Editorial
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Radiotherapy Delivery for Women with Early Breast Cancer

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In a recent editorial, Shahla Massod reviewed the current status of breast cancer among resource-limited countries.[1] One of the highlighted barriers to progress is the frequency of advanced disease stage at presentation, rendering local-regional control more difficult and reducing prospects of cure. As cultural and economic factors improve, a higher proportion of women will present with early stage disease and better prospects of cure after appropriate combinations of surgery, radiotherapy, endocrine, cytotoxic and biological therapies.[2,3] This will present opportunities to offer breast conservation surgery as an alternative to mastectomy to a higher proportion of women.[4] For these women, and many treated by mastectomy, a key requirement for long-term cancer control is the availability of high-quality radiotherapy resources and expertise.[5] The systematic overview of radiotherapy effects in early breast cancer show substantial gains in overall survival as well as local tumor control.[4]

Radiotherapy resources are limiting factors in many countries, including the UK, where adjuvant radiotherapy for early breast cancer accounts for about 30% of radiotherapy resource usage.[6,7] International standard regimens deliver once-daily doses (fractions) of 2.0 Gy for several weeks. For example, a standard regimen for adjuvant radiotherapy to the post-mastectomy chest wall or conserved breast delivers a total dose of 50 Gy in 25 fractions of 2.0 Gy over 5 weeks. The relationship between fraction size and tissue responses is nonlinear, and when fraction size increases, the total dose must be reduced to compensate for increased effect.[8] Attempts in Europe to use fewer larger fractions in the 1970s (a practice called hypofractionation) made inadequate downward adjustments to the total dose, resulting in unacceptable rates of late complications.[9,10] These miscalculations inhibited further research for decades, but renewed interest in fewer fractions delivered over a shorter overall treatment time has been stimulated by randomized clinical trials based on a better understanding of normal tissue and

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tumor responses. Four randomized trials involving a total of >7000 women have tested appropriate downward adjustments in total dose, and all have reported favorable results in terms of local tumor control and late adverse effects.[8, 11-14] Changes in fraction size are modest, involving an increase from 2.0 Gy to 2.67 Gy in two of the trials, but the number of fractions delivered decreases from 25 to 15 (in the UK) or 16 (in Canada). A recent Cochrane review concluded that the use of selective hypofractionation regimens does not affect breast appearance or toxicity, and appears not to affect local cancer relapse.[15] A 15-fraction regimen has since been adopted as the standard of care for adjuvant radiotherapy for all UK women with early breast cancer, in accordance with recommendations by the National Institute of Clinical Excellence.[16] In centers like my own, which previously used 25 fractions, the switch to 15 fractions resulted in a saving of 20% of total radiotherapy fractions, a highly significant benefit for any department. There are obvious benefits for patients too in terms of time away from home or work.

On the basis of these trials, there appears to be no reason to avoid 15- or 16-fraction regimens, but there are some residual uncertainties.[17] Concern that trial follow-up is too short seems unnecessary, given that one of the hypofractionation trials published at a median follow-up of 9.7 years and another published updated 10-year results.[8, 12, 18] Concerns about the sensitivity of the heart to larger fractions have been expressed, but the heart is easily damaged by radiotherapy, and needs to be protected as much as possible whatever schedule is used.[19]

All fractionation trials so far have been conducted in the adjuvant setting after primary surgery for stage 1 - 3 disease. Hypofractionation has not been tested in patients with inoperable local disease, where radiotherapy dose intensity is higher. When a large primary tumor must be left in situ, an additional 'boost' dose to the site of primary disease in the breast is given after whole breast radiotherapy. Following 15 fractions of 2.67 Gy to the whole breast, a boost dose to the vicinity of the primary tumor that delivers 5 fractions of 2.67 Gy is equivalent in terms of late adverse effects to approximately 16 Gy in 2.0-Gy fractions (or 60 Gy in 30 fractions, including the whole breast dose). This schedule of 20 fractions is delivered in 4 weeks rather than the conventional 6 weeks. The main limitation of hypofractionation for countries where lymphatic radiotherapy is frequently needed is that dose escalation using this approach is potentially unsafe for the brachial plexus. High-dose regimens to the axilla, supraclavicular fossa, or both are best delivered using 2.0 Gy fractions, although in my center, 40 Gy in 15 fractions is prescribed when adjuvant supraclavicular fossa irradiation is indicated in the case of heavy node involvement as determined by axillary dissection.

Radiotherapy, whether delivered with hypofractionation or with fractions of 2.0 Gy, must be carefully planned and accurately delivered. There are elementary rules, familiar to specialists in the field, that include the necessity of a stable position for the patient that is reproduced accurately at every stage during treatment planning and daily delivery.[20,21] Planning increasingly takes advantage of X-ray computed tomography (CT) to generate 3D images of the patient's thorax that provide the anatomical and X-ray absorption data needed to generate 2D or 3D dose distributions.[22] Stability of the patient's position is especially important to avoid overlaps at field junctions between the breast and axilla, or supraclavicular fossa beams that can cause complications which include brachial plexus nerve injury. Although 3D dosimetry has proven benefits compared to traditional 2D approaches, the accuracy of patient positioning and radiotherapy beam localization is a higher priority.[23] Accuracy depends primarily on the expertise of the staff with day-to-day responsibilities for treatment planning and delivery, but is helped by X-ray imaging technologies incorporated into linear accelerator design that allow daily verification of radiotherapy beam localization.[24] In women treated after mastectomy, the ribs and lungs serve as reliable reference points for checking beam accuracy, but after breast

conservation surgery, titanium ligaclips fastened to the wall of the excision cavity during surgery and imaged while the woman lies on the linear accelerator greatly help the accuracy of treatment.[25]

Improved treatment accuracy is also of great relevance to the breast cancer community in evaluating partial breast radiotherapy in women at very low (0.5%) annual risk of local tumor relapse after breast conservation surgery and radiotherapy.[26] In the UK, the population recruited into a randomized clinical trial includes women >50 years of age with invasive ductal carcinomas <3.0 cm diameter excised with a minimum of 3 mm margins on pathological examination and affecting no more than 3 axillary lymph nodes. Eligibility criteria vary in randomized trials conducted in different countries, and very different approaches to radiotherapy delivery are being adopted, including intraoperative radiotherapy and external beam conformal radiotherapy. Outcome data are starting to emerge, but it is too early to recommend partial breast radiotherapy outside the context of a well-designed research protocol. Despite the scarcity of mature level I evidence based on randomized clinical trials, women are being offered intra-operative or post-operative partial breast radiotherapy out of protocol, partly in response to pressure from both patients and commercial entities.[27,28]

In conclusion, there is a need to strike a balance between the expertise and resources needed for the safe delivery of sophisticated radiotherapy techniques and the added benefits they achieve for patients.[29] In the UK, hypofractionation has been useful in releasing limited resources to improve the accuracy of treatment delivery and verification. It is not suited to all tumor types, but where radiotherapy to the conserved breast or to the post-mastectomy chest wall features significantly in departmental workload statistics, it is something to consider.

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