could be relatively easily addressed is the presentation of the discussion at the end of each chapter which requires improvement. The questions and comments presented by the audience are often insightful and relevant, not only to the chapter they deal with but also to the subject matter of the book in general. If they were edited it would make them an excellent addendum to each chapter.

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Letters

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Comments on *Inadequacy of Iridium Implant as Sole Radiation Treatment for Operable Breast Cancer,* Fentiman *et al., Eur J Cancer* 1996, 32A, pp. 608–611

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In a recent article published in the *European Journal of Cancer*, Fentiman and associates [1] compared the local tumour control achieved with two alternative treatments of the breast: (a) an existing, well-established treatment, consisting of an external beam regime of 46 Gy in 23 fractions over approximately 4.5 weeks, supplemented 1 week later by a continuous iridium application delivering 20 Gy over 2 days; and (b) a single continuous application of an iridium-192 implant delivering 55 Gy over 5–6 days.

After 6 years median follow-up, the local control rate with treatment (b) was found to be 20% lower than that achieved with treatment (a). The likelihood of such a finding is predictable using standard radiobiological calculations, the results of which are summarised below.

If tumour repopulation during treatment is ignored (probably a reasonable assumption in the case of breast carcinoma), the biologically effective doses (BEDs) may by calculated as follows:

For the teletherapy:

$$BED = nd\left[1 + \frac{d}{\alpha/\beta}\right] \quad (1)$$

where n is the number of fractions, d the dose per fraction (Gy) and α/β the tumour fractionation parameter (Gy) [2].

For the iridium implant:

$$BED = RT\left[1 + \frac{2R}{\mu(\alpha/\beta)}\right] \quad (2)$$

where R is the dose-rate (Gyh^{-1}), T the treatment time (h) and μ the recovery rate (h^{-1}) of sublethal DNA damage [3].

The BED for treatment (a) is found by summing the BEDs calculated from Equation (1); the BED for treatment (b) is found from application of Equation (2) alone.

The BEDs (in units of Gy) have been calculated for four assumed values for α/β and two for μ, and are summarised in Table 1. In all cases, the BEDs associated with treatment (b) are well below those achieved with treatment (a). Consequently, the multivariate analysis performed by Fentiman and associates [1] is essentially based on a comparison of two treatments which, in radiobiological terms, are disparate. It should, therefore, be concluded that this clinical study does not necessarily provide evidence that the use of an iridium implant alone is inferior to the well-established treatment, since the chosen dose was radiobiologically sub-optimal.

Although tumour recovery rates are not known with any absolute certainty, they are probably in the general range 0.5–1.5 per hour, with an increased likelihood of being towards the higher end of the range for tumours [4]. The tumour α/β values are generally greater than 5 Gy and, in individual cases, may be even higher than 20 Gy, the upper end of the range considered here [4]. The normal tissue responses are more likely to be characterised by α/β ratios of less that 5 Gy [5].

Thus, the standard linear-quadratic equations strongly indicate that the local tumour control associated with

Table 1.

α/β (Gy):	3 Gy		5 Gy		10 Gy		20 Gy	
μ (h^{-1}):	0.5	1.5	0.5	1.5	0.5	1.5	0.5	1.5
BEDs for group (a)	107.8	100.4	91.1	86.7	78.5	76.3	72.3	71.1
BEDs for group (b)	85.6	65.2	73.5	61.2	64.2	58.1	59.6	56.5
Difference:	−21%	−35%	−19%	−29%	−18%	−24%	−18%	−15%

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treatment (b) is likely to be less than that of treatment (a), the associated tumour BED value being lower by around 15–25%. Since tumour control probability (TCP) is likely to be strongly influenced by relatively small changes in BED [6], especially when the existing TCP is neither very high nor very low [7, 8], the observed clinical results are consistent with those predicted by simple modelling. Similarly, the concerns of Fentiman and colleagues regarding the likelihood of increased normal tissue toxicity with implant alone are probably unfounded, as evidenced by the tabular data for the two lower α/β values. In practice, it is likely that, provided the iridium-192 dose-rate were not increased, the total dose in treatment (b) could be increased to 60 Gy, or possibly more, without compromising late-normal toxicity.

The purpose of this communication is not to criticise the work of Fentiman and associates, whose article clearly highlights the clinical dilemmas involved in introducing alternatives to long-standing and well-tried treatments. Rather, it is to highlight two facets of radiobiological modelling which can be valuable in the design of clinical trials in radiation oncology. These are:

(i) That modelling has a place in comparing the results of potential alternative treatments and provides indirect evidence that the commonly assumed modelling parameters may often be sufficient for such purposes. The validity of this approach has previously been highlighted elsewhere [9].

(ii) Potentially closer matches can be achieved between the two arms of a particular trial with prospective modelling. Not only does closer matching help guard against the possibility that patients in one arm may be unnecessarily disadvantaged, it also means that the subsequent comparison of the results from two radiobiologically matched arms can help establish finer tolerances on the likely range of the biological parameters involved. In this context, the use of radiobiological modelling should always be considered a prerequisite in the design of clinical trials [8] and ethical committees should have evidence that the radiobiological aspects have at least been considered before approving clinical trials in radiation oncology.

Perhaps it is timely to propose that future published results of clinical trials in radiation oncology should include abbreviated summaries of the tumour and normal tissue Beds associated with the various trial arms, in much the same way as has already been achieved in relation to including standardised statistical summaries.

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Response from I.S. Fentiman and D. Tong

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DALE AND associates provide a possible explanation for the unsatisfactory outcome of our pilot study. We must first correct one inaccuracy. The standard technique which was in use at our unit was that used in EORTC 10801 [1]. This comprised insertion of a single or double plane flexible implant at the time of surgery. The implant was afterloaded the following day with iridium^{192} wires to deliver 20 Gy over approximately 48 h. This was followed by external beam radiotherapy rather than being preceded by it.

At the time that we were contemplating the high dose study, all our experience had been limited to flexible implants delivering a boost to a relatively small volume. Because of the change to a rigid implant occupying a larger volume we were anxious not to overdose the patient. A small pilot of rigid implants had resulted in occasional skin necrosis, infection around implant sites, serious oozing and occasional impaired wound healing. We were also concerned that patients would not tolerate breast compression immediately after surgery if a higher dose was given.

The aim was to achieve gross clearance of tumour and use the rigid implant to irradiate the involved quadrant. We were not implanting intact tumours, but were carrying out the implant at a time of wound healing after tumorectomy and axillary clearance. There was breast oedema associated with this which lead to pressure necrosis in some cases. We consulted with other colleagues at the time of study design and reached a consensus as to the most likely dosage to achieve tumour control without undue morbidity. With hindsight, the dosage was inappropriate but the use of higher doses would undoubtedly have led to greater local morbidity.

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