Editorial

A randomised control trial of salvage radiotherapy and androgen deprivation therapy following prostatectomy: commentary on five year follow-up findings

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The addition of short-term androgen deprivation therapy (ADT) to salvage radiotherapy post radical prostatectomy was recently reported in a multi-centre, phase 3, randomised controlled trial (RCT) by Carrie *et al*. (2016) to improve biochemical and clinical progression free survival at 5 years. The cohort consisted of men with a PSA level of <0.1 for at least 6 months after radical prostatectomy, with salvage radiotherapy commenced at PSA levels between 0.2 µg/L and 2.0 µg/L (1). The primary endpoint was progression-free survival defined as time from randomisation to documented "biological" progression (including a rising PSA), clinical progression or death from any cause. The 5-year progression-free survival was 62% in the external beam radiotherapy (EBRT) alone group and 80% in those who received radiotherapy plus goserelin (P<0.0001). With a halving of the rate of progression (hazard ratio 0.50, P<0.0001), the median duration between randomisation and relapse was increased by 10 months with the addition of ADT to EBRT (P=0.0001). No systematic tests were done to assess testosterone recovery after ADT: the delay in progression was remarkably similar to the expected total duration of castration (therapy plus recovery time) associated with 6 months of goserelin therapy (2). Whether this result is a simple delay of recurrence or secondary to higher rates of cure is unable to be determined at this time point. There has however been no impact on overall survival as yet, with median overall survivals being 56 months for the EBRT alone group versus 58 months for the combined treatment group.

While 589 (80%) of men had a PSA titre of <0.5 µg/L at randomisation (305 and 284 in the EBRT and combined groups respectively), other known risk factors for radiotherapy failure classified 70% of the cohort as high risk meaning that there was a significant risk of extra-pelvic disease in the cohort a priori. Subgroup analyses showed no significant restriction of therapeutic benefits to any particular subgroup.

Although the authors suggest these data may be considered evidence of castration working in synergy to radiosensitise EBRT, it must be kept in mind that the ADT in the study was goserelin monotherapy (i.e., no antiandrogen was used) administered on day 1 of EBRT. As this drug will cause an initial "flare" in testosterone, followed by a slow fall over a couple of weeks, it is unlikely

that a period of castration was present during the initial delivery of EBRT to interact with the local therapy.

As expected, systemic adverse effects with ADT were troublesome having been registered as acute adverse events for 30 (8%) of 366 at grade 2 or worse. The addition of ADT does not appear to have contributed to the toxicity of EBRT, with no differences in rates of genitourinary (GU) or gastrointestinal (GI) toxicity at any level. Overall, grade 2 or more toxicity levels were commensurate with the technology used to deliver the EBRT at approximately 12% and 13% for GU and GI acutely. Severe (Grade 3 or worse) late toxicity was not different between groups at approximately 8% and 2% for GU and GI toxicity, respectively. Unfortunately, only 55% of men returned the 1 year follow up health related quality of life (QoL) surveys (QLQ-C30) and only 22% for the 5 year follow up survey. Of those returning QoL questionnaires, a higher proportion of men had global QoL deteriorations in the combined therapy arm (35%) than in the radiation only arm (26%) at 1 year compared with baseline. No differences were apparent at 5 years however, with approximately 50% and 30% having registered stable or worsened global QoL levels, respectively, in each arm. No differences were seen between arms in terms of sexual function, which reduced from a median QLQ-PR25 score of 50 at baseline to 42 at 1 year and 33 at 5 years.

Completing an RCT such as this in 43 French study centres is an outstanding achievement and the authors are to be congratulated. However there are notable deficiencies, many of which are acknowledged in the manuscript. There was no central review of pathology specimens or of progression, which is important given the stated primary outcome of the trial. Metastatic progression data were not available as this was only recorded if it occurred as part of first progression. Early QoL data were collected at 12 months post-randomisation when most acute EBRT and ADT toxicity would be expected to have mostly settled, and thus limits interpretation. Compliance for QoL surveys was also poor as previously stated.

Will these data impact contemporary practice? Considerable progress has been seen with cancer imaging recently, particularly with magnetic resonance imaging (MRI) and positron emission tomography (PET) in relation to prostate cancer. In health care systems that have seen a rapid uptake of small-ligand prostate specific membrane antigen (PSMA) PET or choline PET, a significant proportion of patients eligible for this study would now have metastases identified outside the salvage radiotherapy field by these scans (3). In these cases, men avoid salvage radiotherapy that would not positively impact on their progression or survival.

Five years is a short time for determining the primary endpoint of this trial viz. progression-free survival, so further reports are to be expected. Nevertheless, these results in a patient cohort with a high risk of progression after post-operative salvage radiotherapy, show use of ADT in an adjuvant manner is beneficial in delaying short term progression and is generally supportive of the findings of previous retrospective studies (4) and that of the RTOG 9601 study (5). However, because of the issues raised above, the veracity of the findings and the subsequent ability to justify this approach as standard therapy may need to be re-evaluated in the era of improving radiological staging techniques.

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Footnote

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

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