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EDITORIAL

Extreme hypofractionation in radiation therapy for patients with early breast cancer: what is the optimal technique?

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Adjuvant external beam radiation therapy following breast-conserving surgery is an integral component of treatment for patients diagnosed with early breast cancer. For many years, the established international standard has been the delivery of 25 daily fractions of 2 Gy encompassing the entire breast over 5 weeks. However, there is now established mature evidence in the form of 5 randomised clinical trials and a meta-analysis[1–6] for moderately hypofractionated radiation therapy of 15 to 16 fractions of 2.6 Gy. These have all demonstrated non-inferior outcomes comparing the 3-week regimen to the traditional 5–6-week regimen in terms of safety and efficacy.

Further to this, there is now emerging evidence supporting the use of an even more hypofractionated schedule of 5 fractions delivered over 1 week as shown by the FAST-Forward trial.[7] This three-arm trial, however, has highlighted the need for careful and meticulous attention to the dosimetry in the radiation treatment plans as the 27 Gy in 5 fraction arm resulted in higher normal tissue effects compared with the 26 Gy in 5 fraction and 40 Gy in 15 fraction arms. At 5 years, the incidence of moderate or marked clinician-assessed normal tissue effects in the breast or chest wall was 9.9% for the 40 Gy arm, 15.4% for the 27 Gy arm and 11.9% for the 26 Gy arm with a significant difference between 40 Gy and 27 Gy ($P = 0.0003$) but not between 40 Gy and 26 Gy ($P = 0.17$). This difference was also corroborated by the patient-reported outcomes and photographic assessment substudies. This means that a difference in an additional 0.2 Gy per fraction per day will result in a significantly higher rate of late normal tissue effects, most notably breast shrinkage, induration and oedema.

In the article accompanying this editorial, Piras et al,[8] retrospectively compared the dosimetry of 21 patients with left-sided early breast cancer who underwent adjuvant external beam radiotherapy after breast-conserving surgery. Three-dimensional conformal radiation therapy (3D-CRT) tangents were compared to volumetric modulated arc therapy (VMAT) technique. The FAST-Forward trial dose fractionation of 26 Gy in 5 daily fractions was employed. Pre-determined dosimetric parameters were analysed including:

a. homogeneity index (HI) and global conformity index (GCI);
b. planning target volume (PTV) coverage – V95%, V105%, V107% and Dmax;
c. dose constraints for organs at risk (OAR) – ipsilateral lung using V30%, heart using V5% and V25% and skin using V103%.

The authors found that the VMAT technique resulted in a better GCI but with a higher heart dose (V5%). In terms of PTV coverage, the VMAT technique resulted in a comparatively lower mean values of both V95% (95.4% vs. 97.2%, $P = 0.03$) and V105% (0.65% vs. 5%, $P < 0.05$). On the contrary, they found that the 3D-CRT tangential technique delivered a higher ipsilateral lung dose (V30%) and skin dose (V103%).

Multiple prior planning dosimetric studies[9-11] have compared various techniques of breast radiotherapy using either conventional dose fractionation of 50 Gy in 25 fractions or 40 Gy in 15 fractions. The significant majority of these studies have demonstrated that the VMAT technique yields better PTV homogeneity and target volume coverage at the cost of higher doses to the ipsilateral and contralateral lung, heart, contralateral

breast and spinal cord. It also delivers higher monitor units (MUs) with a corresponding longer treatment time. It is therefore highly improbable that these results will change with more hypofractionated dose schedules.

A proven alternative method of achieving extreme hypofractionation (treatment duration of 1 week or less) while respecting the surrounding organs at risk is with brachytherapy. This is most frequently delivered in the setting of partial breast irradiation (PBI). There are nine randomised controlled clinical trials investigating PBI using various techniques including 3D-CRT, intraoperative and intracavitary brachytherapy options.[12-20] Unfortunately, due to the heterogeneity in patient selection, target volume delineation and dose fractionation, the results of these trials are inconsistent and highly variable. Despite this, the *only* technique that has the recommendation of all professional radiation oncology societies of ASTRO, ABS and GEC-ESTRO to deliver PBI outside the confines of a clinical trial is multi-catheter interstitial brachytherapy (MCIB). The reasons for this are:

1 it has the most robust and mature data set available;
2 it allows for a complete histopathological examination of the resected specimen with particular attention to the surgical margins;
3 it has the greatest flexibility to conform dose distribution around the target volume.There are now three randomised controlled trials demonstrating the safety and efficacy of MCIB compared to whole breast radiotherapy for PBI in patients diagnosed with node-negative, hormone receptor-positive, unicentric invasive breast carcinomas.[16-18]

These three studies, using 7 to 10 bi-daily fractions of radiation form the backbone for trials investigating more extreme forms of hypofractionation. An example of this is the Triumph-T trial[21] which delivered 3 fractions of 7.5 Gy over 2 days to 175 patients. Early toxicity data are promising but clearly longer follow-up is required with the current report having a median follow-up of up to 3.63 years.

In a similar vein to this study, investigators at St. George Hospital, Australia have launched the HEARTBEAT study (ANZ Clinical Trials Registry No. 12621001410842) aiming to deliver the same dose fractionation as the Triumph-T trial. The study's primary outcomes are firstly to assess technical compliance with planning dosimetric parameters and secondly to compare the 5-year ipsilateral breast tumour recurrence rates to that of the GEC-ESTRO trial's rate of 1.44%.

Compared with VMAT technique, MCIB has been shown to deliver significantly less radiation doses to the contralateral breast, ipsilateral and contralateral lung, heart and ribs at least in the breast tumour bed boost setting.[22] The investigators of the HEARTBEAT study have therefore chosen MCIB as the treatment technique of choice to investigate extreme hypofractionation. Recognising the importance of meticulous attention to optimal dose distribution, it therefore aims to achieve these strict dosimetric specifications:

- 90% of prescribed dose covering ≥90% of PTV;
- maximum skin dose of <100% of the prescribed dose;
- volume of breast tissue receiving 150% prescribed dose (V_{150}) ≤40 cc;
- volume of breast tissue receiving 200% prescribed dose (V_{200}) ≤15 cc;
- dose homogeneity index (DHI) defined by [volume covered by 100% isodose line – volume covered by 150% isodose line]/volume covered by 100% isodose line ≥0.75;
- conformity index (COIN) defined by volume covered by 100% isodose line/CTV ≥0.6.

The study workflow involves identification of eligible patients in the breast multi-disciplinary team meeting, initial consultation with a study investigator, followed by a technical eligibility ultrasound scan (USS) and computed tomography (CT) scan. The seroma cavity needs to be identified on USS as this is the primary imaging modality guiding catheter implantation. At the time of this appointment, other details of the implantation such as the template size, technique and radiation margins required are also determined. The actual implantation would then occur 2–4 weeks later.

At the time of implantation, the seroma cavity is again visualised and ~3–5 mLs of iodinated contrast is instilled into the cavity. A Breast CT/MR Template set is then applied on the breast, dependent on the depth of the cavity in relation to the surface of the breast. It is then securely fixed in situ with its corresponding bridge. From here, needles are then inserted through the breast starting from the deepest plane to the most superficial plane, with the template to ensure parallelity and adequate spacing. Approximately 15–30 needles will be employed such that the entire tumour bed surrounding the seroma cavity is satisfactorily covered. These needles will then be substituted by flexible, hollow 6F OncoSmart (COMFORT™) Catheters.

Upon recovery, the patient is transferred to the CT simulation suite whereby CT-compatible wires are inserted into the OncoSmart Catheters and 2-mm axial images are acquired of the breast. The images are transferred to a 3-D planning software (Oncentra Brachy), which is used to identify and reconstruct the catheters.

The contrast-enhanced surgical cavity is outlined, and a PTV is generated. This is performed by expanding the

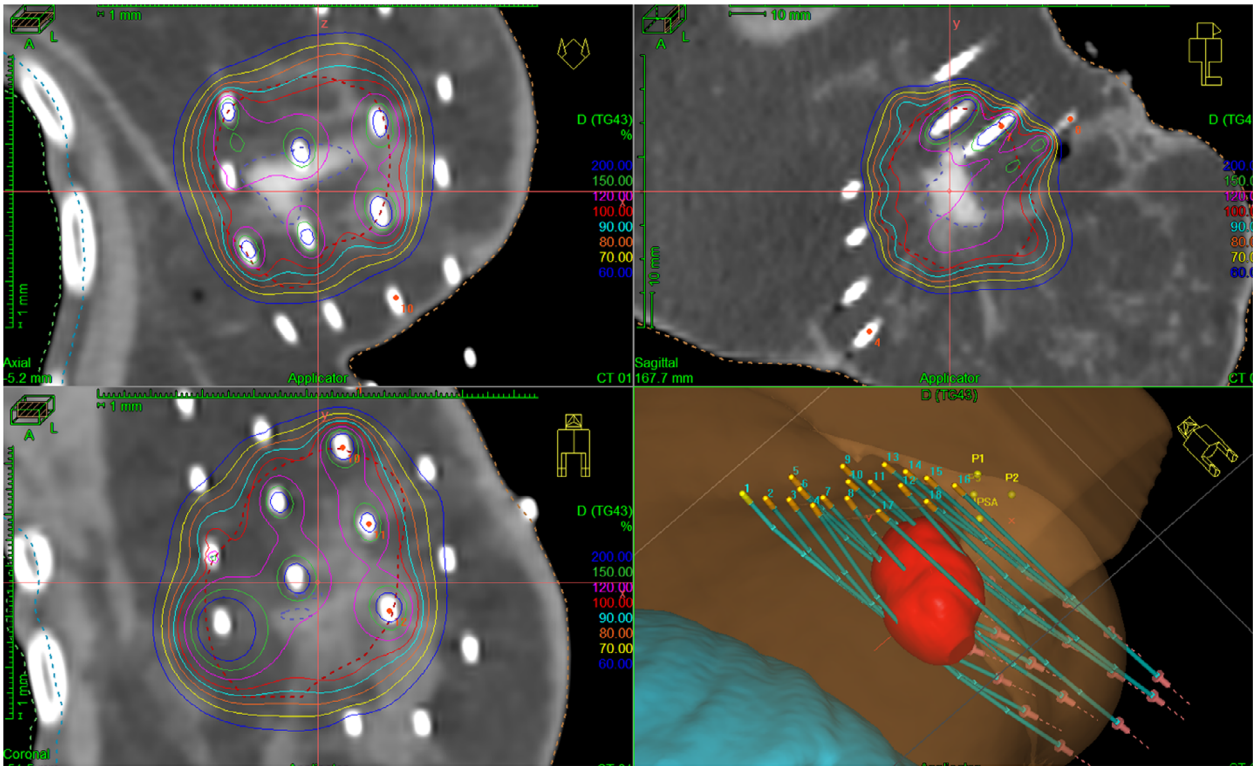

Figure 1. Reconstructed catheters going through seroma cavity/PTV (dotted red line), with optimisation of dose distribution.

margins of the cavity in all six directions (anterior, posterior, superior, inferior, medial and lateral), such that the combined resected and PTV margins equate to 2 cm. A minimum 5-mm margin expansion for the PTV is mandated even if the resected histopathological margin is ≥15 mm.

Treatment planning is performed with the aim of encompassing the PTV within the 90% isodose line (Fig. 1). Optimisation of dwell weights to achieve the desired dose distribution is performed using a combination of inverse planning, graphical and manual optimisation. The prescribed reference dose is 22.5 Gy in 3 fractions (7.5 Gy per fraction). The first fraction of treatment is delivered on day 1 and the second and third fractions delivered on the subsequent day (day 2), with an inter-fraction interval of at least 6 hours.

After the final fraction, all catheters will be removed from breast tissue by severing the ends of the catheters individually. Manual pressure will then be applied to the catheter entry and exit wounds to achieve haemostasis and the patient will undergo regular follow-up for a total of 10 years.

It is hoped that this study will revive interest in the clinical use of MCIB in Australia and New Zealand, as a safe, effective and convenient alternative of delivering adjuvant radiotherapy in the setting of early, node-negative, hormone receptor-positive breast cancer.

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