available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Editorial

Referring to the article published on pp. 443–449 of this issue

Androgen Deprivation Therapy with Postprostatectomy Radiotherapy: For Whom and for How Long?

Charles Dearman, Chris Parker *

Urology Unit, Royal Marsden NHS Foundation Trust, Sutton SM2 5PT, UK

A role for hormone therapy in men receiving salvage radiotherapy (SRT) after radical prostatectomy is well established. RTOG 9601, a phase 3 randomised control trial, demonstrated an overall survival benefit for 24 mo of bicalutamide in this setting, with a hazard ratio of 0.77 (95% confidence interval [CI] 0.59–0.99) [1]. The absolute survival benefit at 12 yr was 5% (76% vs 71%). It is less clear how to select which men with biochemical failure could safely receive SRT alone and be spared the morbidity of additional hormone therapy.

To explore which patients receiving SRT might not benefit from the addition of androgen deprivation therapy (ADT), Fossati et al. [2] analyse data for 1264 patients treated between 1996 and 2012 in this issue of *European Urology*. They studied the association between use of ADT and subsequent clinical recurrence. Cases were classified according to the presence or absence of three adverse risk factors: T stage ≥pT3b, Gleason score ≥8, and prostate-specific antigen (PSA) level at SRT of >0.5 ng/ml. As expected, use of ADT was inversely associated with the risk of clinical recurrence on multivariable analysis (hazard ratio 0.95; $p = 0.022$). However, no such association was seen between use of ADT and clinical recurrence in those patients with none of the three risk factors listed above, suggesting the possibility that men with pT2/3a, Gleason ≤7, and postoperative PSA ≤0.5 ng/ml might be better served by SRT alone.

These findings are unsurprising. In the absence of good evidence to the contrary, it is generally assumed that the relative benefit from an intervention is constant. It follows that the absolute benefit of that intervention will be greater among patients with a worse prognosis. Thus, even if ADT has the same relative benefit for all men undergoing SRT, the absolute benefit will be greater for those men with adverse prognostic features. The absolute benefit of ADT will also be greater for men who, by virtue of their youth and lack of comorbidity, have longer life expectancy.

The question then is who should receive SRT alone and who should receive ADT in addition? On the basis of RTOG 9601, we regard the addition of ADT as standard, but some men, particularly those who are older with relatively favourable disease characteristics in terms of T stage, Gleason score, and postoperative PSA, will very reasonably opt for SRT alone.

A second important question is for how long ADT should be given. Given that RTOG 9601 is the only randomised controlled trial showing a survival benefit in this setting, 2 yr should be regarded as the evidence-based starting point. However, is it possible that a similar benefit could be obtained from a shorter duration? Fossati et al. [2] speculate that <12 mo of ADT may be sufficient for men with only one of the three risk factors (T stage ≥pT3b, Gleason score ≥8, and PSA level at SRT of >0.5 ng/ml).

Two randomised controlled trials have tested 6 mo of ADT using a luteinising hormone–releasing hormone (LHRH) analogue in the SRT setting. Both GETUG-AFU 16 [3] and RTOG 0534 (SPPORT) [4] found that 6 mo of ADT delayed biochemical progression, but until data on longer-term, more meaningful outcomes are available, these findings do little to inform clinical practice. Many trials have compared shorter versus longer durations of ADT in men receiving primary (not salvage) radiotherapy. For example, RTOG 9202 compared 4 mo and 28 mo of ADT in combination with radical radiotherapy in men with prostate adenocarcinoma (cT2c-4 N0 M0) with PSA <150 ng/ml [5]. The longer ADT duration improved overall survival, with

DOI of original article: https://doi.org/10.1016/j.eururo.2019.02.004.
* Corresponding author. Urology Unit, Royal Marsden NHS Foundation Trust, Sutton SM2 5PT, UK. Tel. +44 208 6613425; Fax: +44 208 6613142.
E-mail address: chris.parker@icr.ac.uk (C. Parker).

https://doi.org/10.1016/j.eururo.2019.03.004

a hazard ratio of 0.88 (95% CI 0.79–0.98) and an absolute survival benefit at 15 yr of 3% (30% vs 27%).

How might we attempt to extrapolate these results to the SRT setting? It is striking that men undergoing SRT in RTOG 9601 had a much better prognosis than men undergoing primary radiotherapy in RTOG 9202. The 12-yr risk of death from prostate cancer in RTOG 9601 for men receiving SRT plus 2 yr of bicalutamide was just 6%, compared with a 16% risk at 15 yr among men receiving primary radiotherapy plus 28 mo of ADT in RTOG 9202. Even if the relative benefit of longer ADT duration is generalisable, the absolute benefit in the postoperative setting will be modest. ADT duration is being addressed by the RADICALS-HD trial [6], which randomised 2840 men receiving SRT: 0 mo versus 6 mo versus 24 mo of ADT. Pending the outcome of this trial, our own policy is to administer 6 mo of ADT using an LHRH analogue for most patients, and 24 mo of ADT for younger men with adverse prognostic factors.

While it is good that most men undergoing SRT have an excellent prognosis, it does mean that trials in this setting take a considerable time to complete. While we are still waiting for good-quality evidence regarding the duration of traditional ADT, newer, more effective drugs have been developed. It has been shown that enzalutamide is more active than bicalutamide [7]. The addition of abiraterone to traditional ADT substantially improves biochemical control in men receiving primary radiotherapy for locally advanced disease [8]. It seems likely that these agents would also improve outcomes after SRT, but this hypothesis has yet to be tested in clinical trials.

The development of novel imaging techniques may also have a major impact on the management of men with PSA failure after radical prostatectomy. Until now, SRT, with or without ADT, has been the standard approach. There is growing interest in the possibility of delaying salvage treatment until the site of recurrence is identified on imaging. This has the advantage that the radiotherapy treatment volume can be tailored to the site of recurrence. However, it remains possible that delaying SRT might detract from its efficacy. The impact of positron emission tomography/computed tomography with the ^{68}Ga-labelled ligand PSMA-11 on SRT planning is being assessed in the randomised, prospective, PSMA-SRT phase 3 study [9].

Conflicts of interest: Charles Dearman has nothing to disclose. Chris Parker has received research funding from Bayer and honoraria from AAA, Bayer, Janssen, and Steba.

Acknowledgments: This paper represents independent research part funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at the Royal Marsden NHS Foundation Trust and the Institute of Cancer Research. The views expressed are those of the author(s) and not necessarily those of the NHS or the NIHR.

References

[1] Shipley WU, Seiferheld W, Lukka HR, et al. Radiation with or without antiandrogen therapy in recurrent prostate cancer. N Engl J Med 2017;376:417–28. http://dx.doi.org/10.1056/NEJMoa1607529.

[2] Fossati N, Robesti D, Karnes RJ, et al. Assessing the role and optimal duration of hormonal treatment in association with salvage radiation therapy after radical prostatectomy: results from a multi-institutional study. Eur Urol 2019;76:443–9. http://dx.doi.org/10.1016/j.eururo.2019.02.004.

[3] Carrie C, Hasbini A, de Laroche G, et al. Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial. Lancet Oncol 2016;17:747–56. http://dx.doi.org/10.1016/S1470-2045(16)00111-X.

[4] Pollack A, Karrison TG, Balogh AG, et al. Short term androgen deprivation therapy without or with pelvic lymph node treatment added to prostate bed only salvage radiotherapy: the NRG Oncology/RTOG 0534 SPPORT trial. Int J Radiat Oncol Biol Phys 2018;102:1605. http://dx.doi.org/10.1016/j.ijrobp.2018.08.052.

[5] Lawton CAF, Lin X, Hanks GE, et al. Duration of androgen deprivation in locally advanced prostate cancer: long-term update of NRG Oncology RTOG 9202. Int J Radiat Oncol 2017;98:296–303. http://dx.doi.org/10.1016/j.ijrobp.2017.02.004.

[6] Medical Research Council. Radiation therapy and androgen deprivation therapy in treating patients who have undergone surgery for prostate cancer (RADICALS). https://clinicaltrials.gov/ct2/show/NCT00541047.

[7] Penson DF, Armstrong AJ, Concepcion R, et al. Enzalutamide versus bicalutamide in castration-resistant prostate cancer: the STRIVE trial. J Clin Oncol 2016;34:2098–106. http://dx.doi.org/10.1200/JCO.2015.64.9285.

[8] James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016;387:1163–77. http://dx.doi.org/10.1016/S0140-6736(15)01037-5.

[9] Calais J, Czernin J, Fendler WP, Elashoff D, Nickols NG. Randomized prospective phase III trial of 68Ga-PSMA-11 PET/CT molecular imaging for prostate cancer salvage radiotherapy planning [PSMA-SRT]. BMC Cancer 2019;19:18. http://dx.doi.org/10.1186/s12885-018-5200-1.