Teaching Lecture

E13. Hypofractionated radiotherapy for breast cancer

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Clinical variables that need to be taken into account when using hypofractionation include the total dose to target tissues and organs at risk, fraction size, inter-fraction interval, treatment time, and volume. This presentation discusses how these variables can be exploited to maximise tumour control without exceeding acceptable levels of adverse effects.

Standard adjuvant radiotherapy after breast conservation surgery or mastectomy has long involved once-daily fractions of 1.8–2.0 Gy. The use of fractions <1.8 Gy were never explored in external-beam radiotherapy, although low-dose-rate brachytherapy – which is equivalent to giving smaller fractions – is still used for boosting the tumour bed, an advantage attributed to dosimetry and volume-sparing rather than fractionation. Instead, the focus has been on hypofractionation, defined as fractions >2.0 Gy. This practice emerged from the results of local tumour control data first published in 1952 and re-analysed in 1984 using the new (at that time) linear-quadratic model suggesting α/β values of 4–5 Gy for tumour control. This led to a series of randomised trials, including three UK trials and one Canadian trial, all of which generated results consistent with the hypothesis that breast cancer is, on average, more sensitive to fraction size than is lung cancer, and indeed, many other cancers with the exception, as we now know, of prostate cancer [1–4].

Two of the UK trials had important features that allowed direct estimates of fraction size sensitivity for normal tissue and tumour responses [1,5]. First, the overall duration of treatment (5 weeks) was the same in all arms, thereby avoiding potential confounding effects of tumour repopulation during schedules differing in duration. This explains the selection of a 13-fraction regimen delivered over 5 weeks, allowing two patients to 'share' the same hospital appointment on alternate days. The other feature of the UK trials was the inclusion of two dose levels of the 13-fraction regimens, chosen to reflect the upper and lower dose limits expected to be iso-effective with 50 Gy in 25 fractions in terms of late adverse effects. Assuming α/β values of 4 Gy and 3 Gy, fractions of 3.0 Gy and 3.2 Gy were tested in the START A trial for iso-effect with 50 Gy in 25 fractions. The results suggested an α/β value closer to 3 Gy than to 4 Gy for late adverse effects. The α/β value generated for tumour control had wider confidence intervals due to fewer events, but was comparable to that for late adverse effects.

Fractions of around 3 Gy probably do not represent the limits of hypofractionation, and one UK randomised trial tested a five-fraction regimen delivering once-weekly fractions of >5 Gy, confirming an α/β value of around 3 Gy for late adverse effects [6]. The reduction in the number of fractions raises scope for shortening the treatment time, a matter of convenience to patients even without proven benefit in terms of tumour control, and a 5-day schedule of once-daily fractions is currently under test in a UK phase-III trial.

Although there is no powerful evidence that tumour repopulation is a limiting factor in the adjuvant radiotherapy of breast cancer, current trials of intra-operative and external-beam partial breast radiotherapy test accelerated hypofractionation for logistical rather than biological benefits. Two trials of intra-operative radiotherapy have been performed, and one has reported early results (median 2 years) [7]. In the published study, a single dose of 20 Gy using 50 kV x-rays is delivered to the surface of the tumour excision cavity at the time of lumpectomy, the dose falling to 10 Gy within a few millimetres. In the second phase-III trial, a single fraction of 20 Gy is delivered by intra-operative 8 MeV to the tumour bed, whereas in North America conformal partial breast radiotherapy delivering 38.5 Gy in ten fractions over 5 days is being evaluated in a phase-III trial [8,9]. These schedules remain experimental, but offer clear indications of the direction of current research. They all have in common that high dose intensities are tolerated by partial breast volumes that would exceed tolerance if delivered to the whole breast. For example, accelerated partial breast conformal radiotherapy giving 38.5 Gy in ten fractions over 5 days entails twice-daily fractions of 3.85 Gy separated by 6 hours. An inter-fraction interval of 6 hours is not equivalent to 24 hours in terms of recovery time for repair of sublethal damage. When incomplete repair is taken into account, and assuming an α/β value of 3 Gy for late adverse effects, this schedule gives the equivalent of almost 66 Gy in 2 Gy fractions.

In conclusion, there is level-I evidence based on randomised trials involving >7000 patients that breast cancer is more sensitive to fraction size than previously thought, with a sensitivity comparable to that in late normal tissues. Small fractions therefore spare the cancer

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as much as the normal tissues, opening opportunities for exploiting the convenience, lower cost, and simpler fractionation schedules. If treatment time affects tumour control, there may be added benefits in terms of enhanced tumour control from accelerated schedules of whole or partial breast radiotherapy.

Conflict of interest statement

I have no financial or personal conflicts of interest to declare.

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