Partial breast irradiation: new standard for selected patients

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Routine whole-breast radiotherapy comprises 50 Gy in daily fractions for 5 weeks.[1] The additional application of an external boost of 10–16 Gy to the tumour bed leads to excellent local tumour control, with local recurrence rates around 6% after a median of 10-years' follow-up.[2] However, in view of the low and focal local recurrence rates, the concept of accelerated partial-breast irradiation has gained widespread interest with various methods.

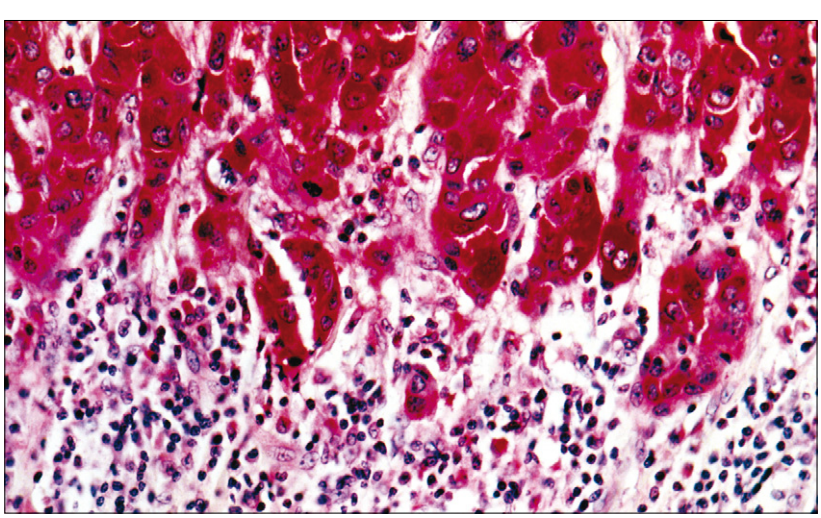
Intraoperative radiotherapy is one method that might offer the advantage of excellent delineation of the tumour bed under visual control, very good dose-homogeneity, and high sparing of normal tissue.[3,4] These advantages were one of the goals of the TARGIT-A randomised phase 3 trial presented in *The Lancet* today.[5] The investigators compared targeted with whole-breast radiotherapy in women with invasive ductal carcinoma who were undergoing breast-conserving surgery. Non-inferiority was shown in the targeted group with less grade 3 acute toxicity but with more wound seroma than in the whole-breast irradiated group. This trial presents major new data for the next decades. There is no doubt that many national health systems will encourage rapid and less expensive adjuvant breast treatments. Such targeted radiotherapy might be such a method, delivering a sufficient dose within the tumour bed and protecting surrounding normal tissues with the unique advantage of a "one-shot" procedure that includes surgery and radiotherapy at the same time.

Nevertheless, this technique has been criticised since it was first developed. The technical limitation is depth of dose due to the 50 kV x-ray delivery. For instance, a dose of 15 Gy prescribed at 2 mm with a typical applicator of 3·5 cm diameter will deliver 10·6 Gy at a depth of 5 mm. The risk is that insufficient breast volume is irradiated and therefore more local recurrences could occur. Clearly, today's TARGIT-A trial contradicts this hypothesis. Additionally, targeted radiotherapy might resolve the problem of cardiac and lung irradiation and the risk of late sequelae.

The oncological keypoint is the selection of the population who will best benefit from this technique. This question does not only apply to the targeted technique but also to all use of accelerated partial-breast irradiation. The ASTRO task force[6] has proposed suitable patients for accelerated partial-breast irradiation if several criteria are present, especially age 60 years or older, tumour size 2 cm or less, and invasive ductal carcinoma that is T1N0 and oestrogen-receptor positive. By contrast, TARGIT-A accepted women with early breast cancer if they were aged 45 years or older and had undergone wide local-excision for invasive ductal carcinoma. Nevertheless, when looking at the characteristics of the tumour and patient in TARGIT-A, the median age was 63 years (IQR 57–69), 86% of the tumours were smaller than 2 cm, nearly 90% expressed oestrogen receptors, and 83% of the nodes were uninvolved. Overall, this profile fits well with the international recommendation.

Additionally, it has been suggested that tamoxifen alone will be sufficient for patients aged 70 years or older.[7] Local or regional recurrences at 5 years were significantly higher in the tamoxifen group than in the tamoxifen plus radiotherapy group. Accelerated partial-breast irradiation is therefore a better alternative than no irradiation at all, and should be widely proposed to these patients. Similarly, the technique could be proposed when: the tumour is less than 1 cm, as suggested by the results of the randomised trial published many years ago by Fisher and colleagues;[8] in patients with oligometastases who have an encouraging response to first-line chemotherapy;[9] or in patients who are hypersensitive to radiation and who present with small tumours.[10]

Frozen-section analysis is clearly one of the limiting aspects of the targeted technique, because the definitive



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Light micrograph of section through ductal cancer cells in female breast

pathology findings might contradict those obtained intraoperatively. This technique thus requires a very close partnership between surgeons, pathologists, radiation oncologists, and physicists. Indeed, in TARGIT-A, 14% of patients received targeted intraoperative radiotherapy plus external-beam radiotherapy. Mixed-modality 3D-conformal accelerated partial-breast irradiation with opposed mini-tangent photon fields and en-face electrons is a promising alternative.[11]

We still await long-term follow-up and the results of another randomised trial from the National Surgical Adjuvant Breast and Bowel Project B-39.[12] Nevertheless, in elderly patients, we are already convinced that accelerated partial-breast irradiation is the new standard and intraoperative radiotherapy an excellent approach.

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Preventing type 2 diabetes with low-dose combinations

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The past decade has seen major advances in clinical trial evidence to support improved care in diabetes. One important area is prevention of type 2 diabetes. Several trials have tested single interventions for their ability to reduce the incidence of diabetes in high-risk individuals.[1–6] Lifestyle interventions aimed at reducing bodyweight, and use of metformin, thiazolidinediones, acarbose, and orlistat, reduce the risk of diabetes by 25–60% over 3–6 years. Generallly, interventions aimed at reducing body fat or its adverse metabolic effects show the best evidence for slowing or stopping progression to diabetes.[7] Indeed, the insulin secretagogue, nateglinide, had no effect in reducing diabetes risk.[8] Despite the positive outcomes of these trials, it remains unclear whether prevention is superior to early treatment in terms of long-term health. Additionally, concerns about cost and side-effects have limited recommendations for use of drugs to prevent type 2 diabetes.

In *The Lancet* today, Bernard Zinman and colleagues[9] report the CANOE trial, the first to test low-dose combination drug therapy for diabetes prevention. During a median follow-up of 3·9 years, metformin and rosiglitazone at about half-maximum doses caused a 66% reduction in the risk of diabetes compared with placebo. Importantly, the treated group had no increase in weight gain, heart failure, fractures, or myocardial infarction. Diarrhoea was infrequent, but occurred more often in the treated group. Circulating concentrations of LDL cholesterol, C-reactive protein, and serum alanine aminotransferase fell more, while HDL cholesterol rose more, in the treated group. The investigators concluded that combination treatment with low-dose metformin and rosiglitazone could