Eur J Cancer Clin Oncol, Vol. 20, No. 2, pp. 189–196, 1984.
Printed in Great Britain.

0277-5379/84$3.00+0.00

Recent Experience in the Radical Irradiation of Primary Breast Cancer at Mount Vernon Hospital

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Abstract—*In order to improve the long-term cosmetic results following the radical irradiation of primary breast cancer at Mount Vernon Hospital, dosage was reduced in the early 1970s. The clinical impression that local recurrence had become more frequent at the reduced dose level led to an early review of the results. This report details the results in 159 patients who formed the two largest groups of patients treated between 1968 and 1980. Sixty-five patients were treated between 1968 and 1973, using 6500 cGy to the whole breast in 25 daily fractions over 5 weeks, with alternate breast fields treated each day. Forty-two of these patients were with TNM stage I and II disease* [TNM Classification of Malignant Tumours, *Geneva, UICC, 1978*] *and had 5-yr actuarial survival and local recurrence figures of 59 and 10% respectively. The corresponding figures in 52 patients with stage I and II disease treated between 1974 and 1980 with 5500 cGy to the whole breast in 25 daily fractions over 5 weeks with both breast fields treated each day were 79 and 26.6%. In spite of the small numbers involved and the bias in favour of the latter group of patients, who had a greater proportion of T1,N0 lesions, the difference in local recurrence rate in favour of the former group (who received 6500 cGy) almost reached statistical significance at the 0.05 level. A difference was also observed when the two subgroups of stage I and II patients who had had their primaries excised prior to irradiation were compared. The 23 patients with TNM stage IIIa and b disease treated with 6500 cGy between 1968 and 1973 had similar local recurrence (49.7% at 18 months) and survival experience (32.5% at 5 yr) to the 42 similarly staged patients treated with 5500 cGy between 1974 and 1980 (48 and 36.4% respectively). It is possible that the addition of combination cytotoxic therapy to the primary management in 12 patients with stage IIIb disease in the latter group favourably influenced the local control data obtained. Cosmetic results were substantially better in the groups receiving 5500 cGy, with approximately 20% developing disfiguring retraction and skin changes. In contrast, these sequelae were almost inevitable in the patients who received 6500 cGy.*

INTRODUCTION

A LARGE experience in the management of advanced and often inoperable primary breast cancer by radiotherapy alone had been accumulated at Mount Vernon Hospital by the mid 1960s. Strickland [1] reported to the *British Journal of Surgery* 385 cases treated since the installation of the Metropolitan Vickers 4 MV linear accelerator in 1955. Disease-free 5-yr survival was achieved in 41 (49.4%) of 83 T2,N0,1,2 cases and 87 (33.7%) of 258 T3,N0,1,2 cases. Using a simple three-field technique the linear accelerator enabled doses as high as 6500–7000 cGy in 5–6 weeks to be delivered to the whole breast before the onset of dose-limiting acute reactions. Inevitably the long-term cosmetic results were poor but were often quite acceptable to the many patients who later succumbed to distant metastases with their primary controlled and to the few alive today apparently cured.

During the 'sixties and 'seventies an increasing number of patients with operable breast cancer were referred for radiotherapy, with mastectomy held in reserve for local failure. Cases tended to fall into two categories: patients with large primaries in whom high-dose post-mastectomy irradiation would have been considered manda-

Accepted 15 June 1983.
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tory to prevent recurrence, and patients with small primaries removed by wedge excision because mastectomy was not desired or not considered essential due to the site of the lesion. Since mastectomy was considered an option in these cases, local control alone became an inadequate endpoint. Clearly it was desirable to produce local control and to leave the patient with a substantially better cosmetic result than the alternative—a mastectomy scar—preferably a breast where the effects of treatment could not be detected at all. Thus, in accordance with the working assumption that all tissues infiltrated by tumour or at high risk of infiltration require elevation to a similar dose level, doses were reduced in cautious steps until 1973, when the minimum tumour dose had fallen to 5500 cGy delivered in 25 fractions over 5 weeks.

In spite of the relatively short median follow-up time in patients treated since January 1974 to a dose of 5500 cGy, it was our clinical impression that the local recurrence rate at the reduced dose level was substantially higher, and this led to a review of the records of 243 patients treated between 1967 and 1980.

MATERIALS AND METHODS

This report details the results of the two largest groups, comprising a total of 159 patients. Selection criteria and treatment methods varied considerably in the remainder, rendering meaningful assessment of the results unsatisfactory. The groups comprise 65 patients who between January 1968 and October 1973 received near-identical treatments of 6500 cGy (±3%) in 24–27 fractions over 5–5½ weeks, and another group of 94 patients who between January 1974 and February 1980 received identical treatments of 5500 cGy in 25 fractions over 5 weeks. Up until 1973, patients were treated on the 4 MV linear accelerator. The breast itself was encompassed by two opposing tangential fields, using wedge filters to compensate for tissue curvature and wax to 'build up' areas where tumour was found to be near the surface. Only one field was treated each day and dosage was prescribed to the minimum composite isodose encompassing the volume. The total dose was fractionated over a period of 5–5½ weeks. A separate anterior field was used to irradiate the apex of the axilla, and the supraclavicular fossa and was treated daily. The applied dose to this field was the same as the total minimum breast dose. Since 1973 treatments have been administered on one of the then-new Mobaltron Cobalt units. Technique differed in that both breast fields were treated each day and a posterior axillary field was often used to bring midline axilla dosage to 4500–5500 cGy. While the earlier 6500 cGy contained very few patients with T1 (under 2 cm diameter) primaries, the later 5500-cGy series contained a significant number of patients with stage IIIb disease, 12 of whom received combination cytoxic agents, including intravenous cyclophosphamide, methotrexate, 5 fluorouracil and adriamycin in addition to radiotherapy in their primary management.

Table 1. Composition of the 6500-cGy 1968–1973 series and the 5500-cGy 1974–1980 series according to TNM stage grouping and TNM staging

	6500 cGy	5500 cGy		6500 cGy	5500 cGy
Stages I and II					
Stage I	3(3)	15(15)	T1,N0	3(3)	15(15)
Stage II	39(21)	37(26)	T2,N0	30(19)	27(20)
			T2,N1	9(2)	10(6)
	42(24)	52(41)		42(24)	52(41)
Stages IIIa and IIIb					
			T2,N2	1	3(1)
Stage IIIa	14(1)	19(4)	T3,N0	6	6(3)
			T3,N1	6(1)	6
			T3,N2	1	4
			T2,3,N3	2	2
			T4,N0	1(1)	0
Stage IIIb	9(1)	23(1)	T4,N1	4	7(1)
			T4,N2	2	11
			T4,N3	0	3
	23(2)	42(5)		23(2)	42(5)

There were no M1 cases in either series. (Number who had wedge excision of their primaries prior to irradiation in parentheses).

Relapse and survival in the two groups have been analysed separately. After stratifying according to the size of primary and nodal status, substratification and analysis according to possible explanatory variables such as prior wedge excision, histology, age, menstrual status, referring hospital, etc. was carried out. Wedge excision was considered particularly important in the light of the referral pattern. Usually it had been carried out in cases where the primary had been less than 5 cm diameter and where there was no clinically positive axillary lymphadenopathy (T1,2N0; see Table 1, detailing the case composition of the two series according to TNM stage). Patients referred for radiotherapy after biopsy alone tended to have larger primaries (none less than 4 cm diameter) and often had clinically positive axillary lymphadenopathy.

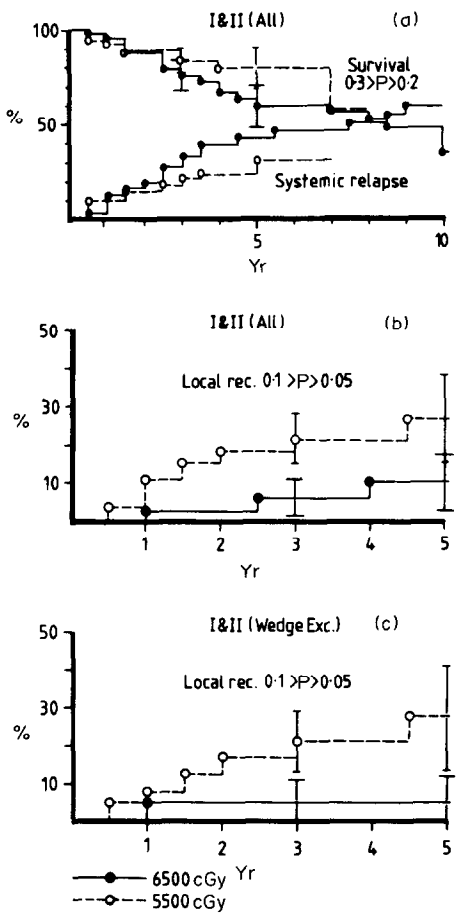

Fig. 1. Actuarial survival, local and systemic recurrence in TNM stage I and II cases (T1,N0, T2,N0,1) (n = 94). (a) Actuarial survival and systemic recurrence in cases treated with 6500 cGy in 5 weeks between 1968 and 1973 (——●——, n = 42), and cases treated with 5500 cGy in 5 weeks between 1974 and 1980 (——o——, n = 52). (b) Actuarial local recurrence in the same patients. 6500 cGy (——●——, n = 42) and 5500 cGy (——o——, n = 52). (c) Actuarial local recurrence in only those stage I and II cases who had the primaries excised before irradiation. 6500 cGy (——●——, n = 24) and 5500 cGy (——o——, n = 41).

Since follow-up times have differed in the two series, results have been presented in actuarial form [2]. Possible differences have been tested using the Log rank test [3].

RESULTS

Tumour control

Five-year actuarial local recurrence was greater in the later series of patients with stage I and II disease, who received the 5500-cGy schedule (26.6 compared to 10%, $\chi^2 = 3.29$, d.f. = 1, $0.10 > P > 0.05$; see Fig. 1b). The difference, which could not be accounted for by any factor other than the treatment itself, was rendered more significant by the fact that this group contained a significantly greater proportion of patients with earlier T1 primaries (Table 1). Indeed, actuarial 5-yr survival was somewhat better in the later series (79 compared to 59.5%, $\chi^2 = 1.379$, d.f. = 1, $0.3 > P > 0.2$; see Fig. 1a). There was also a difference when the two stage I and II groups who had their primaries excised prior to irradiation were compared (27.6 compared to 5%, $\chi^2 = 2.83$, d.f. = 1, $0.10 > P > 0.05$; Fig. 1c). Local control rates in stage I and II cases did not appear to be significantly influenced by the presence of axillary lymphadenopathy (Table 2), but the numbers involved were not great enough to rule out an association.

Table 2. Total number of local recurrences in stage I and II groups according clinical assessment of axilla

	Total	Local recurrence	(%)
T1,2,N0	75	11	(14.8%)
T1,2,N1	19	4	(21%)
	94	15	(16%)

The number of cases with persistent locoregional disease or who developed local recurrence was depressingly high in the two groups of patients with stage IIIa (up to T3,N2) and IIIb disease (any T4 or N3). Persistent disease was less common in the later and somewhat more advanced group, who received 5500 cGy, but 12 of the patients (all with stage IIIb disease) received cytotoxics in addition to radiation. This possible difference was short-lived, and at 18 months following the start of treatment 48% of the later series and 49.7% of the earlier series had active locoregional disease (Fig. 2b). Five-year survival experience was similar in the two groups (32.5 compared to 36.4%, Fig. 2a). A few patients in both the earlier and later groups with stage IIIb disease were also submitted to oophorectomy or artificial menopause induced by radiation, but little benefit was observed in these cases.

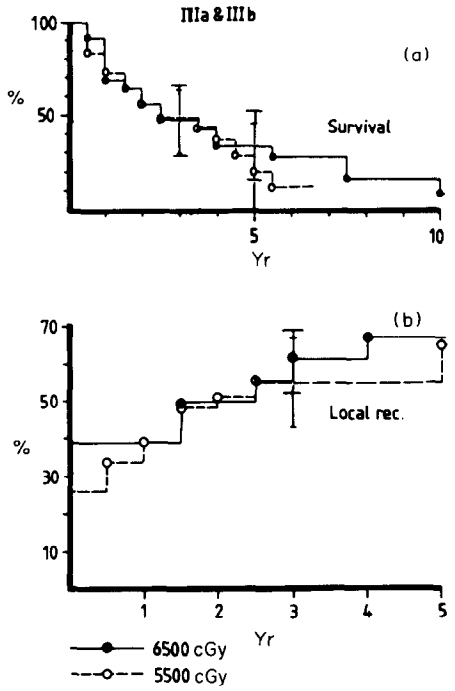

Fig. 2. Actuarial survival and local recurrence in TNM stage IIIa and IIIb cases (n = 65). (*a*) *Actuarial survival.* 6500 cGy (——●——, n = 23) *and* 5500 cGy (——○——, n = 42). (*b*) *Actuarial local recurrence.* 6500 cGy (——●——, n = 23) *and* 5500 cGy (——○——, n = 42).

Cosmetic results

All patients living 18 months or more after 6500 cGy developed gross retraction of the breast due in varying degrees to fatty atrophy, subcutaneous fibrosis and healing of the tumour with cicatrisation. The skin invariably became atrophic, with areas of depigmentation, excessive pigmentation and teliangectasia, especially at sites of entry of the beam and where build-up had been used (Figs. 3 and 4). In contrast, the cosmetic results seen in those patients treated with 5500 cGy and followed for longer than 18 months were excellent, with minimal or no retraction in 80% of cases and skin changes confined only to areas where build-up had been used (Fig. 5). Wedge excision of lesions greater than 2.5 cm in small breasts frequently result in some asymmetry, as seen in Fig. 6.

DISCUSSION

Although this study represents a retrospective comparison in which subgroups were heterogeneous, numbers were small and follow-up times disparate, two important points did emerge. The first concerned evidence of a dose–response relationship for stage I and II disease. Even though the difference between local control rates for the two treatment schedules did not reach significance at the 0.05 level, it is likely that a genuine difference was present because the 6500-cGy group, which had the better local control experience, had a less favourable composition in terms of T and N stage. Since analysis of the data failed to disclose any other cause for the differences in local control rates and cosmetic results, it is likely that differences between the treatment schedules themselves were solely responsible for the observed differences. Overall dose was not the only difference between than two schedules, however. Fractionation and treatment machine also differed. Whereas in the earlier series alternate fields were treated daily using a linear accelerator, both breast fields were treated each day in the later series using tele-Cobalt. Without area or volume correction factors, the midplane C.R.E. value [4] for the 6500-cGy schedule was 2050 ret and for the 5500-cGy schedule 1750 ret. However, while the C.R.E. values for the 'both fields daily' 5500-cGy tele-Cobalt schedule differed little across the volume, the C.R.E. values for the 'alternate fields' 6500 cGy linear accelerator schedule varied considerably across the volume, with figures 10–15% higher than the midplane value at the medial and lateral beam entrance and exit points.

Unfortunately the results obtained cannot be compared directly with the experience of investigators in France [5–9] and in the U.S.A. [11–14]. This is because the techniques employed by these authors differed from ours in that a supplementary dosage of 1500–2000 cGy using teletherapy apparatus, or 2500–3500 cGy using a radioactive implant, was administered to the tumour or lumpectomy site after the breast and glandular drainage areas had been taken to a dose of 4500–5000 cGy in 4½–5 weeks, with the intention of keeping normal tissue damage down to an acceptable minimum.

The dual objective of permanent local control with minimal normal tissue damage appears to have been achieved in 50–80% of cases in the French and American series. Cosmetic results have been reported as excellent (no visible sequelae) in 25–49% and fair (minimal telangectasis and/or retraction) in a further 45–49% [5, 6, 8 11]. The best results have been in women with moderately sized breasts whose tumours were small and excised prior to radiation, while the worst results have been obtained in women with large tumours that have been left *in situ*. In this series, however, the dual objective of local control and good cosmesis was realised in only 50–60% of the patients who received 5500 cGy after wedge excision of small tumours. In patients who received 6500 cGy cosmetic results were uniformly poor, which no doubt reflects the fact that a high dosage was administered to the whole breast. The results may also reflect the fact that the daily

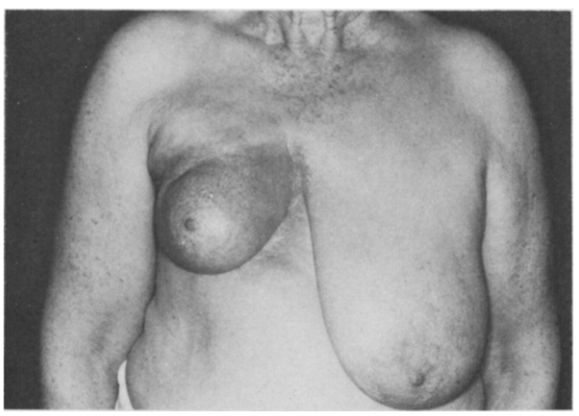

Fig. 3. Late changes 12 yr *after* 6500 cGy *in* 5 weeks.

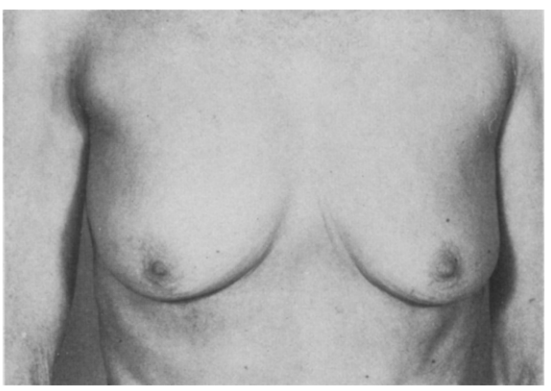

Fig. 5. Five years after wedge excision followed by 5500 cGy *in* 5 weeks. *It is the right breast that has been treated.*

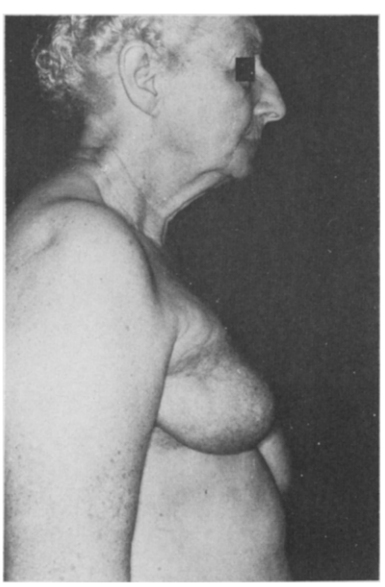

Fig. 4. Lateral view of the same patient.

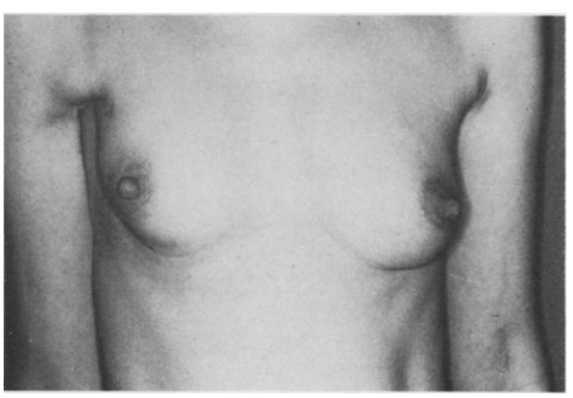

Fig. 6. Wedge excision of a relatively large primary from the axillary tail of the right breast led to asymmetry in this patient.

fractional dose, particularly for the 6500-cGy schedule, was significantly higher than the 185–200 cGy employed by the French and American therapists.

Crude local recurrence rates of between 4.5 and 14% have been reported in patients with T1 and 2,N0 lesions that have been excised prior to radiation [5, 6, 8, 11, 12, 14]. This is similar to our experience using the 6500-cGy schedule but better than our experience with the 5500-cGy schedule. Bataini *et al.* [7] could find no evidence of a dose–response relationship in 67 patients who had had up to 3-cm-diameter primary lesions excised prior to radiation, but the findings of Harris *et al.* [15] were different. Harris *et al.* witnessed no local recurrences in patients in whom ret doses above 1700 had been administered. Our data would tend to suggest that ret doses above 1800 may be necessary, but it must be pointed out that average tumour size was probably greater in our cases than in those of Harris *et al.*

In more advanced cases where the primary had been left *in situ*, higher crude local recurrence rates have been recorded. Of Calle's 394 cases considered unsuitable for wedge excision, and which included 86 with T3,N0 and 105 with T3,N1b lesions, 48% had immediate mastectomy for palpable residual disease and a further 11.4% later developed locoregional recurrence [6]. Pierquin *et al.* [8] experienced local recurrence in 10 of 43 T3,N0,1 cases treated using a radioactive implant to supplement dosage to the primary site, while Amalric *et al.* [9] witnessed local recurrence in 76 of 201 T1,2,3 cases treated using teletherapy alone. In his series of 122 T2,3,N0,1 cases treated by radiation alone Bataini *et al.* [7] used the Ellis formula [16] to estimate that probability of local control was 23% for ret doses under 1950, 30% between 1950 and 2150 and 64% above 2150, and these estimates would appear to be quite compatible with our results.

The second point to emerge from this study concerned the high local failure rate in patients with stage III disease. Persistent locoregional disease was common after both schedules, and at 18 months following treatment, probability of local control was only just over 50%. No dose–response effect could be detected, but this is hardly surprising because groups were small and because several patients in the 5500-cGy group had received prior cytotoxic therapy. Except in the occasional elderly patient, our experience of adjunctive endocrine manipulation was as disappointing as the experience of Bruckman *et al.* [17], but unfortunately too few of our patients received prior cytotoxic therapy to confirm their opinion, which was shared by Balawajder *et al.* [18], that the latter approach has a meaningful beneficial effect. Poor local control rates have been reported for tumours greater than 5 cm in diameter by other investigators too [17–20] and it would appear that doses of the order of 8000–10,000 cGy are necessary to ensure a high probability of local control. However, doses of this magnitude have been reported to cause considerable local morbidity [21]. Combinations of radiation and surgery appear to yield the best local control rates [6, 18, 21, 22], but the outlook in terms of freedom from metastasis and survival for patients with stage IIIb disease still remains abysmal.

CONCLUSIONS

In summary, our results in stage I and II cases were less satisfactory than the experience reported elsewhere. Doses of the order of 6500 cGy in 5–6 weeks appear to be necessary to promote long-term control of small cancer deposits such as those left behind after wedge excision, but which applied to the whole breast result in unwanted soft tissue sequelae. The dual objective of local control with conservation of good cosmetic appearance can be achieved by supplementing dosage to the tumour site alone to a dose of 6500–7000 cGy after the remaining breast and glandular drainage areas have been taken to 5000–5500 cGy. The treatment of both tangential breast fields each day and the limitation of fraction size to levels under 220 cGy appear to be important factors in minimising the chances of producing unwanted soft tissue sequelae.

Our experience in patients with more advanced primaries was as disappointing as others, and it seems that there is very little hope of obtaining local control *and* preserving good cosmetic appearances in patients with primaries larger than 5 cm in diameter. In patients with very locally advanced disease it would appear that a combination of radiation, mastectomy and cytotoxics may offer the most favourable local control results.

Acknowledgements—We wish to thank Mrs Gail Fuller (Mount Vernon Cancer Registry), The Middlesex Hospital Photographic Department and Mrs Elizabeth Denham for their help in preparing this report. We would also like to thank Dr Stanley Dische, Dr Gisela Reinartz and the referees for their helpful comments and criticism.

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