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Original Paper

Lymphatic Relapse in Women with Early Breast Cancer: a Difficult Management Problem

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The aim of this study was to review the ability to control symptoms of regional lymphatic relapse in women with early breast cancer. A retrospective study was made of 759 consecutive women presenting with stage 1 or 2 breast cancer treated by breast conserving surgery and radiotherapy between June 1984 and December 1994, 291 (38.3%) of whom were managed by a policy of observation on the lymphatic pathways. Patterns of lymphatic relapse, relapse management and morbidity caused by recurrent malignancy were reviewed from the case notes. The overall rate of relapse in the ipsilateral axilla and/or supraclavicular fossa was 76/759 (10%) at any time prior to death or last follow-up. 34 of 65 patients who relapsed in the axilla did so despite prior axillary surgery and/or radiotherapy. 41 of 76 patients with regional recurrence presented with symptoms, including lymphoedema, arm pain or sensory motor changes. These symptoms were poorly controlled by palliative surgery, radiotherapy or systemic therapy in 23 cases, including 12 who progressed to arm paralysis. Symptomatic control of patients with regional lymphatic relapse can be very difficult, even in women under regular surveillance in a multidisciplinary breast cancer clinic. © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

For at least two decades, the failure to show a clear overall survival benefit for women treated with local-regional radiotherapy after primary surgery for early breast cancer has strongly influenced management policies. Over this period, radiotherapy recommendations have been based on arguments related to quality of life issues rather than overall survival. Arguments against the routine use of lymphatic radiotherapy, for example, were given added prominence by tragic cases of radiation-induced brachial plexopathy discovered in some U.K. radiotherapy centres [1, 2].

Recent surveys of current U.K. practice confirm these changes in practice [3]. Fear among patients of radiotherapy-induced brachial plexopathy and other morbidities has persuaded some clinical oncologists to confine axillary irradiation to women at elevated risk of nodal relapse. The risk of litigation may also have contributed in unknown ways to changes in practice [4]. It is recognised that 50% of patients with ipsilateral lymphatic relapse have clinical evidence of metastatic relapse and life expectancies limited to a few years. The implication is that the management of lymphatic symptoms is often undertaken in the broader context of metastatic disease. However, the focus on adverse effects of lymphatic radiotherapy has distracted attention from the potential morbidity of recurrent lymphatic disease, which may now be under-rated.

There are relatively few data relating to the morbidity of regional relapse, and these do not present a consistent clinical picture. The possibility that deferred treatment of the lymphatic pathways offers a worthwhile alternative to prophylactic treatment was first raised by the NSABP-B04 study [5]. In this classic trial, 365 women were treated by total

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mastectomy without axillary dissection or lymphatic radiotherapy. Subsequently, 65 (17.8%) required axillary dissection for axillary recurrence, of whom only 4 (1.1% of 365) women failed to gain tumour control at this site. In contrast, a 20 year update of the CRC trial [6], reported the outcome of 1424 women randomised to simple mastectomy alone. 277 (19.5%) developed axillary relapse, of whom 89 (6.3%) died with uncontrolled axillary disease. The number of patients developing axillary relapse in the 1376 women randomised to local-regional radiotherapy was 79 (5.7%), of whom 36 (2.6%) died with uncontrolled axillary disease.

We report a group of women with early stage breast cancer who suffered lymphatic relapse following breast preserving surgery and radiotherapy for early breast cancer. Lymphatic surgery and radiotherapy were withheld selectively in order to minimise treatment-related morbidity. The policy was implemented in 1984, and an interim report in 1992 described a favourable short-term outcome in terms of disease-related morbidity in the axilla and supraclavicular fossa [7]. Longer follow-up of the same group, supplemented by more recently treated patients, now paints a different picture, with cancer-related morbidity, including malignant brachial plexopathy, developing in a small but significant minority.

PATIENTS AND METHODS

759 consecutive women were retrospectively evaluated following treatment with breast conserving surgery and radiotherapy between January 1984 and December 1994. The majority of patients were treated and followed-up in the context of a multidisciplinary breast clinic. The median age of the patients was 56 years (range 25–78) and 229 women were under 50 years of age at presentation. The survivors have now been followed for a median of 72 months.

The treatment policy included complete excision of the primary tumour. All women <50 years and women ≥ 50 years of age with palpable axillary nodes, were recommended a level II/III axillary dissection. Patients in whom recommendations for adjuvant systemic therapy did not rely on pathological lymph node status, and in whom there were no palpably enlarged axillary lymph nodes, were offered observation to the lymphatic pathways. After surgery, radiotherapy to the breast was delivered by tangential fields using an isocentric technique and 6 MV X-rays, with the patient lying supine and both arms abducted at right angles to the trunk. The upper border of the treatment volume encompassed the axillary tail of the breast without any intention to include lower axillary lymph nodes. Between 1984 and 1991 women with >3 pathologically positive axillary lymph nodes were given radiotherapy to the supraclavicular fossa regardless of age; thereafter, this policy was extended to patients with any pathologically positive axillary lymph nodes. Treatment to the supraclavicular fossa involved a direct 6 MV photon field. In patients having axillary radiotherapy as well, the supraclavicular field was lengthened inferiorly and a smaller posterior axillary field was added to raise the dose in the axillary mid-plane. Doses were prescribed as an applied dose to the supraclavicular fossa and a mid-plane dose to the axilla. The standard dose prescription to the reference points in the breast and lymphatic pathways was 50 Gy in 25 fractions given over 5 weeks until 1996. After 1986, a proportion of patients were randomised with informed consent into a radiotherapy fractionation study comparing three alternative schedules; 39 Gy in 13 fractions over 5 weeks versus 42.9 Gy in 13 fractions over 5 weeks versus 50 Gy in 25 fractions over 5 weeks.

Pathologically node positive women <50 years were offered six cycles of adjuvant CMF (cyclophosphamide, methotrexate, 5-fluorouracil) or MMM (methotrexate, mitoxantrone, mitomycin C). Women ≥ 50 years were recommended at least 2 years' adjuvant tamoxifen regardless of prognostic indicators and oestrogen receptor status. Many of these women were subsequently randomised with informed consent into the Cancer Research Campaign trial comparing 2 and 5 years' adjuvant tamoxifen. Few women ≥ 50 years of age received adjuvant chemotherapy over this time period.

Details of lymphatic treatment are summarised in Table 1. 311 women with impalpable nodes did not undergo any form of axillary surgery. 291 of 311 (93.6%) were offered a policy of observation of the lymphatic pathways, with clinical assessment every 3 months for years 1–3, every 6 months for years 3–5 and annually thereafter. The other 20 (6.4%) patients undergoing no axillary surgery were given lymphatic radiotherapy out of protocol, many during 1988. Over the whole period, 28/448 (6.3%) patients received axillary radiotherapy off protocol after axillary surgery, typically when positive axillary lymph nodes were recovered by an operation considered to be less than a level II/III dissection.

Women were encouraged to return to the clinic if symptoms developed between scheduled out-patient visits. Patient records were maintained on an electronic database and updated at each clinic attendance. The case notes of patients recording a relapse at a local, regional or distant site were reviewed for details of primary treatment and clinical features associated with disease. Specifically, any instance of ipsilateral lymphoedema, arm pain, motor weakness or sensory disturbance in the arm or hand were recorded. Symptoms were classified as 'mild' (no intervention required or lasting less than 3 months) or 'severe' (intervention required or lasting >3 months). Data considered inadequate to make any clinical judgement were classified 'not evaluable'. An attempt was made to judge the success in palliating symptoms and signs of lymphatic disease at any time prior to death. Symptoms were scored as 'controlled', 'not controlled' or 'not evaluable'. The management of regional relapse depended on previous treatment and on whether relapse was associated with distant disease. The therapeutic modalities used at relapse to palliate symptoms were recorded. Where appropriate, referrals were made to specialist support services, including a lymphoedema clinic and a pain clinic. Survival analyses were performed using the Kaplan–Meier method.

RESULTS

76 (10%) patients developed lymphatic relapse, 38 in the ipsilateral axilla, 11 in the supraclavicular fossa and 27 in both (Table 2). In 30 (39%), the lymphatic relapse coincided

Table 1. *Details of primary lymphatic treatments in* 759 *patients*

	No RT	RT to SCF	RT to axilla	RT to axilla+SCF	Total
No axillary surgery	291	0	1	19	311
Axillary surgery	356	64	3	25	448
Total	647	64	4	44	759

RT, radiotherapy; SCF, supraclavicular fossa.

Table 2. Pattern of lymph node relapse in 76 women at any time prior to death or last follow-up

Site of nodal relapse	*n*	Concurrent metastases (before nodal relapse or within 1 month of nodal relapse)	Metastases later (more than 1 month after nodal relapse)	No metastases prior to death or last follow-up
All	76	30	30	16
Axilla	38	12	15	11
SCF	11	8	1	2
Axilla and SCF	27	10	14	3

SCF, supraclavicular fossa.

with distant metastases. The primary treatment of these 76 women prior to ipsilateral axillary and/or supraclavicular fossa relapse is summarised in Tables 3 and 4 (27 patients appear in both tables). Table 3 describes 65 patients who relapsed in the axilla (± supraclavicular fossa relapse), and Table 4 describes 38 women who had supraclavicular fossa relapse (± axillary relapse). In Table 3, 29/65 (45%) axillary relapses appeared in patients who had received neither axillary surgery nor axillary radiotherapy at presentation. These represented a subgroup of women ≥50 years of age at presentation without palpable axillary lymph nodes who received only breast radiotherapy and adjuvant tamoxifen after excision of the primary tumour. 34 of the 65 (52%) patients with axillary relapse did so despite previous axillary surgery, of whom 22 had been pathologically node positive at presentation, including 5 who had been prescribed axillary radiotherapy as well. One third (34%) of the whole group had clinical evidence of distant metastases at the time of first axillary relapse. In Table 4, 38 patients relapsed in the supraclavicular fossa, 27 after primary axillary surgery, of whom 22/27 had been axillary node positive at presentation. A further 5 cases relapsed in the ipsilateral supraclavicular fossa despite previous high-dose radiotherapy to this area. Approximately half (18/38) the patients had clinical evidence of distant metastases at the time of supraclavicular fossa recurrence.

41 (54%) of 76 women experienced morbidity associated with cancer recurrence in the axilla and/or supraclavicular fossa at some stage prior to death or last follow-up, (Table 5). The timing of axillary relapse was similar for symptomatic and asymptomatic women, at a median of 32 and 34 months from primary treatment, respectively (range 1–120 months). There were 35 instances of arm lymphoedema and 25 instances of arm pain. 18 women developed some degree of sensory and/or motor deficit in their upper limb, of whom 12 progressed to arm paralysis. The absolute risk of this devastating complication was 12/759 (1.6%).

Regional lymphatic recurrence presented without associated distant metastases in 46/76 (61%) of all patients and in 25/41 (61%) of patients who were symptomatic at relapse or who experienced cancer-related symptoms at some stage prior to death or last follow-up. Treatment of the 25 symptomatic women with isolated regional nodal relapse included axillary surgery (10 women), palliative chemotherapy and/or endocrine therapy (15 women), high-dose radiotherapy (10 women) and low-dose radiotherapy (2 women). Most patients were given several of these treatment modalities, but only 2/41 (5%) women gained complete and permanent control of all symptoms prior to death or last follow-up. Of the 76 women with regional relapse, 56 have died. The median survival after nodal relapse was 16 months. The response to treatment of severe symptoms is shown in Table 6. Overall, 13/55 (24%) severe symptoms (instances of lymphoedema, pain, sensory change and motor loss) were properly controlled by subsequent interventions. Symptoms were poorly controlled by palliative surgery, radiotherapy or

Table 3. Primary treatment of 65 women who presented with axillary (±SCF) relapse prior to death or last follow-up (excludes those with relapse only in SCF)

	n⋆	No axillary RT†	Axillary RT‡
All axillary relapses	65	58	7
No axillary surgery	31	29	2
Axillary surgery	34	29	5

⋆22/65 (34%) associated with metastases at initial relapse, 51/65 (78%) associated with metastases at any time prior to death or last follow-up. †42 received adjuvant tamoxifen; 5 received adjuvant CMF. ‡5 received adjuvant tamoxifen; 2 received adjuvant CMF. SCF, supraclavicular fossa; RT, radiotherapy; CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

Table 4. Primary treatment of 38 women who presented with SCF (± axilla) relapse prior to death or last follow-up (excludes those with relapse only in axilla)

	n	No SCF RT†	SCF RT‡
All SCP relapses	38⋆	33	5
No surgery	11	11	0
Axillary surgery	27	22	5 (3 as sole site relapse)

⋆18/38 (47%) associated with metastases at initial relapse. †25 received adjuvant tamoxifen; 5 received adjuvant CMF. ‡4 received adjuvant tamoxifen; 0 received adjuvant CMF. SCF, supraclavicular fossa; RT, radiotherapy; CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

Table 5. Upper limb morbidity in 41 symptomatic patients with axillary/supraclavicular fossa (SCF) relapse at any time prior to death or last follow-up

	Sites of relapse		
	Axilla only	SCF only	Axilla +SCF
Any symptoms of relapse ($n=41$)	21	1	19
Lymphoedema ($n=35$)	16	1	18
Pain in arm/hand ($n=25$)	11	0	14
Sensory motor changes ($n=19$)	7	1	11

Table 6. *Severity of presenting symptoms (and symptom control) in* 41 *patients with regional relapse*

Symptom	Severity			
	None	Mild	Severe	Not evaluable
Lymphoedema	6	7	25 (3)*	2
Pain in arm/hand	16	4	21 (7)	0
Sensory motor changes	23	4	9 (3)	6

*Severe symptoms controlled by palliative treatment.

systemic therapy in 23 cases, including 12 who progressed to arm paralysis. Seventy per cent of surviving women continued to experience at least one cancer-related lymphatic symptom 3 years after lymphatic relapse. The majority of women who gained symptom control did so within 6 months of developing symptoms and starting palliative therapy.

DISCUSSION

We report a group of 759 women with early stage breast cancer in whom a policy was adopted such that women considered to be at low risk of regional nodal relapse avoided elective adjuvant treatment to the axilla by surgery or radiotherapy, as well as the potential morbidity associated with these modalities. 291 women (38%) avoided primary axillary surgery or radiotherapy. This group of 759 women provides information on the morbidity of regional node relapse and the success of delayed nodal treatment in controlling symptomatic regional recurrence.

Adequate axillary surgery or radiotherapy at the time of breast conserving surgery is known to reduce the risk of regional recurrence to 1–4%. However, there have been many reports on the morbidity of axillary surgery [8–10], axillary radiotherapy [10–13] and combined modality treatment [8–11]. In particular, the impact of radiotherapy-induced brachial plexopathy [1] following adjuvant nodal irradiation has led many clinical oncologists in the U.K. to avoid axillary irradiation in all but those women at high risk of nodal relapse. Historically, regional nodal relapse was not considered to influence overall survival [5] in view of its association with distant metastases. Women with lymphatic relapse were assumed to be salvageable with appropriate local therapy integrated with management of their disseminated disease.

There are very few data in the literature relating to the morbidity suffered by patients as a consequence of lymphatic relapse, regardless of prior treatment, and to the efficacy of measures aimed at controlling symptoms. Recht and colleagues [14] reported the outcome of treatment for regional nodal failure following breast conserving surgery and either axillary dissection or axillary radiotherapy. Sixty-one per cent (11/18) of women with isolated axillary relapse were salvaged, with multiple treatment modalities in many cases. Significant pain or 'other distressing symptoms' were present in 32% (12/38) of the patients with relapse in any regional nodes, but was not described for separate sites of relapse. The CRC data [6], referred to already, suggest that regional control is difficult to obtain, but do not describe specific symptoms associated with relapse.

In our patient group, 41/76 (54%) patients developing lymphatic relapse at any stage prior to death or last follow-up suffered some morbidity as a consequence. In the majority (61%), the nodal relapse preceded distant metastases by at least 1 month. Symptoms attributed to regional relapse were not documented systematically in the case notes according to any international system, but were recorded by the attending clinician according to relative importance at a given clinic attendance. It is very possible, therefore, that our data on the severity of symptoms represent an underestimate of the true morbidity of regional cancer recurrence. We have not attempted to make any quantitative comment on the psychological impact of intractable symptoms, for the same reason. Death seems to have been the only relief from regional disease morbidity in a proportion of symptomatic patients, in marked contrast to the NSABP experience described earlier [5].

These data, considered together with the overall survival benefits for local-regional radiotherapy recently reported [15, 16], prompt us to abandon a policy of observation in any subgroup of patients with early breast cancer, even when regular surveillance is undertaken. Since our previous publication [7] we have recorded a larger number of patients with symptomatic regional relapse, chiefly, we think, because the sample size is larger and the follow-up longer. It is clear that a small minority of patients suffer regional relapse despite elective lymphatic surgery and/or radiotherapy. Future prospects for the management of lymphatic pathways, including sentinel node biopsy [17], may allow better selection of women who do not need axillary treatment as part of initial management.

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