

Is there an association between late normal tissue response and tumour control after local tumour excision and radiotherapy for early breast cancer?

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INTRODUCTION

- Factors influencing risks of ipsilateral local tumour relapse and late adverse effects after local tumour excision and radiotherapy for early breast cancer include the intrinsic radiosensitivity of tumour cells and normal host cells, respectively¹.
- Common single nucleotide polymorphisms at multiple genetic loci may be important in explaining inter-patient variation in normal tissue responses to radiation².
- Mutations and/or polymorphisms in genes regulating DNA repair, cell cycle and other cellular responses might be expected to influence local tumour control probability as well as late normal tissue effects. If so, patients with marked late adverse effects of radiotherapy would have lower than average local tumour relapse rates, provided a range of variables, especially treatment volume, dosimetry and prescribed dose were adequately controlled for.
- A retrospective unplanned analysis has been performed of patients entered into a randomised trial of alternative radiotherapy fractionation regimens following complete excision of early breast cancer, with primary endpoint of change in breast appearance and tumour control as a secondary endpoint^{3,4}. Systematic and prospective recording of late adverse effects of radiotherapy and tumour control over a 10-year period allows testing for an association between the risk of late adverse effects and the probability of local tumour control.

AIM

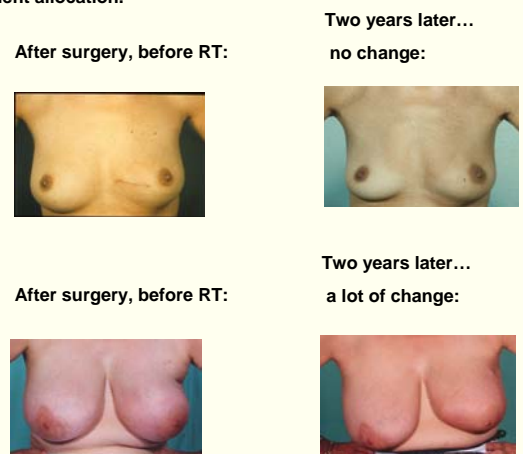
To test for an association between the risk of late adverse effects and local tumour control.

METHODS

- From 1986-98, 1410 early breast cancer patients randomised to 50 Gy in 25 fractions (control), 42.9Gy or 39Gy (both in 13 fractions), following conservation surgery.
- Electron boost allocation (10 Gy in 5 fractions) determined independently.
- Frontal photographs taken after surgery and repeated annually to 5 years and then at 10 years. Patients were no longer eligible for photographs after relapse, as further treatment would confound the assessment of the initial radiotherapy.
- Change in breast appearance from baseline scored at each time point as none, mild or marked (see box).
- Changes after 5 years ignored for this analysis since unlikely to identify radioresponsive individuals.
- Endpoint for this analysis=local relapse.
- Cox proportional hazards (PH) regression used to model time to local relapse (or date last seen or date of death), allowing for the time at which change in breast appearance occurred, and adjusting for factors associated with relapse and late adverse effects.

MEASUREMENT OF CHANGE IN BREAST APPEARANCE

Change in breast appearance (none, mild, marked) scored blind to treatment allocation.



RESULTS

Table 1: Characteristics of 1410 patients randomised

| Patient characteristic | Number (%) |
|--|--------------------|
| Age: mean (SD), [range] yrs | 54.5 (9.7) [25-78] |
| Breast size (from photographs) | |
| Small | 186 (13.2) |
| Medium | 952 (67.5) |
| Large | 203 (14.4) |
| Not known | 69 (4.9) |
| Adjuvant treatment | |
| None | 289 (20.5) |
| Tamoxifen only | 918 (65.1) |
| Chemotherapy only | 40 (2.8) |
| Tamoxifen + chemotherapy | 156 (11.1) |
| Other | 7 (0.5) |
| Axillary/SCF ^a treatment | |
| None | 337 (23.9) |
| Axillary/SCF RT ^b , no axillary surgery | 231 (16.4) |
| Surgery, no RT | 782 (55.5) |
| Surgery and SCF RT | 59 (4.2) |
| Not known | 1 (0.1) |
| Breast boost | |
| Randomised to no boost | 359 (25.5) |
| Randomised to boost | 364 (25.8) |
| Non-randomised boost | 687 (48.7) |

^a supraclavicular fossa; ^b radiotherapy

- 1202 patients had a baseline and at least one follow-up photographic assessment.
- Of the 320 patients who experienced some change in breast appearance within 5 years of radiotherapy, 267 were mild and 53 were marked changes, and 125 had an ipsilateral breast relapse during follow-up (Table 2).
- Risk of local relapse was reduced for patients who had mild or marked change in breast appearance within 5 years of radiotherapy, although this was not statistically significant (Table 2, trend test p=0.16). The confidence intervals were wide due to the small number of events.

Table 2: Results of Cox PH regression analysis of the effect of change in breast appearance within 5 years of radiotherapy on local relapse

| Change in breast appearance within 5 years | Number local relapses / total (%) | Adjusted HR ^a (95%CI) |
|--|-----------------------------------|----------------------------------|
| No change | 97 / 882 (11.0) | 1 |
| Mild change | 25 / 267 (9.4) | 0.59 (0.29-1.18) |
| Marked change | 3 / 53 (5.7) | 0.64 (0.15-2.77) |

^a hazard ratio, adjusted for fractionation schedule, boost, axillary treatment, tamoxifen, breast size and age. Breast size fitted as a proxy for dose inhomogeneity.

CONCLUSIONS

- Statistical power is low, but results suggest a possible association between reduced risk of local tumour relapse and change in breast appearance after primary tumour excision and whole breast radiotherapy for early breast cancer.
- Results need to be confirmed by independent studies that effectively control for dose inhomogeneity.
- If proved, this would support a strategy of predictive testing to identify patients in whom the severity of late adverse effects could be reduced by modest dose reductions while retaining acceptable rates of tumour control.

References

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