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BENEFICIAL EFFECTS OF INTRAOPERATIVE RADIOTHERAPY ON TUMOR MICROENVIRONMENT COULD IMPROVE OUTCOMES (*INT J RADIAT ONCOL BIOL PHYS* 2008;72:1575–1581)

Herksind and colleagues have created an elegant and plausible model that simulates the effects of radiation on tissues surrounding a source typically applicable to targeted intraoperative radiotherapy (TARGIT).

Their model suggests that the ''sphere of equivalence'' with TARGIT could be large enough to achieve local control for breast cancer. A mathematical model (1) arrived at a similar conclusion via a different concept, namely, that peritumoral tissues harbor cells that have a loss of heterozygosity in key tumor suppressor genes. These cells may survive fractionated radiotherapy but may not be able to survive the relatively high dose delivered locally, potentially yielding a superior result. Results from both models concur with clinical data from a large pilot series of 300 patients who received a TARGIT boost and achieved a very low local recurrence rate (1.52% actuarial at 5 years), far below that expected for that average risk population (2, 3).

There is however an altogether different aspect to consider. Traditionally, radiotherapy is meant to work by killing cancer cells. However, its effect on patients with close margins is very similar to that on patients with wider margins, a two-thirds proportional reduction in recurrence risk, so radiotherapy perhaps beneficially alters the ''soil'' (4).

To investigate this, wound fluid collected in the 24-hour period immediately after lumpectomy, with or without targeted intraoperative radiotherapy (TARGIT), was tested for its ability to stimulate proliferation and motility of breast cancer cells and their invasion of Matrigel. It was found that while normal wound fluid is stimulatory, a disconcerting fact, fluid taken from patients who had received TARGIT was not, demonstrating for the first time that radiotherapy had a beneficial effect on tumor microenvironment; proteomic analysis revealed a series of factors that are altered by TARGIT (5).

Arguably, conventional radiotherapy is effective. It reduces local recurrence risk by two-thirds, but it leaves behind one-third the risk. In younger women, this is significantly large (up to 13.5%) (6). Perhaps the evolutionary pressure for brisk wound healing is the highest in patients below the age of 45 and conventional radiotherapy delivery may be too late to have its effect on tumor microenvironment. Accurately applying TARGIT to the tumor beds of young patients with a boost at the right time may give superior results. In older women, the effect of TARGIT on tumor microenvironment would increase the sphere of equivalence, allowing us to omit external beam radiotherapy. Both of these approaches are being tested in randomized trials (TARGIT-A[lone] and TARGIT-B[oost]) (3, 7, 8).

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IS THERE MORE TO INTRAOPERATIVE RADIOTHERAPY THAN PHYSICAL DOSE?

To the Editor: We thank Vaidya *et al*. for their comment on our article (1). They raise an important point regarding the microenvironment of residual tumor cells or premalignant stem cells in a surgical wound exposed to cytokines in the wound fluid, stimulating proliferation, adhesion, and invasion.

Belletti *et al*. (2) convincingly demonstrated that intraoperative radiotherapy (IORT) with Intrabeam can inhibit growth stimulation by wound fluid from patients undergoing breast-conserving surgery. These biological effects on the microenvironment are not included in our model (1) because up to now, no quantitation of these novel effects has been published. The lack of quantitative experimental data on the cellular response to large single doses of radiation due to the experimental difficulties in detecting single clonogenic cells on a large background of inactivated cells is certainly a shortcoming of our—and indeed any—modeling approach. The mathematical model of Enderling *et al*. (3) represents a mechanistic approach describing the effect of irradiation on continuous cell transformation and tumor growth, which differs fundamentally from our more pragmatic approach based on clinical and experimental data (1, 4). Nevertheless, this model provides insight into the expansion of tumor cells in the tumor bed and its inhibition by irradiation. Which of these and possibly other models are more applicable to IORT awaits experimental and clinical validation.

It is suggested that the biological effects may be different after large single doses (above 10–15 Gy) compared with the lower dose range (0–10 Gy) normally studied. Clinical studies have reported better than expected local control rates after IORT as a boost for breast cancer (5, 6) or SBRT for lung cancer (7). In solid tumors, high doses may cause vascular damage in addition to tumor cell kill (8). In normal tissue, vascular damage seems to be caused by endothelial cell apoptosis induced by release of ceramide after high doses, leading to an antiangiogenic effect in the tumor bed (9). Furthermore, irradiation induces expression of proinflammatory cytokines and immunogenic signals in tumours (10).

We agree with Vaidya *et al*., that the biological effectiveness of IORT may well be underestimated by focusing on clonogenic cell inactivation and radiation dose alone. This might partly compensate for the criticism that the L-Q model may overestimate cell inactivation at high doses. Therefore, more clinical and experimental studies should be performed to test the biological effect of high doses and the role of the microenvironment in IORT.

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