Intraoperative radiotherapy for breast cancer

Intraoperative radiotherapy was developed to optimise local outcomes of radiotherapy because it offers excellent delineation of the tumour bed under visual control, very good dose homogeneity, and spares normal tissue. The technique was applied to many tumour sites with controversial results, and initial reports by French and US teams showed that intraoperative radiotherapy for breast cancer led to increased rates of local recurrence compared with whole-breast irradiation of 50 Gy given in daily fractions over 5 weeks plus an external boost of 10–16 Gy to the tumour bed, which offers excellent local tumour control, with local recurrence of about 6% after 10-year median follow-up. Despite increased risk of local recurrence, intraoperative radiotherapy remains an attractive option for some patients because it removes the need to attend a radiotherapy centre for 25–33 fractions for whole-breast irradiation.

In The Lancet, Jayant Vaidya and colleagues present results of the TARGIT-A trial, while in The Lancet Oncology, Umberto Veronesi and colleagues present results of the ELIOT trial. Each trial compared a different type of intraoperative radiotherapy with external whole-breast irradiation. Both groups of authors should be commended for their work in this very challenging area.

The TARGIT-A findings add to the first report. This non-inferiority study compared one intraoperative dose of 20 Gy using a spherical applicator (point source of 50 kV energy x-rays) with whole-breast irradiation using tangential fields without node irradiation. The predefined non-inferiority margin was an absolute difference of 2.5% in local recurrence in the conserved breast between groups. Initially, intraoperative radiotherapy was delivered concurrently with lumpectomy (prepathology stratum, n=2298), but some centres delivered intraoperative radiotherapy as a second procedure after definitive tumour pathology reports, to improve selection of patients and allow enrolment of patients after lumpectomy (postpathology stratum, n=1153). Overall, the 5-year risks for local recurrence in the conserved breast for intraoperative radiotherapy versus whole-breast irradiation were 2.1% (95% CI 1.1–4.2) with intraoperative radiotherapy and 1.1% (0.5–2.5) with whole-breast irradiation (p=0.31). This particularly important finding confirms the need for concomitant delivery of intraoperative radiotherapy and lumpectomy.

By contrast, ELIOT did not allow a postpathology procedure. The authors randomised 1305 patients after quadrantectomy to receive either whole-breast irradiation (50 Gy in 25 fractions followed by a boost of 10 Gy in five fractions using an external electron beam without node irradiation) or intraoperative radiotherapy with electrons (21 Gy in one fraction to the tumour bed using electrons of 6–9 MeV, prescribed to the 90% isodose). Local recurrence of less than 7.5% in the intraoperative radiotherapy group was deemed to show equivalent efficacy compared with whole-breast irradiation; the primary outcome was occurrence of ipsilateral breast tumour recurrence (IBTR). After median follow-up of 5.8 years, the 5-year event rate for IBTR was 4.4% (95% CI 2.7–6.1) with intraoperative radiotherapy and 0.4% (0.0–1.0) with whole-breast irradiation. Thus, the rate of local recurrence with intraoperative radiotherapy was within the prespecified equivalence margin, but was significantly worse than that for whole-breast irradiation. Perhaps the most important information gained from these results regards the site of IBTR: the authors distinguished true local relapses from new ipsilateral breast tumours outside the index quadrant. Occurrence of true local...
relapses (p=0.0003), local relapses outside the index quadrant (p=0.0001), and axillary or regional lymph node metastases (p=0.03) were significantly increased with intraoperative radiotherapy.

Of 35 local recurrences in the intraoperative radiotherapy group of ELIOT, 14 (40%) occurred outside the index quadrant and 21 (60%) were true local recurrences. In the prepathology stratum of the TARGIT-A trial, the crude number of local recurrences was ten of 2234 patients. However, when examining tumour characteristics in TARGIT-A versus ELIOT, 12% versus 14% were 2 cm or bigger, 17% versus 26% were node positive, and 15% versus 20% were grade 3, making comparisons difficult. In a multivariable analysis of the ELIOT results, tumour size, the presence of four or more positive nodes, a poorly differentiated tumour, and triple-negative subtype were associated with increased likelihood of IBRT. These data are in accordance with the patient selection criteria in our phase 2 trial. The American Society for Radiation Oncology (ASTRO) task force recommendations also confirmed that the most relevant inclusion criteria for accelerated partial-breast irradiation were: age 60 years or older, tumour size 2 cm or less, and invasive ductal carcinoma that is T1N0 and oestrogen-receptor positive. Selection of patients might affect the final margin status. An absence of information about margins at the time of irradiation is a frequent criticism of intraoperative radiotherapy and, unfortunately, these margins were not described in either study.

The main difficulty encountered in comparing the ELIOT and TARGIT-A results is the difference between both conventional whole-breast irradiation groups. In ELIOT, whole-breast irradiation included a systematic 10 Gy electron boost, whereas no information was available from TARGIT-A concerning the number of patients who received a boost after whole-breast irradiation. In ELIOT, only four (0-6%) of 654 patients in the whole-breast irradiation group had a local recurrence, which is excellent in comparison with the group given a 16 Gy boost in the EORTC boost trial (4-0% [95% CI 3-3–4-6] in T1 and 4-5% [3-9–5-2] in T2 tumours).

After intraoperative radiotherapy, discovery of definitive adverse histological features theoretically requires additional postoperative external irradiation. That was the case for 22% (219 of 1012) of patients in the prepathology stratum of TARGIT-A and for 5% (31 of 647) of patients in ELIOT. Interpretation of the effect of additional whole-breast irradiation is difficult because the ELIOT protocol specified additional irradiation only for patients with four or more positive axillary nodes. Surprisingly, additional irradiation was only delivered to the affected breast in both studies, whereas in clinical practice, the breast and supraclavicular and internal mammary chain nodes are normally irradiated. This decision might partly explain the poor effect of additional irradiation on breast-cancer mortality in TARGIT-A (8% when intraoperative radiotherapy was followed by whole-breast irradiation vs 1-8% with intraoperative radiotherapy alone in low-risk patients). In September, 2013, Poortmans and colleagues presented results of EORTC trial 22922-10925, which investigated the contribution of radiotherapy to the internal mammary and medial supraclavicular lymph nodes (IM-MS) in terms of overall survival, disease-free survival, and metastasis-free survival. 4004 patients were randomised to whole-breast and IM-MS radiotherapy or whole-breast radiotherapy alone. IM-MS radiotherapy improved outcomes at 10 years: overall survival 82-3% versus 80-7% (HR 0-87), disease-free survival 72-1% versus 69-1% (HR 0-89), and metastasis-free survival 78% versus 75% (HR 0-86). The treatment effect on overall survival was independent from the number of involved lymph nodes.

Other notable points are that nearly 75% of patients received adjuvant hormone therapy alone in ELIOT (72% in TARGIT-A), which might be insufficient since adjuvant chemotherapy is deemed necessary for many patients presenting with hormone-receptor positive tumours. Also, in ELIOT, the presence of more than 1% of immunoreactive cells was defined as hormone-receptor positivity. Had a higher threshold been specified as in many other trials, a non-negligible number of patients would have been defined as hormone-receptor negative and thus been given adjuvant chemotherapy, potentially leading to improved breast-cancer mortality. Importantly, the median follow-up durations of 2 years and 5 months for TARGIT-A and of 5-8 years for ELIOT are too short to draw definitive conclusions about the risk of breast-cancer death, particularly in patients selected outside the ASTRO recommendations.

One argument might be that in the low-risk populations included in ELIOT and TARGIT-A, adjuvant radiotherapy is unnecessary because no beneficial effect on breast-cancer-related mortality has been shown.
However, we do not support omission of radiotherapy after lumpectomy in view of the increased rate of IBTR over time in the absence of radiotherapy, and the life expectancy of patients diagnosed after 65 years, who are likely to live long enough to experience recurrence and metastatic disease. Intraoperative radiotherapy has few side-effects and thus might be an attractive option for some low-risk patients.

One way to improve the acceptability of external radiotherapy might be to reduce either the number of fractions or the irradiated volume, with or without shortening overall treatment time. Studies with at least 10 years of median follow-up have confirmed that hypofractionation in radiotherapy for breast cancer is safe and effective. These approaches are increasingly being used in clinical practice, but only for patients who are not suitable for protracted radiotherapy or intraoperative radiotherapy. Indeed, it is most often proposed to patients aged between 55 and 65 years presenting with tumours of less than 2 cm and node negative disease. Hypofractionated radiotherapy is convenient for patients and has reduced waiting lists in many centres.

The new data from TARGIT-A and ELIOT reinforce our conviction that intraoperative radiotherapy during breast-conserving surgery is a reliable alternative to conventional postoperative fractionated irradiation, but only in a carefully selected population at low risk of local recurrence.

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We declare that we have no conflicts of interest.