated RT for prostate cancer can be an attractive strategy to reduce the burden of care without losing clinical effectiveness. Meanwhile, improvements in treatment planning and delivery may lead to a further reduction in the number of treatment sessions, thus enhancing its thriving cost-effectiveness profile.

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