Editorial

Prostate cancer and hypofractionation: really a new standard of care?

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Comment on: Dearnaley D, Syndikus I, Mossop H, *et al*. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol 2016;17:1047-60.

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The *Lancet Oncology* published in June 2016 results of the CHHiP trial (1): a randomized phase 3, non-inferiority trial testing a standard radiotherapy treatment for localized prostate cancer (74 Gy in 37 fractions over 7.4 weeks) compare to two more protracted schedules: 60 Gy in 20 fractions/4 weeks or 57 Gy in 19 fractions/3.8 weeks. The majority of enrolled patients had low or intermediate-risk disease and the prognostic factors are well balanced between the three arms. Half of the patients have been treated with no image guidance and only one third have been treated with inverse planning intensity modulated radiation therapy (IMRT) that could be considered today as a standard.

After a mean follow-up of 62 months, 3,216 patients were randomized with a primary endpoint defined as time to biochemical or clinical failure. A critical hazard ratio of 1.2 was set as the limit to consider a non-inferiority of the hypofractionated protocols: results shown a similar outcome regarding primary endpoint between the standard arm and 60 Gy group but no firm conclusion can be done for the 57 Gy arm. No differences have been shown regarding late toxicity but acute bowel and bladder toxicity developed earlier and occurred significantly more frequent at the peak in the two hypofrationated arms. However the three arms had a very low rate of grade 2 or more even if the rate is higher for the arm 57 Gy.

These results are more or less in accordance with those previously published by Arcangeli in 2011 (2) with a similar schedule as experimental arm which allowed the authors to consider that hypofractioned radiotherapy could be recommended as a standard of care for localized prostate cancer.

However in the same *Lancet Oncology* issue in June 2016 Incrocci (3) publish the final results of the HYPRO protocol comparing 78 Gy (2 Gy/Fr/5 days per week) with a hypofractionated schedule delivering 64.6 Gy with 16 fractions of 3.4 Gy 3 fractions per week: with only 3 fractions per week the biological dose could be equivalent to 3 Gy per Fr/5 Fr a week. Finally 820 patients with intermediate or high-risk prostate cancer were enrolled. This trial is a more classical superiority design trial and results are clearly in disfavor of the experimental arm after the same follow-up of 60 months: no benefit either on relapse free survival or failure rate was observed and the difference is observed on the side effects rate. Despite the use of IMRT for 95% of cases and the use of fiducial markers for daily image guidance (not performed in the CHHiP trial), the cumulative incidence of grade 2 or worse is significantly higher in the hypofractionated arm as well as the overall grade 3 or worse genitourinary toxic side effects (19% *vs.* 13%): conclusions of authors are as clear as those drawn by Dearnaley but opposite: hypofractionated radiotherapy cannot be regarded as a standard of care.

The HYPRO trial use more modern technics compared to the CHHiP and probably the mean dose received by rectal and bladder wall were higher at each fraction in the Dutch trial: with no image guidance it is unlikely that critical organs always received the same dose at each fraction due to the change of bladder or rectal filling

(or vacuity) and so differences between the two regimens regarding the toxicity could be mitigated with less advanced technic.

Hypofractionated regimens for prostate cancer has never been demonstrated as superior as conventional arm and toxicity have always been the limiting factors :perhaps randomized trials testing the benefit of spacers to spare rectal wall could be of concern but have only been reported in small series.

Before considering hypofractionated schedule as a standard of care, we could consider this regimen as an option: perhaps for small prostate volume, at least intermediate risk group in order to not expose low risk patient to exceed of toxicity and without intent to increase the biological efficiency but only with the aim to shorten the overall treatment time and decrease the overall cost of treatment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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