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Editorial

RADICALS-HD: Reflections before the Results are Known

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We have previously described the rationale for, and the design of, the RADICALS (Radiotherapy and Androgen Deprivation In Combination After Local Surgery) trial [1]. Fifteen years and almost 4000 patients later, this report provides a brief update on the progress of the RADICALS-HD trial part of the protocol. The primary results of RADICALS-HD are not yet known, but are due to be reported in late 2022. Much has changed since the trial was originally designed. Therefore, we describe here the evolution of the trial and the external evidence that has emerged since the trial launched that may inform the interpretation of the forthcoming outcome data. We reiterate that, at the time of writing, the RADICALS-HD results are unknown, and so cannot possibly be inferred from this article.

Initial RADICALS Design

RADICALS was designed as a single clinical trial protocol, comprised of two separate randomisations (Figure 1) asking complementary questions in overlapping populations. The first randomisation, addressing radiotherapy timing, was for men who had recently had radical prostatectomy and compared adjuvant versus salvage radiotherapy. This was called 'RADICALS-RT'. The second randomisation, addressing hormone duration, was for men about to have postoperative radiotherapy (either adjuvant or salvage). This was called 'RADICALS-HD' and was planned as a three-way comparison of 0 months versus 6 months versus 24 months of hormone therapy. One aim of this second randomisation was to support balance in the use of hormone therapy across both arms of RADICALS-RT. To that end, when RADICALS-RT first opened, patients entering that radiotherapy timing randomisation also entered the hormone duration randomisation, RADICALS-HD, at the same time if they were allocated to RADICALS-RT's adjuvant therapy group. Patients for whom the site was convinced needed adjuvant radiotherapy could join RADICALS-HD alone. Patients who did not receive adjuvant radiotherapy, but who subsequently needed salvage radiotherapy, could also join RADICALS-HD alone prior to that salvage radiotherapy.

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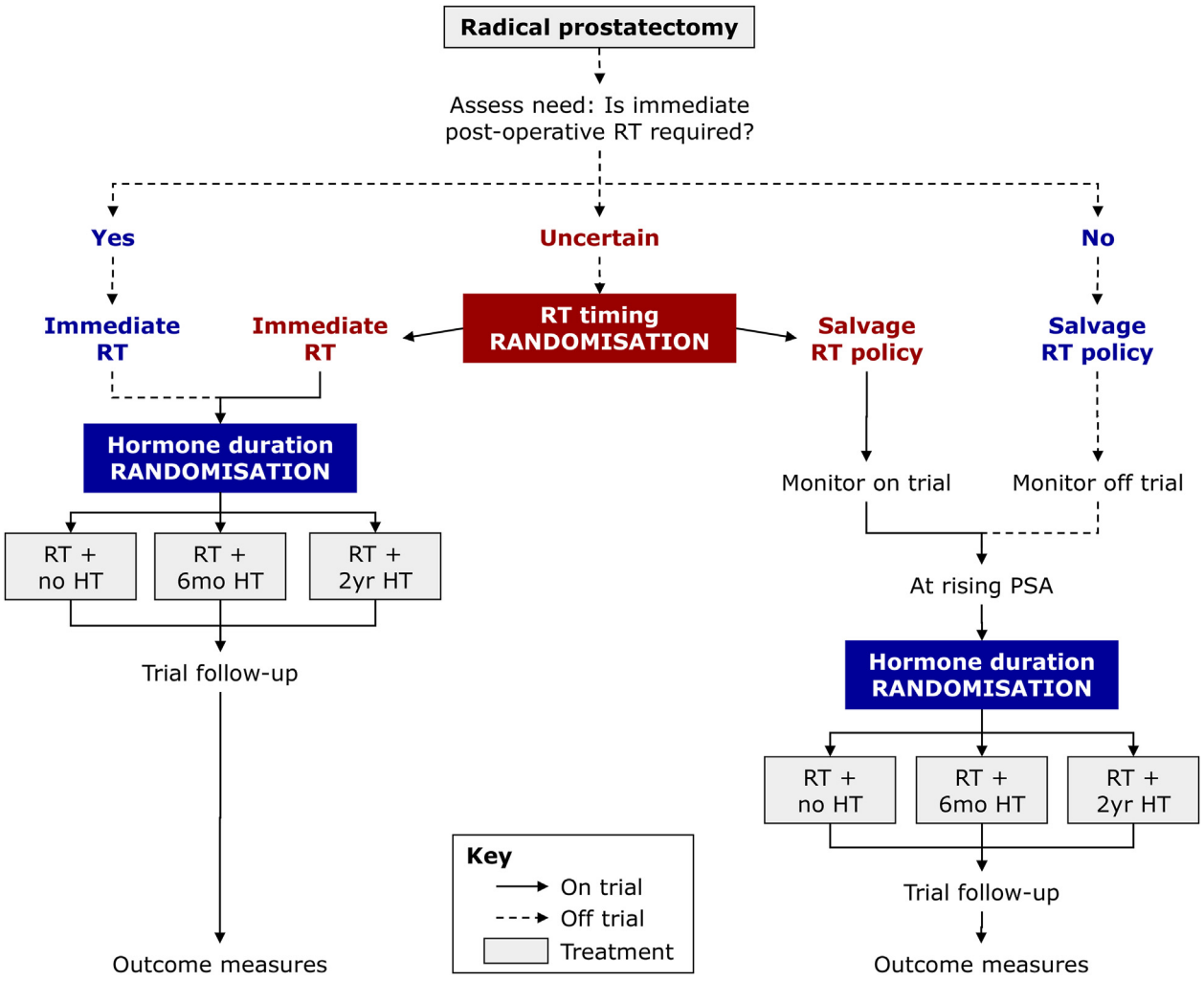

Fig 1. Original trial design.

The Evolution of RADICALS-HD: Conscious Uncoupling

After the RADICALS protocol opened to accrual, it soon became apparent that it was difficult to recruit patients to both randomisations at the same time. Discussing issues around both radiotherapy timing and hormone duration together added complexity to the recruitment process. In order to simplify matters, and to encourage accrual to both elements of the RADICALS protocol, we uncoupled the two randomisations (Figure 2). Patients entering RADICALS-RT and randomised to the adjuvant radiotherapy group were now able to enter RADICALS-HD immediately if they wanted to but were not obliged to do so. Patients entering RADICALS-RT and randomised to the salvage radiotherapy group had no need even to consider the RADICALS-HD question until a later date, if and when they required salvage radiotherapy. In this way, RADICALS evolved into two more separate trials, still within the same protocol and sharing a common infrastructure. This change was made by the Trial Management Group on the advice of the Independent Data Monitoring Committee and the Trial Steering Committee, which includes further independent members, and after peer review organised by the funder, Cancer Research UK.

We also invested time and effort into producing materials to support trial entry. In collaboration with Professor Lesley Fallowfield, Professor of Psycho-Oncology at the University of Sussex, and with patient support groups, we produced videos describing the trial and including mock clinic appointments between investigators and actors playing the part of the patient (http://www.radicals-trial.org/patients/patient-information-video/).

Without these resources, together with the uncoupling from RADICALS-HD, it is unlikely that the RADICALS-RT trial would have completed recruitment.

The Evolution of RADICALS-HD: Three-way and Two-way Randomisation

RADICALS-HD was planned to be a three-way comparison of 0 months ('none') versus 6 months ('short') versus 24 months ('long') of hormone therapy. However, during the

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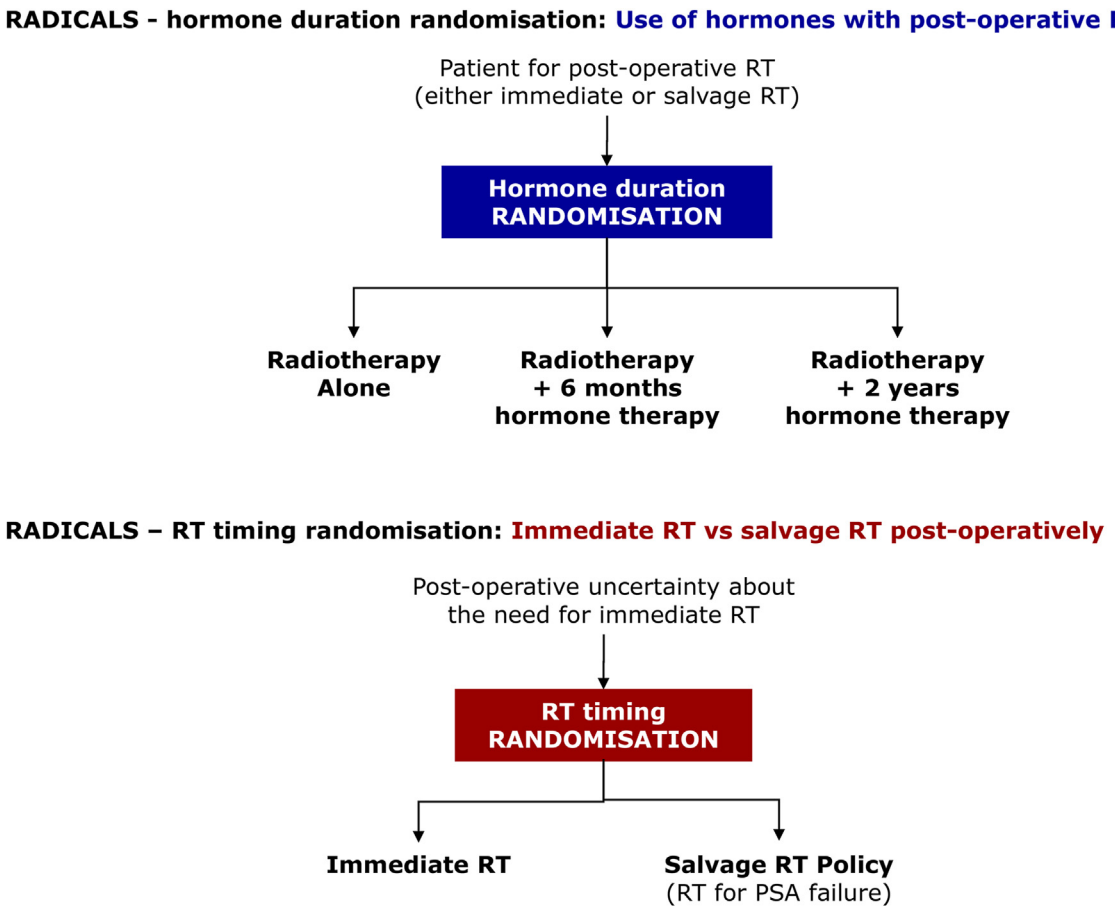

Fig 2. Revised trial design with two separate randomisations.

feasibility phase, the trial permitted two-way randomisation between none and short or between short and long in order to assess the feasibility of recruitment. The three-way comparison was strongly encouraged in RADICALS-HD materials as this would be the most efficient. As it turned out, most patients in RADICALS-HD entered a two-way randomisation during the feasibility stage. Therefore, the Trial Management Group agreed to maintain the two-way randomisation options as RADICALS-HD would otherwise not successfully recruit and would not serve its role of balancing in RADICALS-RT. In effect, rather than a single three-way trial of hormone duration, RADICALS-HD functionally became two two-way comparisons with a common name. The sample size calculations were re-drawn so that each two-way comparison was powered separately. This was carried out without reference to any accumulating comparative data and using the anticipated event rates.

Ultimately, 1480 patients were randomised between none versus short and 1523 between short versus long (492 patients were randomised between all three arms, of whom 164 allocated to the short treatment contribute to both comparisons). RADICALS-HD will have adequate power to test none versus short hormone therapy and to test short versus long hormone therapy; it will not be adequately powered to compare 0 versus 24 months, although this comparison will be presented in those patients randomised between these two options.

The Evolution of RADICALS-HD: Primary Outcome Measures

The primary outcome measure of RADICALS-HD, when RADICALS was first designed, was cause-specific survival. We initially assumed a 10-year cause-specific survival of 82% in patients receiving adjuvant radiotherapy alone without hormone therapy. However, data emerging subsequently showed that long-term outcomes in this patient group were considerably better than we had predicted (GETUG-16 [2], RTOG 9601 [3]). This is good news for patients, but it meant that the comparisons of RADICALS-HD would be underpowered at the planned time of reporting.

The work of the Intermediate Clinical Endpoints in Cancer of the prostate (ICECaP) collaboration [4] brought a timely solution. Based on an individual patient meta-analysis of 24 000 patients with non-metastatic prostate cancer, it found that metastasis-free survival (MFS) was a usable ‘surrogate’ for overall survival in localised prostate cancer trials. We therefore changed the primary outcome measure in RADICALS-HD to MFS. This was, again, carried

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out under guidance of the Trial Steering Committee with its independent members, after peer review by the funder, and without knowledge of any accumulating comparative data from the trial. Although we will be reporting the trial outcomes fully 15 years after the trial opened, this is several years earlier than would have been possible using cause-specific survival as the primary outcome.

New Evidence from Other Clinical Trials

There are three other randomised controlled trials that have tested the use of hormone therapy in combination with postoperative radiotherapy that have completed recruitment after accrual started to RADICALS-HD: RTOG 9601 [3], GETUG-16 [2] and the RTOG SPORRT trial [5]. All three trials were run in the salvage (not adjuvant) radiotherapy setting. The results of the SPORRT trial have not yet been published.

RTOG 9601 tested the use of 24 months of bicalutamide monotherapy and reported an overall survival benefit compared with no hormone therapy. Subgroup analyses have subsequently suggested that benefit may be confined to men with relatively high prostate-specific antigen (PSA) levels at the time of salvage radiotherapy. Indeed, that trial raised the concern that 24 months of bicalutamide might have an adverse effect on overall survival in men with a low PSA at the time of salvage radiotherapy [6].

GETUG-16 tested 6 months of an Luteinising Hormone Releasing Hormone (LHRH) analogue and reported an improvement in MFS compared with no hormone therapy (hazard ratio 0.73; 95% confidence interval 0.54–0.98; $P = 0.0339$), but no advantage in overall survival (12-year overall survival: 86% for radiation therapy plus goserelin versus 85% for radiation therapy alone; hazard ratio 0.93; 95% confidence interval 0.63–1.39; two-sided $P = 0.73$). Although the MFS benefit was statistically significant, the magnitude of the effect may not be clinically significant, and MFS was not a pre-specified end point in that trial. Furthermore, if 6 months of androgen deprivation merely served to delay the detection of metastases by 6 months, then that would not make it a useful intervention.

In the light of the results of these two trials, there remains considerable uncertainty about the use and the duration of hormone therapy in combination with postoperative radiotherapy. Some clinicians recommend 24 months treatment, based on RTOG 9601. Others recommend radiotherapy alone, particularly in those receiving salvage radiotherapy at a relatively low PSA level. RADICALS-HD was designed on the assumption that any effect of hormone therapy on outcomes would be consistent across the range of pre-treatment PSA levels. However, it will be important to investigate whether hormone therapy might have an adverse effect on survival in some patient groups, as suggested by RTOG 9601. We will therefore carry out subgroup analyses of RADICALS-HD according to PSA at the time of postoperative radiotherapy and according to comorbidity. If there is an adverse effect of hormone therapy on survival in some patients, one might expect to see it in men with lower PSA levels at the time of treatment and with greater comorbidity.

The First Findings of RADICALS-RT

The first results for the radiotherapy timing randomisation, RADICALS-RT, in patients for whom there was uncertainty about the use and timing of postoperative radiotherapy were reported in 2019 [7]. These were published simultaneously with two, smaller, complementary trials, GETUG-17 [8] and RAVES [9], together with the ARTISTIC meta-analysis prospectively combined the results of all three trials [10]. All patients in GETUG-17 were planned for short hormone therapy with any postoperative radiotherapy, whereas hormone therapy was not used in RAVES. Any impact of hormone therapy was not analysed in RADICALS-RT, partly in order not to jeopardise the findings of RADICALS-HD. These three trials did not show a benefit in biochemical progression-free survival to the use of adjuvant radiotherapy, and thus supported a policy of early salvage radiotherapy in the event of PSA failure after surgery.

Postoperative radiotherapy is now mostly used in the salvage setting, whereas adjuvant radiotherapy is seldom used after radical prostatectomy. The primary results of each RADICALS-HD comparison will include patients receiving postoperative radiotherapy in either the adjuvant or the salvage setting. This will be supplemented by separate analyses in the adjuvant and in the early salvage setting. These subgroups will not, of course, be fully powered, but we anticipate that the findings will help decision-making in the context of current practice.

Conclusion

We would like to thank all the patients and healthcare professionals who have made the RADICALS trial possible. The trial has benefitted from the long-term commitment of patients and staff from 149 centres in four countries: UK, Canada, Denmark and Ireland. Whatever the results turn out to be, we hope that they will be useful to inform clinical practice in men receiving postoperative radiotherapy after radical prostatectomy.

Conflicts of Interest

C.C. Parker reports a relationship with Bayer Corporation that includes: consulting or advisory. C.C. Parker reports a relationship with Janssen Pharmaceuticals Inc. that includes: speaking and lecture fees. C.C. Parker reports a relationship with Clarity Pharmaceuticals that includes: consulting or advisory. C.C. Parker reports a relationship with Myovant Sciences Ltd that includes: consulting or advisory. C.C. Parker reports a relationship with ITM Radiopharma that includes: consulting or advisory. C. Catton has received honoraria and research funding from Abbvie Corp.; Tersera Corp.; Bayer Corp. and Knight Pharmaceuticals.

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W. Cross, outside this work, has consulting and advisory for Bayer, Janssen, Astellas and Myriad Genetics.

H. Payne has, outside of this work, attended and received honoraria for advisory boards, travel expenses to medical meetings and served as a consultant for AstraZeneca, Astellas, Janssen, Sanofi Aventis, Ferring, Bayer and AAA Novartis.

N.W. Clarke, outside of this work, received honoraria from Astellas & Janssen; took a consulting/advisory role for Astellas, Janssen, Ferring, Bayer & Sanofi; was paid speakers fees b Janssen & Astellas; received funding for the institution from Astra Zeneca; received meeting and travel expenses from Janssen, Astellas, Sanofi, Astra Zeneca, Ferring & Ipsen.

M.K.B. Parmar, outside of this work, received research funding to the Unit he directs from Acoria Pvt Ltd, Akagera, Amgen, Aspirin Foundation, Astellas, AstraZeneca, Baxter, Bayer, BMS US, Bri-Bio, Cepheid, Cipla, Clovis Inc, CSL Behring, Eli-Lilly, Emergent Biosolutions, Gilead Sciences, GlaxoSmithKline, Grifols, Janssen Products LP, Janssen-Cilag, Johnson & Johnson, Micronoma, Modus Theraputics, Mylan, Novartis, Pfizer, Sanofi, Serum Institute of India, Shionogi, Synteny Biotechnology, Takeda, Tibotec, Transgene, ViiV Healthcare, Virco and Xenothera.

M.R. Sydes, outside of this work, received research funding to the institution from Astellas, Clovis, Janssen, Novartis, Pfizer, Sanofi-Aventis; received speaker fees from Lilly Oncology & Janssen.

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Author Contributions

CP is the guarantor of integrity of the entire study. CP, NC, MS, MP, CC, HK, JL, RP, FS and WP were responsible for study concepts and design. CP was responsible for literature research. All authors prepared and edited the manuscript.

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