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Original Article

Acute Toxicity and 2-year Adverse Effects of 30 Gy in Five Fractions over 15 Days to Whole Breast after Local Excision of Early Breast Cancer

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ABSTRACT:
Aims: **A pilot study was undertaken with the aim of documenting acute skin reactions and 2-year late adverse effects of a five-fraction course of adjuvant whole breast radiotherapy delivered over 15 days after local tumour excision of early breast cancer.**
Materials and methods: **Thirty women with early invasive breast cancer aged $\geq$ 50 years with a pathological tumour size $<$3 cm, complete microscopic resection, negative axillary node status and no requirement for cytotoxic therapy were prescribed 30 Gy in five fractions over 15 days to the whole breast using tangential 6—10 MV X-ray beams and three-dimensional dose compensation with written informed consent. Post-surgical baseline photographs of the breasts were taken, and acute skin erythema and moist desquamation were each scored weekly for 7 weeks using four-point graded scales (grade 0 = none, 1 = mild, 2 = moderate, 3 = severe). This was followed by an annual clinical assessment, including repeat photographs at 2 years.**
Results: **Nine patients (30%, 95% confidence interval 14.7—49.4%) developed grade 2 erythema, with the remaining 21 patients developing milder degrees of reaction. Four (13.3%, 95% confidence interval 3.7—30.7) patients developed moist desquamation, grade 1 in three women and grade 2 in the fourth. At 2 years after treatment, 23/30 (77%) patients scored no change in photographic breast appearance compared with the pre-treatment baseline; seven (23%, 95% confidence interval 9.9—42.3) scored a mild change in breast appearance, and none developed a marked change. After a mean follow-up of 3.1 years (standard deviation 0.37, range 2.1—3.9 years) there have been no ipsilateral local tumour relapses.**
Conclusions: **Further evaluation of a five-fraction regimen of adjuvant whole breast radiotherapy in a phase III randomised trial is justified, including a regimen delivered in a total of 5 days. Martin, S. *et al*. (2008). *Clinical Oncology* 20, 502—505**

Key words: Breast cancer, fractionation, hypofractionation, radiotherapy

Introduction

Interest in hypofractionation for adjuvant breast radiotherapy re-emerged in the mid-1980s after a re-analysis of historical data, using the linear-quadratic model, suggested that breast cancer is as sensitive to fraction size as the dose-limiting late responding normal tissues [1,2]. Two prospective randomised trials subsequently reported results consistent with this suggestion, including the Royal Marsden NHS Foundation Trust/Gloucestershire Oncology Centre (RMH/GOC) trial, which tested two dose levels of a 13-fraction regimen over 5 weeks against 50 Gy in 25 fractions, and the Ontario trial, which tested a 16-fraction regimen over 3.2 weeks against 50 Gy in 25 fractions [3—5]. Subsequently, the UK Standardisation of Breast Radiotherapy (START) trials tested two 13-fraction schedules over 5 weeks and 40 Gy in 15 fractions over 3 weeks, each against 50 Gy in 25 fractions over 5 weeks. The 5-year results of the START trials are also consistent with the hypothesis that breast cancer has a comparable sensitivity to fraction size as the late responding normal tissues of the breast [6]. If true, it means that the current use of small fraction sizes spares the tumour as effectively as the late responding normal tissues.

Thirteen-, 15- or 16-fraction schedules are unlikely to represent the limits of hypofractionation. To explore this further, the UK National Cancer Research Network FAST trial randomised 900 patients to five fractions of 5.7 Gy or 6.0 Gy delivered in 5 weeks vs 25 fractions of 2.0 Gy with late adverse effects as primary end points [7]. The

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FAST trial is currently in follow-up. In preparation for a future phase III randomised trial of a five-fraction regimen delivered in 5 days, a pilot study evaluated erythema and moist desquamation in patients receiving 30 Gy in five fractions delivered twice weekly to the whole breast in 15 days. This intermediate time period was chosen to be sure of complete cellular recovery between fractions (minimum 48 h). The early results of this experience are reported here.

Materials and Methods

Patients

Patients eligible for entry into this pilot study were women aged ≥ 50 years after breast conservation surgery for invasive breast carcinoma with a pathological tumour size <3 cm, complete microscopic resection, no lymphovascular invasion, negative axillary node status and no requirement for neoadjuvant or adjuvant cytotoxic therapy.

Radiotherapy

Patients were treated in the supine position, with both arms abducted at 90°. The reproducibility of positioning was verified by orthogonal laser beams. The planning target volume was defined as the entire breast with a 1 cm margin to palpable breast tissue. The reference point for dose prescription was chosen according to International Commission on Radiation Units (ICRU 50) guidelines. Dose homogeneity complied with ICRU 50 recommendations. Full-dose compensation was delivered using multiple static fields [8] if the maximum dose was >105%. Megavoltage 6 or 10 MV photons were used in all patients. No tumour bed boost was delivered to any patient.

Assessment of Normal Tissue Reactions

Clinical assessments of early normal tissue reaction were carried out once weekly during radiotherapy and for 5 weeks after the end of treatment (7 weeks overall). These recorded the degree of erythema and moist desquamation on four-point graded scales (grade 0 = none, 1 = mild, 2 = moderate, 3 = severe) on case report forms. The maximum orthogonal dimensions of moist desquamation were also recorded.

Patients consented to have frontal photographs taken of their breasts before radiotherapy and 2 years after treatment under standard conditions. Pairs of photographs were taken, one with both arms on hips and a second with both arms raised above the head. Additional photographs were also collected in selected patients with acute skin reactions $\geq$ grade 2 erythema. A change in breast appearance compared with the baseline before radiotherapy photographs was scored on a three-point graded scale (0 = no change, 1 = mild change, 2 = marked change) by two observers (LG and JY). Breast size was also assessed from the baseline photographs on a three-point scale (small, medium, large).

Statistical Methods

The sample size for this pilot study was chosen to be 30 patients on the grounds of feasibility rather than statistical considerations. Considering a rate of moist desquamation $\leq$20%, this sample size is associated with a standard error $\leq$7%. The percentages of patients experiencing erythema and moist desquamation and change in breast appearance (photographic) at 2 years were calculated with exact 95% confidence intervals.

Results

Written informed consent to participate in the pilot study was obtained from 30 patients between March 2004 and March 2005. Nine (30%) patients required three-dimensional radiotherapy dose compensation, delivered using multiple static fields. No cases of grade 3 erythema were seen, although one patient was downgraded from grade 3 to grade 2 (moderate) after reviewing a photograph of the peak reaction. Nine (30%, 95% confidence interval 14.7—49.4%) patients developed grade 2 erythema that subsided in eight patients to grade 1 or less within 2 weeks. In the ninth patient, grade 2 erythema settled within 3 weeks. The maximum erythema scores are summarised in Fig. 1a. Four (13.3%, 95% confidence interval 3.7—30.7) patients developed moist desquamation, grade 1 in three women and grade 2 in the fourth (see Fig. 1b). The maximum dimension in these four cases ranged from 5 to 50 mm; all lesions developed in the inframammary fold or axilla. Moist desquamation healed within 2 weeks in three of the four

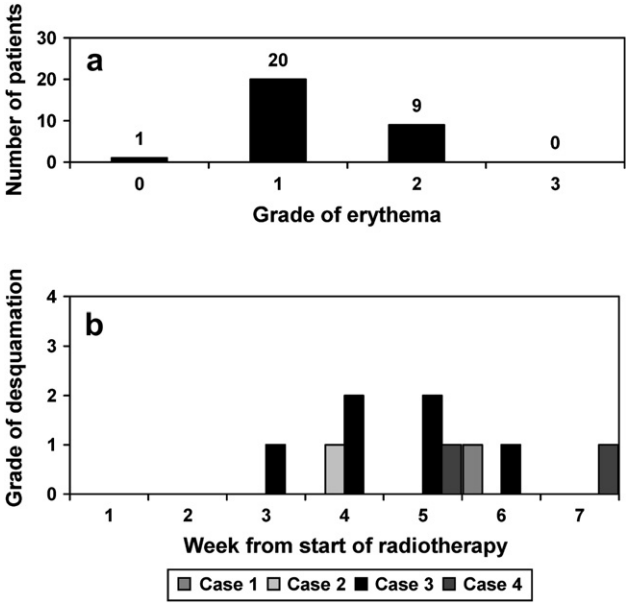

Fig. 1 — (a) Maximum grade of erythema developing in 30 patients receiving 30 Gy in five fractions over 5 weeks to the whole breast. (b) Grade and duration of moist desquamation developing in 4/30 women receiving 30 Gy in five fractions over 5 weeks to the whole breast.

Table 1 — Early skin reactions and late change in breast appearance (scored from baseline and 2-year photographs) according to breast size

Breast size	Erythema (%)	Moist desquamation (%)	Change in breast appearance (photographs) at 2 years (%)
Small	3/14 (21.4)	1/14 (7.1)	2/14 (14.3)
Medium	5/13 (38.5)	2/13 (15.4)	4/13 (30.8)
Large	1/3 (33.3)	1/3 (33.3)	1/3 (33.3)

women. At 2 years after treatment, 23/30 (77%) patients scored no change in photographic breast appearance compared with the before treatment baseline; seven (23%, 95% confidence interval 9.9—42.3) scored mild change in breast appearance, and none developed marked change. From the baseline photographs, breast size was recorded as small in 14 (46.7%), medium in 13 (43.3%) and large in three (10%) women. There was some evidence that the risk of acute skin reactions and change in breast appearance (photographic) increased with larger breast size, but the small sample size prevented formal statistical testing (see Table 1). To date, there have been no ipsilateral local tumour relapses over a mean follow-up of 3.1 years (standard deviation 0.37, range 2.1—3.9 years).

Discussion

The early and 2-year normal tissue responses scored in this pilot study were generally very mild, and not different from those expected after standard regimens. A reliable comparison of these effects after 30 Gy in five fractions over 15 days with the effects of 50 Gy in 25 fractions is limited by the lack of a randomised comparator group. A Radiation Therapy Oncology Group trial (RTOG 97-13) testing supportive care of skin toxicity in women undergoing breast radiotherapy, combined with the results of previous RTOG experience, reported 7% grade 0, 58% grade 1, 32% grade 2, 3% grade 3, and no grade 4 acute skin toxicity [9]. Retrospective re-grading of skin reactions in the present pilot study, applying RTOG criteria, produced comparable rates: 3% grade 0, 67% grade 1, 30% grade 2 and no grade 3 or 4 toxicity. However, differences in breast size and radiation dosimetry limit the reliability of this comparison [10,11]. A correlation between breast size and acute toxicity was reported in the RTOG 97-13 study, with small-breasted women developing 11—21% grade 2 or higher skin toxicity compared with 43—50% in large-breasted women. There was some evidence of a similar association between acute and late toxicity and breast size in the pilot study, but numbers were too small for formal statistical testing.

Changes in breast appearance 2 years after treatment were very mild, and comparable with the 2-year rates reported after 50 Gy in 25 fractions in the RMH/GOC and START trials [3,6]. However, the same limitations apply to this comparison as discussed for acute skin toxicities. In addition, the nine (30%) patients in the pilot study treated with full (three-dimensional) dose compensation may have developed slightly lower levels of late normal tissue effects than if standard two-dimensional dosimetry had been used [10,11]. Late changes in normal tissues are also more sensitive to fraction size than early skin reactions [12]. A meta-analysis of the RMH/GOC and NCRI START trials generated an α/β value of 3.4 Gy for late adverse effects, making the present dose schedule equivalent to a total dose of 52 Gy in 2.0 Gy fractions. This estimate assumes complete repair between fractions, whereas it is clear that this is incomplete in human skin even after 24 h [13]. If an incomplete repair model is applied, 30 Gy in five fractions over 5 days is expected to be equivalent to 50 Gy in 2.0 Gy fractions [14].

The longer term aim is to explore a whole breast radiotherapy schedule of five fractions delivered in 5 days in a randomised clinical trial. It is not expected that reducing the overall treatment time from 15 to 5 days will enhance acute skin reactions, as accelerated repopulation in basal epidermis starts only after 15 days, but a small dose adjustment may be needed to compensate for incomplete repair [15]. Where late effects are concerned, long-term follow-up of a large number of patients will be needed for full evaluation.

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