

Clinical theme: General medicine

Methodological theme: Therapeutics

Author's declarative title: The IMPORT-LOW trial re-confirms the validity of targeted radiation for breast cancer but still requires daily travel for 3-weeks.

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Commentary

Context

The evidence-based local treatment for early breast cancer is breast conserving surgery and radiotherapy, requiring 3-6 weeks of daily whole breast external beam radiation (EBRT), which is inconvenient for patients and expensive.

The suggestion that targeted radiation to the tumour bed with modern techniques may be adequate was proposed in 1995¹. This was heralded as a new standard² with the publication of the TARGIT-A trial^{3,4} of single-dose targeted intraoperative radiotherapy (TARGIT-IORT), later confirmed by other European studies using brachytherapy⁵ that requires 5 days of inpatient stay, or EBRT⁶.

Methods

In 30 UK centres, from 2007-2010, women aged ≥ 50 years, who had undergone breast-conserving surgery for unifocal invasive ductal carcinoma ≤ 3 cm in size with a 2mm non-cancerous excision margin, were randomly assigned (1:1:1) to receive daily over 3 weeks one of three regimens: 1) 40 Gy whole-breast irradiation (WBI); 2) 36 Gy WBI with 40 Gy partial breast irradiation (PBI); or 3) 40 Gy PBI targeted to the tumour bed. The primary endpoint was ipsilateral local relapse with a non-inferiority margin of 2.5% at 5 years. For quality of life, 72 different patient-reported outcomes (PROMS) were analysed and radiotherapy toxicity was assessed by photographs and clinicians. Neither patients, clinicians nor data-analysts were masked to treatment allocation.

Findings

Five-year estimated incidence of local relapse was 1.1% (95% CI 0.5–2.3) with WBI (n=674), and 0.5% (0.2–1.4) with PBI (n=669); non-inferiority was confirmed.

Unlike in prior trials³⁻⁶, radiotherapy toxicity was not reduced. Of the 72 PROMS assessed, only two (breast appearance and texture) were reported to have better cumulative scores with PBI. The incidence of only one PROM ('breast appearance changed') was reduced at 5 years (from 27% to 15%).

Commentary

IMPORT-LOW provides further mature randomised evidence supporting PBI. However, PBI with IMPORT-LOW protocol offers little advantage to patients or the healthcare system. The 2mm clear margins this protocol requires, renders many patients ineligible; acceptable margins are currently much smaller, e.g., >0 mm in USA⁷. The authors emphasise the benefit in two quality of life domains, although 72 were tested, with 5-year benefit seen in only one.

Clearly, IMPORT-LOW patients had considerably better-prognosis cancers than in other trials that have proven non-inferiority of targeted radiation to whole breast radiation. Compared with TARGIT-A, only 3% vs. 16% were node positive, and 9% vs. 15% were grade 3. Therefore, the low

recurrence rate is not surprising.

Who benefits from the IMPORT-LOW protocol? For the patients and healthcare systems, its 3-weeks' daily radiation which has adverse physical, social, financial⁸, and environmental impacts⁹ offers no advantage over conventional radiation. PBI using IMPORT-LOW is also resource-consuming (and therefore expensive), and keeps radiotherapy departments very busy. Conversely, TARGIT-IORT delivered during the operation enables over 80% of patients to avoid visiting the radiotherapy centre at all. The relevance here is that although published twice in *The Lancet*, with an independent editorial concluding that it should be offered as an alternative to conventional EBRT, TARGIT-IORT is not even mentioned in the IMPORT-LOW paper. We find this surprising since the number of patients with a median follow up of 5-6 years is similar (~1200 vs 1300), and both proved non-inferiority.

Implications for practice

Targeted radiation methods range from the 3-week daily course required for IMPORT-LOW with 16 hospital visits, to single-dose TARGIT-IORT given during lumpectomy. Several other approaches are also available^{5 6}, and as all are effective, patients are entitled to choose what is right for them, based on convenience, personal cost, quality of life, and side-effects.

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