Intraoperative radiotherapy: the debate continues

In the April issue of The Lancet Oncology, Harry Bartelink1 commented on our recent review2 of intraoperative radiotherapy for breast cancer. It is heartening to note that Bartelink agrees with us that in a subgroup of patients, local irradiation of the tumour bed after breast-conserving surgery might be sufficient. And we believe that advances in molecular biology need to be complemented by clinical trials to fully elucidate the biological sensitivity and natural history of breast cancers that can be safely treated by new therapies other than the current standards. In particular, it is essential that randomised clinical trials are done, and the long-term results fully understood, before intraoperative radiotherapy is offered as the only treatment. Hence the importance of the ongoing TARGIT and the ELIOT studies.

We disagree with Bartelink’s remark, however, that “the biological arguments used [in our review] to defend intraoperative radiotherapy have several shortcomings”. Over the past 20 years, follow-up data from patients who received single-dose radiotherapy (such as radiosurgery) for brain, liver, and lung cancer has been accumulated. Results on structural damage3 (eg, necrosis) as well as the functional consequences4 (eg, cognitive effects) are available. The Swedish and Dutch rectal-cancer trials prescribed five 5-Gy fractions to the pelvis. Thousands of patients have been treated and long-term follow-up data are available. On the basis of these data, severe long-term side-effects would not be expected after administration of 5 Gy to 1 cm of breast tissue surrounding an excision cavity, although caution should be exercised when giving high single doses to skin and ribs.5

When debating whether a dose of 20 Gy to the surface of an excision cavity and 5 Gy to 1 cm of tissue is adequate, it is important to remember that external-beam radiotherapy after breast-conserving surgery reduces local recurrence from about 30% to about 10% after 10 years. The effectiveness of a fractionated dose of 50 Gy, starting 6–8 weeks after surgery (or even later if a patient is scheduled to receive systemic therapy as well), is decreased by tumour-cell repopulation during this time. We know from the experiences reported in radiosurgery that a single dose of 20 Gy is sufficient to sterilise even macroscopic tumours, and that model calculations (despite their limitations) estimate recurrences of fewer than 1% in the region of tissue close to the radiation applicator during intraoperative radiotherapy. This hypothetical recurrence increases with distance from the applicator because of a decrease in dose and can theoretically reach 30% in those regions of the breast that receive no irradiation (assuming a homogeneous distribution of tumour cells irrespective of the distance to the centre of the original tumour—which is a worst case scenario). Therefore, there must be a region of equivalence around the tumour in which intraoperative radiotherapy results in the same recurrence to that seen after external-beam radiotherapy.6

We do not believe that patients enrolled in intraoperative radiotherapy trials would run the risk of increased mortality. Moreover, because the radiation dose to the heart and lungs during intraoperative radiotherapy is almost negligible, it is possible that death from cardiac ischaemia—commonly seen in conventional radiotherapy trials—could be reduced.7,8 Targeted intraoperative radiotherapy might reduce the number of deaths from breast cancer as a consequence of administering timely and truly conformal radiation, thus avoiding geographic misses. Indeed, a study9 of 7800 patients found that a delay of conventional radiotherapy by 20–26 weeks after surgery resulted in decreased patient survival.

The TARGIT trial is testing two approaches: conventional treatment with whole-breast radiotherapy for all patients versus a pragmatic therapy in which all patients receive intraoperative radiotherapy and one (depending on their risk of recurrence) also receive external-beam radiotherapy. If the latter group of patients were eventually found to have equivalent, or better, local control and cosmetic outcome, then the convenience, lower cost, and increased feasibility of breast-conserving surgery would tip the balance in favour of intraoperative radiotherapy.

References

10 Meinardi MT, van Veldhuisen DJ, Gietema JA, et al. Prospective evaluation of early cardiac damage induced by...
In a recent issue of The Lancet Oncology, Harry Bartelink\textsuperscript{1} criticised an extensive review by Vaidya and colleagues\textsuperscript{2} that presented a robust defence of the effectiveness of intraoperative radiotherapy after breast-conserving surgery as an alternative treatment to conventional whole-breast irradiation. Bartelink suggested that replacing postoperative, fractionated radiotherapy with a single intraoperative dose of radiation, could increase the likelihood of local recurrence and mortality. To support this perspective, Bartelink drew on the conclusions of Hung and Verschraegen; namely, the omission of radiotherapy after breast-conserving surgery increases the risk of breast-cancer recurrence and patient mortality.\textsuperscript{3}

We would like to point out some important considerations. First, intraoperative radiotherapy is not an omission of radiotherapy. In our experience, based on radiobiological modelling to predict radiation effects,\textsuperscript{4} a dose of 60 Gy delivered in 2-Gy fractions each day—the standard dose in postoperative, fractionated radiotherapy—is biologically equivalent to a single intraoperative fraction of 22 Gy.

Second, although the omission of radiotherapy after breast-conserving surgery increases the risk of breast-cancer recurrence, it is unknown whether it also decreases patient survival. The results of a randomised trial done at our institute in Milan, Italy, on the effects of postoperative, fractionated radiotherapy after breast-conserving surgery showed that 90% of local relapses occurred within the operative area.\textsuperscript{5} The remaining 10% of cases, which occurred in different quadrants, must be considered as new ipsilateral carcinomas. Because most local recurrences after breast-conserving surgery are therefore expected to be found in the region surrounding the dissection, irradiation of the whole mammary gland might only prevent development of new ipsilateral carcinomas. Furthermore, after 12 years of follow-up, we have seen no significant difference \((p=0.326)\) in survival between the two groups of patients in our trial (patients given quadrantectomy, axillary dissection, and radiotherapy versus patients given quadrantectomy and axillary dissection without radiotherapy).\textsuperscript{6}

Third, the only other difference between intraoperative radiotherapy and postoperative, fractionated radiotherapy is the irradiated target region, which, intraoperatively, is a wide area around the tumour bed. As noted above, this part of the breast is the most common site of recurrence and the long-term effectiveness of specific irradiation to this area has been shown by several researchers.\textsuperscript{7}

Finally, however, we do agree with Bartelink on one issue: postoperative, fractionated radiotherapy should continue to be the standard method of treatment for breast cancer until such time that the results of long-term endpoints in continuing clinical trials have been fully reported and the absolute sequelae have been elucidated.\textsuperscript{8}

Even though the potential of intraoperative radiotherapy has yet to be fully established, there might be other groups of patients who will benefit from the technique. Mastectomy is generally regarded more effective or safer than breast-conserving surgery and postoperative, fractionated radiotherapy for some patients, such as women who have been treated with radiotherapy for Hodgkin’s disease,\textsuperscript{9} those who have undergone cosmetic augmentation to the breast, those who have cancer of the left breast associated with severe cardiopathy, or those have been affected by vitiligo or other dermatological diseases and collagenopathies. Intraoperative radiotherapy might, however, be an effective alternative therapeutic option that can decrease the number of avoidable mastectomies in these women.

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References