INTRODUCTION

Within the last 2 years, two randomized controlled trials by the European Organisation for the Research and Treatment of Cancer (EORTC) -22911 and the Southwest Oncology Group (SWOG)-8794, have reported the effects of adjuvant or early salvage treatment with external beam radiotherapy (RT) after radical prostatectomy (RP) [1,2]. The results of these trials have generated considerable debate [3–5], as although biochemical progression-free survival (bPFS) was clearly improved using additional RT, as yet there is no proof that there is a favourable effect on prostate cancer-specific or overall survival. Nevertheless, the long-term results of these studies might change perceptions of the biology of the persistence and recurrence of prostate cancer after RP. A recent update from the SWOG 8794 trial emphasized that local disease persistence is the predominant pattern of treatment failure [6]. Adjuvant RT appeared not only to reduce the incidence of local recurrence but also approximately halved the proportion of patients developing metastases. The inference is that this ‘second wave’ of metastases resulting from disease persistence can be abolished by RT.

Nevertheless, the clinical balance remains uncertain. On the one hand, adjuvant RT reduces PSA recurrence, which causes anxiety and decreases clinical failure and the use of salvage hormonal treatment. On the other hand, there is the risk of potentially unnecessary treatment of men with pT3 disease with the attendant side-effects of adjuvant RT. About half of such men will not develop disease recurrence and of those who do, many might still die from causes unrelated to prostate cancer.

What is the evidence so far? In the EORTC trial, 1005 men with a mean age of 65 years were recruited between 1992 and 2001, and randomized to receive adjuvant RT after RP, or be managed by an initial policy of observation; 75% of them had positive surgical margins or extraprostatic extension, and 25% seminal vesicle involvement. At the time of randomization, 70% of men after RP had PSA levels of <0.2 and 30% of ≥0.2 ng/mL. The RT dose was 50 Gy delivered to a wide field with a subsequent boost of 10 Gy. The results were reported after a median follow-up of 5.0 years and the primary endpoint was bPFS. There was an advantage to the adjuvant therapy group, with a 5-year estimate of bPFS of 74% vs 53% (hazard ratio 0.48, P < 0.001). Also, there was a reduction in the 5-year estimate of clinical progression, from 19% to 9% (P < 0.001) and a reduction in the 5-year estimate of local failure, from 15% to 5% (P < 0.001). However, there was no difference between the randomized groups in the development of metastases (overall 4%), prostate cancer-related deaths (overall 3%) or overall mortality (9%). There was an increase in treatment-related side-effects, from 10% to 18% (P < 0.001). A multivariate analysis of prognostic factors for bPFS showed that a PSA level of ≥0.2 ng/mL after RP, the initial PSA level (≤10 vs 10–20 vs ≥20 ng/mL), histological tumour grade, seminal vesicle invasion and the absence of positive surgical margins were adverse features. A prognostic model was created and patients divided into low-, intermediate- and high-risk groups. Importantly, the mean (so) risk reduction for PSA failure after adjuvant RT was the same in all three groups, at 54 (8)%. There was possibly a smaller benefit in patients with negative surgical margins but this was not statistically significant [7]. Notably, the review pathology of surgical margin status was a stronger predictor of bPFS than local pathology [8].

By comparison, the SWOG trial was smaller, recruiting 425 men, but also with a mean age of 65 years, and it recruited between 1988 and 1997. The median follow-up from this study was thus longer, at 10.9 years, and the primary endpoint was defined more appropriately as metastasis-free survival (MFS). Similar proportions of patients had extraprostatic extension or positive margins (67%) and seminal vesicle involvement (33%). A similar proportion of patients (66%) had an undetectable PSA level (<0.2 ng/mL), 34% having PSA levels after RP of ≥0.2 ng/mL. Radiotherapy was given to a dose of 60–64 Gy but to the ‘pelvic fossa’ alone. The hazard ratio for MFS was 0.75 in favour of men receiving adjuvant RT (64% vs 57%) but was not statistically significant (P = 0.06). The median time to metastases was 15 years and 13 years in the RT and control groups, respectively. However, the hazard ratio for biochemical recurrence-free survival was 0.43 in favour of RT (65% vs 36%, P < 0.001), the median time to failure being 10 and 3 years, respectively. By 5 years, 21% of the observation group had received salvage hormonal therapy, vs 10% in the RT group (hazard ratio 0.45, P < 0.001). The hazard ratios for bPFS were remarkably similar between the trials (0.43 and 0.48), as were those for clinical recurrence (0.62 and 0.61). The similarity of the trial results so far might suggest that there will be a statistically significant reduction in the development of metastases in the larger EORTC trial with further follow-up. A broadly similar proportion of patients received salvage RT in the observation groups, i.e. 33% and 23% in the SWOG and EORTC trials, respectively.

ADDITIONAL TREATMENT FOR pT3 PROSTATE CANCER: NOW, LATER OR NEVER  
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However, the side-effects after RT approximately doubled in each trial. Table 1 shows the proportion of patients receiving treatment or developing recurrence and complications in the SWOG trial. It can be approximated that two additional courses of RT are required to avoid one PSA failure, four extra courses to avoid one patient receiving hormonal treatment, seven extra to avoid one patient developing metastases, and 12 extra to avoid one death.

The trials have some limitations. Neither has yet shown a significant improvement in the most important endpoints of MFS or overall survival. Both treated a ‘mixed’ population of patients; ∼30% had PSA levels of ≥0.2 ng/mL and therefore were not given true adjuvant therapy. Nevertheless, there was homogeneity for the benefit of RT across groups and the hazard ratio for benefit of 0.53 on PSA control, from the German ARO 96–02 trial, is very similar despite the patients being restricted to men who had strictly undetectable PSA levels after RP [9]. Finally, side-effects were significantly increased in the immediate RT group but the use of modern conformal or intensity-modulated RT would now be expected to moderate toxicity, shifting the balance towards rather than against adjuvant therapy.

Further follow-up from the SWOG study [6] was informative. The pattern of clinical failure was predominantly local rather than distant. This strongly suggests that adjuvant studies using solely systemic treatments are misguided. Recurrence was clearly related to the PSA level after RP, but as in the EORTC trial, there was homogeneity of the benefit of adjuvant RT between the groups. For patients with a PSA level after RP of ≤0.2 ng/mL there were reductions in the 10-year risk of PSA failure of 72% to 42%, local failures of 20% to 7%, and distant failure of 12% to 4%. For men with PSA levels of 0.2–1.0 ng/mL, reductions for PSA failure were 80% to 73%, local failures 25% to 9% and distant failure 16% to 12%. The poorer results could reflect both the increased likelihood of more bulky residual local disease, and the presence of micrometastatic disease in a small proportion of patients. Strategies to improve the results include modification of RT using dose-escalation or pelvic lymph node treatment (but with the attendant risks of increased side-effects) or the use of short course neoadjuvant [10–12] or longer periods of adjuvant androgen suppression [13–15]. A new North American trial (Radiation Therapy Oncology Group, RT0G 0534) in men with PSA levels of 0.2–2.0 ng/mL after RP will compare three groups; treatment with prostate RT alone, or with an additional 5 months of androgen suppression, or similar androgen suppression with pelvic RT. The latter group reflects the improved outcome seen in RT0G 94–13 [16] which added pelvic to prostate RT in men treated by primary RT for a high-risk presentation. The new EORTC trial 22043–30041 aims to recruit 600 men with a PSA level of ≤0.2 ng/mL and tests the addition of 6 months of hormone treatment to RT, again using PSA failure-free survival as the endpoint rather than MFS or overall survival. This strategy fails to take potential advantage of the use of ‘supersensitive’ PSA assays, which now give the possibility of detecting very early PSA recurrence. Could RT given at this point be as effective as the true adjuvant therapy when PSA levels should be undetectable? A recent analysis of a multicentre cohort of 1540 patients treated with salvage RT alone after PSA failure suggests that this might be the case [17]. Of men with a PSA level of ≤0.5 ng/mL after RP but before RT (the lowest level studied), 48% were recurrence-free at 6 years, a similar reduction in the risk of progression as in the EORTC and SWOG trials, but only 26% of men remained recurrence-free if the PSA level before RT was ≥0.5 ng/mL. Using sensitive assays after RP, early PSA recurrence can be identified with PSA levels of ≤0.2 ng/mL. The new Medical Research Council trial ‘RADICALS’ aims to test this hypothesis by comparing such ‘pseudoadjuvant’ treatment with true adjuvant therapy in men with high-risk features after RP, potentially sparing about half of such men from unnecessary treatment. In a second randomization, RT with 6 or 24 months of androgen suppression will be compared with RT alone, either as above immediately after RP, or at the time of the subsequent PSA recurrence in men who have not had initial adjuvant therapy. All of these new trials will use modern conformal RT methods.

We have learnt that RT reduces recurrence after RP in men with pT3 disease, and that local disease persistence is the predominant pattern of failure. Standard care should now include either immediate adjuvant or salvage treatment using conformal RT as soon as PSA recurrence is defined using sensitive assays. The new phase III studies will, in due course, inform on the appropriate timing of intervention and the merits of early hormone treatment.

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### CONFLICT OF INTEREST

None declared.

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LAPAROSCOPIC RADICAL PROSTATECTOMY IN THE UK: DEFINING AND OVERCOMING THE OBSTACLES

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INTRODUCTION

Laparoscopic radical prostatectomy (LRP), when done by experienced surgeons in high-volume centres, offers unique advantages over other surgical approaches, but it is a particularly complex procedure which requires intensive training [1,2]. The development of LRP in the UK has been slower than in most other Western countries, despite considerable enthusiasm for the technique. In this comment we explore the obstacles to its implementation and the solutions to overcome them.

COMMENT

There is little doubt that LRP is among the most challenging procedures in urology. The initial experience in many centres in the UK and abroad involved an operative duration of >8 h. However, in recent years the procedure has become more standardized, improving operative times and allowing for a structured, modular approach to training [2]. In several centres in Europe and North America LRP is performed daily, allowing rapid learning by repetition. From a European perspective it seems obvious that this level of volume and is unlikely to do so unless there are changes related to referral practice, funding and training. From a European perspective it seems obvious that too many British centres are carrying out the procedure. In this comment we explore the obstacles to its development and propose some potential solutions to overcome them.

EXPERTISE

There is little doubt that LRP is among the most challenging procedures in urology. The