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Editorial Comment

Shorter fractionation schedules in breast cancer radiotherapy: Clinical and economic implications

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An accumulating body of level I evidence from randomised trials of adjuvant radiotherapy in early breast cancer supports the safety and efficacy of giving a lower total dose in fewer larger fractions (hypofractionation) than the historical standard of 50 Gy in 25 fractions of 2.0 Gy over 5 weeks.[1–4] The published phase 3 trials relate to patients prescribed whole breast radiotherapy, but the principle is being extended to trials evaluating partial breast irradiation restricted to the tumour bed.[5–11] Interest in hypofractionation is based not only on the practical advantages to patients and health services of fewer hospital visits, but also on two postulated clinical benefits. The first is that breast cancer is more sensitive to fraction size than formerly thought, so that fewer larger fractions maintain current levels of anti-tumour effect without increasing late adverse effects. The second is that shorter overall treatment times (accelerated hypofractionation) may be more effective in patients with rapidly proliferating tumours.

The use of accelerated schedules had been resisted until recently by memory of severe late toxicities after hypofractionated schedules based on misapplication of dose algorithms in the 1960s and 1970s.[12] Since then, approximately 8000 patients have been enrolled in five randomised trials testing hypofractionated radiotherapy to the whole breast, and the clinical outcome of over 7000 of these has been reported in recent years.[1–4] The majority of patients were enrolled in the two UK Standardisation of Breast Radiotherapy (START) Trials of which the 5-year results were published last year: trial A[2] tested two 13-fraction (3.2 Gy to 41.6 Gy or 3.0 Gy to 39 Gy) schedules against 50 Gy in 25 fractions, with each arm delivered over 5 weeks; trial B[1] compared 40 Gy in 15 fractions delivered in 3 weeks with the same control arm as trial A. After 5.1 years of follow up, rates of local-regional tumour relapse at 5 years did not differ significantly in the three arms of trial A. Photographic evaluation and patient self-assessment of late normal tissue effects showed no difference between the control arm and the 41.6 Gy arm, while suggesting significantly lower rates of late toxicity after 39 Gy than after 50 Gy. In trial B, after a median follow up of 6.0 years, the rate of local-regional tumour relapse at 5 years did not differ significantly in the two groups either, being 3.3% (95% CI 2.2–4.5) in the control arm and 2.2% (95% CI 1.3–3.1) in the experimental arm. Photographic evaluation and patient self-assessment suggested lower rates of late normal tissue effects after the 3 week regimen than after the 5 week regimen. The remaining patients were enrolled in two prospective randomised trials, the Royal Marsden NHS

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Foundation Trust/Gloucestershire Oncology Centre (RMH/GOC) trial[3] and the Canadian trial.[4] The former tested two dose levels (39 Gy and 42.9 Gy) of a 13-fraction regimen over 5 weeks against 50 Gy in 25 fractions; the latter tested a 16-fraction regimen over 3.2 weeks against the same control arm. Findings of both trials were consistent with those of the START trials. Therefore, results published to date of randomised trials testing accelerated whole breast radiotherapy in early breast cancer are all concordant in supporting the introduction of 3-week schedules in clinical practice. Furthermore, in a cost-comparative analysis of various radiotherapy treatment courses, performed in the US, the 16-fraction schedule had a total cost of $ 6100, while the 25-fraction regimen had a total cost of $ 8500.[13] Differences in the organisation and funding of health systems between countries make generalisations difficult, but savings in costs of treatment delivery are closely related to fraction number.

Accelerated regimens have found immediate acceptance for partial breast irradiation based on the assumption that a reduction in the treated volume counterbalances unexpected adverse effects of increased fraction size on normal tissue reactions. Since 2000, seven randomised trials testing accelerated partial breast irradiation have been launched, with an overall accrual target of almost 16,000 patients. In all experimental arms, number of fractions and overall treatment time are reduced compared to commonly used breast radiotherapy regimens: two use a single fraction,[5,6] four deliver 10 fractions twice-daily over a period of 5 to 10 days,[7–9,11] and one uses a 3-week schedule.[10] Most of these trials are still recruiting; therefore, a reliable analysis of the outcome of the majority of patients participating in them will not be available for another 5 to 10 years.

While most radiotherapy centres in the UK and Canada have routinely adopted 15 or 16-fraction regimens for postoperative whole breast irradiation in early breast cancer, present and future research is aimed at evaluating safety and efficacy of 5-fraction schedules. Currently in follow up is the UK National Cancer Research Network (NCRN) FAST trial, in which 900 patients were randomised to receive 5 weekly fractions of 5.7 Gy or 6.0 Gy versus 25 daily fractions of 2.0 Gy. Around the same time, a pilot study tested in a group of 30 patients the safety, in terms of acute normal tissue reactions, of another 5-fraction schedule delivering 30 Gy in twice-weekly 6 Gy fractions over a period of 15 days.[14] Results of this study were recently published showing very mild early normal tissue responses and 2-year rates of changes in breast appearance comparable with those reported after 50 Gy in 25 fractions. The consequent logical research objective is testing a 5-fraction schedule delivered in 5 consecutive days. This proposal appears to be feasible especially in an era when routine use of optimisation of dose distribution and cardiac shielding guarantees a very low incidence of normal tissue reactions.

Conflict of interest statement

None declared.

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