The Editor,
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Sir,

ELIOT is very different from TARGIT-IORT

Describing the long-term outcomes of the ELIOT trial[1], the authors point out "the possible local side-effects of the [ELIOT] technique (immediate fat necrosis, skin flap-temporary suffering, or late parenchymal fibrosis)", which is an important detail.

Electron intraoperative radiotherapy (also known as ELIOT) requires extensive dissection of the breast gland from the chest wall muscles and overlying breast skin. The tumour bed walls are then apposed with a metal shield placed behind the gland, and radiotherapy is delivered via a large (4–12 cm diameter) acrylic cylinder placed over the gland surface. This extensive dissection is likely to create substantial hypoxia of the target tissue that is farthest from the vascular blood supply, leading to the observed fat necrosis, skin flap damage, and fibrosis, particularly with high-dose rate of electron intraoperative radiotherapy. Crucially, hypoxia greatly reduces sensitivity to radiotherapy,[2] which might also explain the higher local relapse rate with electron intraoperative radiotherapy than with whole-breast irradiation.

There were fewer deaths from non-breast cancer causes with electron intraoperative radiotherapy than with whole-breast radiotherapy (20 *vs* 30, hazard ratio [HR] 0·68 (95% CI 0·39–1·19); p=0·17), potentially due to avoidance of the inevitable scatter to nearby vital organs that happens with whole-breast radiotherapy. However, the higher mortality "from breast cancer" or not "from other causes"[1]in the electron intraoperative radiotherapy group (78 deaths) than in the whole-breast irradiation group (65 deaths) appears to reduce the benefit of electron intraoperative radiotherapy.

Electron intraoperative radiotherapy should not be confused with targeted intraoperative radiotherapy, which employs a very different surgical and radiotherapeutic technique (although the patient cohorts in the ELIOT trial[1] and in the TARGIT-A trial[3] were similar).[4,5] Targeted intraoperative radiotherapy is delivered without disturbing the fresh tumour bed. Immediately after lumpectomy, a spherical applicator is inserted at the site of the excised cancer, and a carefully placed purse-string suture gently wraps the soft pliable tumour bed around it. Targeted intraoperative radiotherapy is thus delivered to well vascularised and undamaged tissue (figure). Radiotherapy delivery takes 20–40 min, allowing time for normal tissue repair.

Unlike the results of the ELIOT study, the long-term breast cancer outcomes (median 9 years, maximum 19 years follow-up) of TARGIT-IORT were similar to the outcomes of whole- breast irradiation.[3,5] Importantly, most patients in the TARGIT-A trial who had high-risk features (including 78% of patients with grade 3 tumours, 82% of patients with oestrogen receptor-negative tumours, and 63% of patients with node-positive tumours) did not receive supplemental external beam radiotherapy after targeted intraoperative radiotherapy.[3,5] With effective local control, breast cancer mortality with targeted intraoperative radiotherapy is no different from whole-breast irradiation (as shown by the superimposed Kaplan-Meier survival curves), and the reduction in non-breast cancer mortality is substantial: HR 0·59 (95% CI 0·40–0·86; p=0·005), 41% relative risk reduction, and 4·4% in absolute risk reduction (from 9·85% to 5·41% at 12 years).[3,5]

There are many other benefits to targeted intraoperative radiotherapy. Notably, unlike electron intraoperative radiotherapy, it does not require linear accelerator-style radiation protection. Targeted intraoperative radiotherapy can be done in a standard surgical theatre,[4,5] has lower toxicity, improved quality of life, superior cosmetic outcomes, and lower health-care costs than whole-breast radiotherapy.[6,7]

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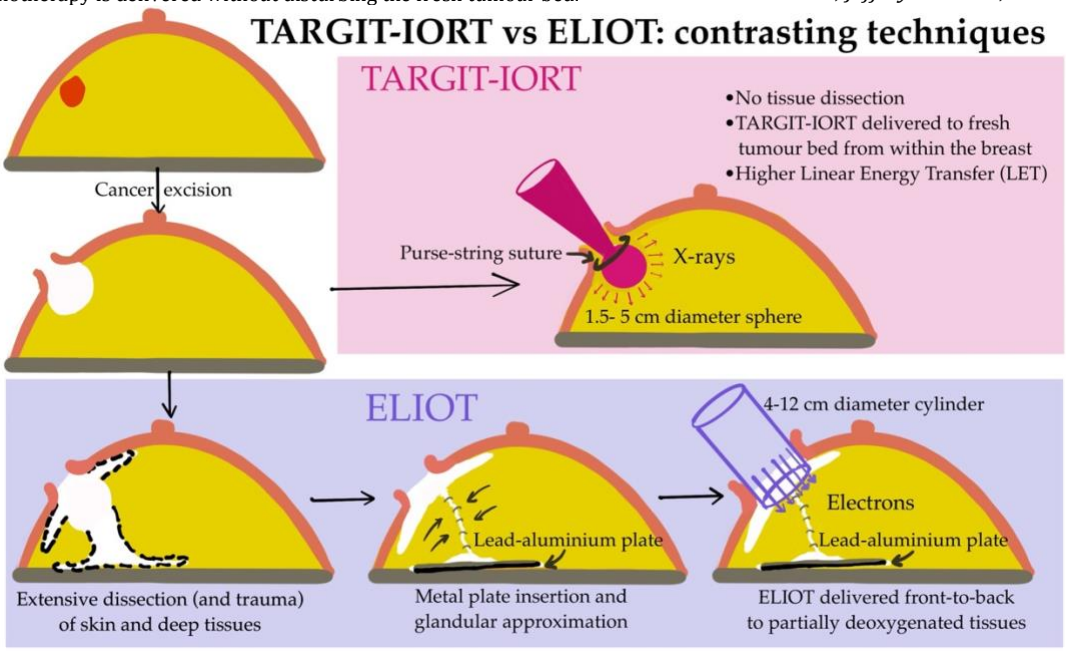

Figure: **Contrasting techniques of TARGIT-IORT (during lumpectomy for breast cancer) versus ELIOT**
ELIOT=electron intraoperative radiotherapy. TARGIT-IORT=targeted intraoperative radiotherapy.

References

1. Orecchia R, Veronesi U, Maisonneuve P, et al. Intraoperative irradiation for early breast cancer (ELIOT): long-term recurrence and survival outcomes from a single-centre, randomised, phase 3 equivalence trial. *The lancet oncology* 2021 doi: 10.1016/s1470-2045(21)00080-2
2. Rockwell S, Dobrucki IT, Kim EY, et al. Hypoxia and radiation therapy: past history, ongoing research, and future promise. *Curr Mol Med* 2009;9(4):442-58. doi: 10.2174/156652409788167087 [published Online First: 2009/06/13]
3. Vaidya JS, Bulsara M, Baum M, et al. Single-dose intraoperative radiotherapy during lumpectomy for breast cancer: an innovative patient-centred treatment. *British journal of cancer* 2021 doi: 10.1038/s41416-020-01233-5
4. Vaidya JS, Baum M, Tobias JS, et al. The novel technique of delivering targeted intraoperative radiotherapy (Targit) for early breast cancer. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology* 2002;28(4):447-54. doi: S0748798302912758 [pii] [published Online First: 2002/07/09]
5. Vaidya JS, Bulsara M, Baum M, et al. Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial. *BMJ* 2020;370:m2836. doi: 10.1136/bmj.m2836 [published Online First: 2020/08/19]
6. Welzel G, Boch A, Sperk E, et al. Radiation-related quality of life parameters after targeted intraoperative radiotherapy versus whole breast radiotherapy in patients with breast cancer: results from the randomized phase III trial TARGIT-A. *Radiat Oncol* 2013;8(1):9. doi: 10.1186/1748-717X-8-9
7. Alvarado MD, Mohan AJ, Esserman LJ, et al. Cost-effectiveness analysis of intraoperative radiation therapy for early-stage breast cancer. *Annals of surgical oncology* 2013;20(9):2873-80. doi: 10.1245/s10434-013-2997-3