Psychological impact of adjuvant chemotherapy in the first two years after mastectomy

A V M HUGHSON, A F COOPER, C S McARDLE, D C SMITH

Abstract

Psychological symptoms were assessed over two years in a randomised trial of three forms of treatment given to women after mastectomy for stage II breast cancer. The treatments were: three weeks' radiotherapy; one year's adjuvant chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil; and radiotherapy followed by chemotherapy. Analysis of the results on an intention to treat basis showed no substantial differences in depression or anxiety among groups at one, three, or six months after the operation. At 13 months, however, patients who had been allocated chemotherapy had significantly more symptoms, especially depression, than control patients treated with radiotherapy alone. Conditioned reflex nausea and vomiting increased considerably during the second six months of chemotherapy and persisted for up to a year afterwards.

The psychological morbidity of adjuvant chemotherapy could be substantially reduced if courses of treatment were restricted to about six months.

Introduction

Anxiety and depression are common after mastectomy for breast cancer.[1] Mutilating surgery contributes to this morbidity,[2] and in addition the patient has to cope with the suspicion that she has an incurable disease. A recent analysis of 10 000 patients showed that adjuvant chemotherapy reduced the number of early deaths in postmenopausal women by about one sixth and in premenopausal women by about one third.[3] On this basis adjuvant chemotherapy is likely to be used more widely.

Although the extent of physical toxicity associated with the use of adjuvant chemotherapy is well documented, less attention has been paid to the incidence of psychological morbidity.[4,5] We report the results of a detailed evaluation of the morbidity associated with adjuvant chemotherapy.

Patients and methods

Consecutive patients aged under 70 with histologically proved stage II breast cancer were studied over five years. Within the framework of an existing trial of adjuvant chemotherapy after simple mastectomy patients were randomised to receive: (*a*) conventional postoperative orthovoltage radiotherapy (15 fractions over three weeks) to chest wall, axilla, infraclavicular and supraclavicular fossas, and internal mammary region (average tumour dose 37·8 Gy (3780 rads)); (*b*) chemotherapy alone; or (*c*) radiotherapy followed by chemotherapy.

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The chemotherapy regimen was based on that described by Bonadonna *et al* except that all drugs were administered intravenously.[6] Cyclophosphamide (300 mg/m^2), methotrexate (40 mg/m^2), and 5-fluorouracil (600 mg/m^2) were administered on an outpatient basis on days 1 and 8 of consecutive 28 day cycles. Treatment was started within six weeks of mastectomy and continued until recurrence of disease or for one year. Patients allocated to combined radiotherapy and chemotherapy began their course of radiotherapy four to six weeks after the operation; chemotherapy was started four to six weeks after radiotherapy had been completed.

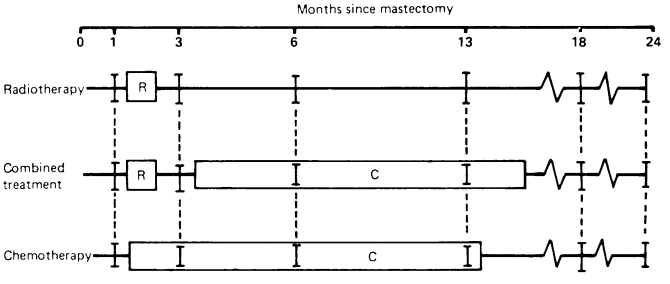
Psychological morbidity was measured with observer rating scales of depression and anxiety (0=absent, 1=mild, 2=moderate, 3=severe) developed by Maguire *et al* to study a postmastectomy population.[7] The Leeds general scales for the self assessment of depression and anxiety and the general health questionnaire were also used.[8,9] The Leeds scales were modified slightly to cover the same period as the general health questionnaire and observer scales—namely, the previous few weeks. Scores on the Leeds scales range from 0 to 18, and scores of seven or above indicate a high probability of clinical depression or anxiety.

Scores on the general health questionnaire range from 0 to 60. The usual threshold for probable psychiatric illness is a score of 12 or above, but the questionnaire contains somatic items such as lack of energy, which might be endorsed by patients with purely physical distress. The severe depression subscale of the questionnaire, which contains specific psychic items such as ideas of suicide, worthlessness, and hopelessness, was therefore analysed separately. Scores on this subscale range from 0 to 21, but there is no recognised threshold score. To determine such a threshold scores obtained a year after mastectomy from an earlier cohort of 44 patients participating in the same chemotherapy trial were examined. With a Maguire depression observer rating of two or above as the criterion for psychological morbidity scores of three or above on the severe depression subscale gave satisfactory discrimination between cases and non-cases. Six of eight cases and 32 of 36 non-cases were correctly classified—that is, the sensitivity was 75% and the specificity 89%.

A simple arbitrary physical symptom score was devised based on the presence or absence of several key symptoms in the month before assessment. These included anorexia, nausea, vomiting, mucosal irritation, hair loss, complete alopecia, skin reaction, pain, and dyspnoea. One point was allotted for each symptom present. The presence of conditioned reflex symptoms was also noted.[10]

The figure shows the times of assessment, which allowed psychological and physical morbidity to be measured before treatment, after radiotherapy, during the course of chemotherapy, shortly before completion of chemotherapy, and five and 11 months after the completion of chemotherapy. Patients receiving chemotherapy were reviewed at the end of the "rest" period—that is, as close as possible to day 28 of each cycle, when physical toxicity was minimal. Patients receiving radiotherapy were interviewed two to three weeks after completion of treatment.

The analysis was performed on an intention to treat basis—that is, all patients were included in the analysis regardless of whether they had relapsed or failed to complete chemotherapy. Statistical tests (two tailed)



Design of trial showing timing of psychological assessments. R=Radiotherapy. C=Chemotherapy. Bars represent times of interview.

were as follows: χ^2 test, Fisher's exact test, and Kruskal-Wallis analysis of variance for comparison among groups; and McNemar's χ^2 test for correlated proportions and the binomial test for comparison within groups.

TABLE I—*Number of patients who refused further interviews or further chemotherapy, relapsed, or died during study*

	Radiotherapy	Chemotherapy	Combined treatment
Agreed to participate	24	27	23
Refused further interviews	1	5	0
Refused further chemotherapy (but not further interviews)		3	3
Recurrence:			
Local	0	4	0
Systemic*	10	4	1
Died	9	3	3

*A few patients who developed systemic relapse died before they could be reinterviewed.

TABLE II—*Number of patients receiving each type of treatment during study*

Months since operation	Radiotherapy	Chemotherapy	Combined treatment
1	24	27	23
3	23	25	23
6	23	24*	23
13	21†	24*	22
18	18†	21	20
24	14	19	20

*Sample size one less for self rating scales as one patient felt too depressed to complete them. †Sample size two less for self rating scales as patients felt too unwell physically to complete them.

The prevalence of psychological morbidity is shown in tables III and IV. The prevalences of anxiety and depression measured by Maguire's observer scales at one month after mastectomy in the group treated with radiotherapy alone were 33% and 38% respectively, both falling to 14% at one year. The prevalences of anxiety and depression in the two groups treated with chemotherapy were similar at one, three, and six months. At 13 months, however, both anxiety ($p<0·05$) and depression ($p<0·1$) were significantly greater in these two groups.

At one month psychological morbidity was slightly more evident on all self rating scales in patients allocated to combined treatment. At 13 months both groups allocated to chemotherapy showed greater psychological morbidity compared with the control group treated with radiotherapy alone. This excess was significant on both the Leeds depression and severe depression scales ($p<0·03$).

During the second year the prevalence of psychological morbidity decreased in both groups allocated to chemotherapy. In contrast, at 18 months psychological morbidity in the group treated with radiotherapy alone apparently increased. Examination of individual scores showed, however, that virtually all the psychological morbidity in that group occurred in patients with systemic relapse. On the Maguire scales all five patients with systemic disease scored positively for depression or anxiety compared with none of the 11 disease free patients ($p<0·001$). Only one of the five relapsed patients was still alive at 24 months.

Physical symptom scores among groups (table V) were similar up to three months after operation but at six and 13 months were significantly higher ($p<0·001$) in the two groups treated with chemotherapy. At 18 months the trend was reversed ($p<0·1$), reflecting the systemic relapse in the group treated with radiotherapy alone.

Three months after the operation two patients who had received radiotherapy alone and three who received chemotherapy alone experienced conditioned reflex nausea without vomiting. Thereafter this problem stopped in patients who had received radiotherapy alone. At six months in both groups allocated to chemotherapy 15 of 46 patients (33%) had conditioned reflex nausea and 6 (13%) conditioned reflex vomiting. At 13

TABLE III—*Number (%) of patients with psychological morbidity as assessed by Maguire observer rating scales (score ≥1) and Leeds self rating scales (score ≥7)*

	Anxiety			Depression		
Months since operation	Radiotherapy	Chemotherapy	Combined treatment	Radiotherapy	Chemotherapy	Combined treatment
			Maguire observer rating scales			
1	8 (33)	10 (37)	8 (35)	9 (38)	13 (48)	9 (39)
3	6 (26)	7 (28)	8 (35)	8 (35)	10 (40)	7 (30)
6	5 (22)	7 (29)	6 (26)	3 (13)	4 (17)	7 (30)
13	3 (14)*	12 (50)	10 (45)	3 (14)†	11 (46)	8 (36)
18	5 (28)	7 (33)	3 (15)	3 (17)	5 (24)	2 (10)
24	0	2 (11)	4 (20)	1 (7)	4 (21)	1 (5)
			Leeds self rating scales			
1	4 (17)	5 (19)	7 (30)	2 (8)	3 (11)	6 (26)
3	5 (22)	6 (24)	5 (22)	2 (9)	4 (16)	3 (13)
6	5 (22)	5 (22)	7 (30)	2 (9)	4 (17)	4 (17)
13	2 (11)	3 (13)	8 (36)	0‡	5 (22)	6 (27)
18	2 (13)	3 (14)	2 (10)	2 (13)	1 (5)	1 (5)
24	2 (14)	3 (15)	5 (25)	0	2 (11)	2 (10)

*$p<0·05$; †$p<0·1$ (χ^2 test 2 df). ‡$p<0·03$ (Fisher's exact test on combined data from groups who received radiotherapy and combined treatment because of small expected frequencies).

Results

Of 79 patients invited to participate in the study, five (four in the group treated with radiotherapy and chemotherapy combined and one in the group treated with chemotherapy alone) refused to do so. The mean age of the remaining 74 patients was 52·4 years. The social class distribution (Registrar General's classification) showed that there were two patients (3%) in class I, 23 (31%) in class II, 37 (50%) in class III, eight (11%) in class IV, and four (5%) in class V. Of the 74 patients, 24 were allocated to receive radiotherapy, 27 to receive chemotherapy, and 23 to receive combined treatment. The treatment groups were similar in respect of age, social class, marital state, and previous psychiatric history.

During the study six patients refused further psychiatric interviews (table I). A further six refused to continue chemotherapy but agreed to further interviews. Four patients developed local regional recurrence and 15 (20%) disseminated disease. Nine (38%) of the 24 patients undergoing radiotherapy had died by 24 months compared with only six of 50 (12%) in the two groups receiving chemotherapy ($p<0·03$). Table II gives sample sizes at each time interval after the operation. (Further details of the patient samples are available from the authors on request.)

TABLE IV—*Number (%) of patients with psychological morbidity as assessed by general health questionnaire (score ≥12) and severe depression self rating scales (score ≥3)*

Months since operation	Radiotherapy	Chemotherapy	Combined treatment
	General health questionnaire		
1	5 (21)	7 (26)	8 (35)
3	9 (39)	8 (32)	6 (26)
6	6 (26)	4 (17)	8 (35)
13	3 (16)	7 (30)	9 (41)
18	3 (19)	1 (5)	3 (15)
24	2 (14)	1 (5)	3 (15)
	Severe depression subscale		
1	1 (4)	2 (7)	4 (17)
3	2 (9)	4 (16)	2 (9)
6	3 (13)	2 (9)	4 (17)
13	0*	5 (22)	6 (27)
18	0	0	2 (10)
24	0	1 (5)	3 (15)

*$p<0·03$ (Fisher's exact test on combined data from groups who received radiotherapy and combined treatment because of small expected frequencies).

TABLE V—*Mean scores for physical symptoms*

Months since operation	Radiotherapy	Chemotherapy	Combined treatment
1	0·2	0·2	0·3
3	3·2	3·4	3·1
6	0·4*	3·8	3·6
13	0·7*	3·7	3·8
18	1·3†	0·3	0·3
24	1·0	0·1	0·3

*p<0·001; †p<0·1 (Kruskal-Wallis test).

months in those 46 the prevalence of conditioned reflex nausea and vomiting had increased considerably, the corresponding figures being 27 (59%) (p<0·002) and 16 (35%) (p<0·01). Furthermore, conditioned reflex symptoms persisted after treatment had stopped. At 18 months 11 of 41 patients (27%) had conditioned reflex nausea and 3 (7%) conditioned reflex vomiting. Even at 24 months seven of 39 (18%) still had conditioned reflex nausea.

At the assessment at six months patients treated with radiotherapy and chemotherapy combined were asked to compare the two forms of treatment. All but two of the 23 patients considered the adverse effects of chemotherapy to be worse than those of radiotherapy (p<0·001).

Discussion

Adjuvant chemotherapy in women with early breast cancer might be expected to induce greater morbidity during treatment but also perhaps to prevent it at a later stage by delaying relapse. Previous studies have tended to rely on single estimates of psychological morbidity during treatment. Our own preliminary results were in this category and were confined to an earlier, smaller sample of survivors free of disease with incomplete follow up. In patients completing treatment with chemotherapy excess psychological morbidity, notably depression, seemed to persist for a year after treatment.[11]

Two other randomised controlled studies in the United Kingdom are known to us. Palmer *et al* found that nine of 24 patients (37%) who had completed a six month course of chemotherapy with five drugs reported severe disruption to their lives compared with two of 21 (9%) receiving the single agent chlorambucil.[12] Maguire *et al* judged that 20 of 26 patients (77%) receiving cyclophosphamide, methotrexate, and 5-fluorouracil for one year had experienced anxiety or depression compared with nine of 18 (50%) receiving no treatment and that of 15 patients receiving melphalan, 4 (27%) had experienced anxiety and 5 (33%) depression, though some patients received psychiatric treatment during a counselling project.[13-15]

As a result of the high prevalence of morbidity reported in these studies, and the failure to show appreciable benefit in terms of survival, serious reservations have been expressed in the United Kingdom about the use of adjuvant chemotherapy.[12 16] In the United States, where adjuvant chemotherapy has been more widely adopted as routine treatment, the need for quantitative psychosocial studies has been emphasised recently.[17] The lack of controlled studies has presumably been because withholding adjuvant chemotherapy has been thought to be unethical. In an uncontrolled study Meyerowitz *et al* found that up to 40 of 50 patients (80%) receiving cyclophosphamide, methotrexate, and 5-fluorouracil for a year reported emotional distress.[18] Follow up indicated that quality of life was often impaired for several months after treatment.[19]

The present study failed to show appreciable differences in anxiety or depression up to six months after mastectomy. By that time, however, patients receiving chemotherapy alone or in combination had suffered more physical and conditioned reflex symptoms than those allocated radiotherapy alone. Furthermore, patients receiving combined treatment were already almost unanimous in stating that chemotherapy was the more unpleasant treatment. By 13 months nearly all patients allocated radiotherapy alone seemed to have recovered emotionally while depression, anxiety, and conditioned reflex symptoms had risen to a peak in both groups treated with chemotherapy. At 13 months about a quarter of the patients allocated chemotherapy alone or in combination showed evidence of clinical depression as judged by both the Leeds and severe depression scales. About one third had conditioned reflex vomiting.

During the second year those patients who had received radiotherapy alone and who remained free of disease seemed to fare well emotionally, unlike those who developed systemic disease. Anxiety and depression decreased in the groups allocated to chemotherapy; systemic relapse, a rare event in those groups, had no perceptible impact on morbidity. Depression and anxiety due to adjuvant chemotherapy may persist slightly after treatment has finished, and conditioned reflex symptoms undoubtedly do so. Such symptoms, however, are probably counterbalanced by the distress, both emotional and physical, associated with systemic relapse in patients treated with radiotherapy alone.

The results of this study therefore indicate that adjuvant chemotherapy has its main psychological impact during the second six months of intended treatment, but the period of observation was limited arbitrarily to two years. It is not absolutely certain that the psychological cost to the patient and her family over her lifetime due to adjuvant chemotherapy exceeds that due to radiotherapy alone. A large scale randomised study to answer this question has not been performed and would present formidable problems: detailed lifetime follow up would be necessary. Meanwhile we can only speculate about what might occur beyond two years. The present study indicates that systemic relapse induces psychological morbidity; Silberfarb *et al* reported a similar finding.[20] Not all treatment for systemic relapse, however, induces morbidity. Baum *et al* found that chemotherapy given for systemic relapse enhanced wellbeing, despite physical toxicity, provided that remission occurred; if remission did not occur the patient's suffering could be limited by stopping treatment.[21] Thus the psychological effects of chemotherapy may vary according to the stage of disease at which it is prescribed. Many complex biological, psychosocial, and ethical questions remain unanswered.

How can the excess psychological morbidity due to adjuvant chemotherapy be modified? Psychological techniques such as relaxation treatment have been reported as reducing conditioned reflex symptoms in some patients with cancer,[22 23] but extra resources are required. It is not yet certain whether depression caused by adjuvant chemotherapy responds to treatment, though patients with breast cancer suffering from depression generally benefit from counselling and referral for psychiatric treatment.[15] Recent studies have shown that reducing the duration of adjuvant chemotherapy from 12 to six months does not compromise survival benefit.[24] In the absence of a clear advantage for more prolonged chemotherapy our results suggest that on psychological grounds adjuvant chemotherapy should be restricted to six months.

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Childhood respiratory infection and adult chronic bronchitis in England and Wales

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Abstract

The high mortality from chronic bronchitis in England and Wales and the excess of urban over rural mortality are unexplained. On dividing England and Wales into 212 local authority areas a strong geographical relation was found between death rates from chronic bronchitis and emphysema in 1959-78 and infant mortality from bronchitis and pneumonia during 1921-5. It was concluded that this relation provided strong evidence of a direct causal link between acute lower respiratory infection in early childhood and chronic bronchitis in adult life. Regression analysis suggested that infection in early childhoood had a greater influence than cigarette smoking in determining the geographical distribution of chronic bronchitis. National time trends reflected the influence of both factors.

Chronic air pollution in adult life may be less important a cause of chronic bronchitis than previously supposed.

Introduction

Britain has a higher mortality from chronic bronchitis than any other country in western Europe.[1] This cannot be explained by international differences in environmental influences such as cigarette smoking and atmospheric pollution, nor by differences in death certification practices.[2] The excess of urban over rural mortality and morbidity from bronchitis, which is characteristic of Britain, is also unexplained.[3]

Reid and others conjectured that respiratory disease in childhood was a cause of chronic bronchitis in later life.[4-6] Recent findings have shown that bronchiolitis, bronchitis, and pneumonia in infancy lead to persisting damage to the airways during childhood, with cough, wheeze, bronchial reactivity, and impaired ventilatory function.[7-10] In the long term follow up of a national sample of British children born in 1946 young adults who had had one or more lower respiratory infections before 2 years of age had a higher prevalence of chronic cough.[11,12] There is, however, no direct evidence to link respiratory infection during childhood with clinically established chronic bronchitis in adult life.

We have examined the geographical relation between past infant death rates from lower respiratory tract infection and current adult mortality from chronic bronchitis in England and Wales. We have also analysed the time trends in mortality from chronic bronchitis over the past 40 years.

Methods

The Office of Population Censuses and Surveys made available extracts from all death certificates in England and Wales during 1959-78. Our previous analysis of these data in relation to past infant mortality was based on the 11 years 1968-78,[13] the period covered by the eighth revision of the International Classification of Diseases (ICD). For this analysis we added data on four selected causes of death during 1959-67. Mortality rates at ages 35-74 years were calculated for each sex and each local authority area grouped according to boundaries before 1974. For 1968-78 rates were based on data from the 1971 Census, while for 1959-67 data from the 1961 Census were used. Rates were expressed as standardised mortality ratios. We used published mortality rates[14] for 1941-80 to analyse the time trends of chronic bronchitis and emphysema (ICD codes 106 b,c, 113 (5th revision); 501-502, 527 (6th revision); 501-502, 527.1 (7th revision); 490-492 (8th and 9th revisions)).

In England and Wales numbers of infant deaths by specific cause were published only from 1921, and this analysis is based on the years 1921-5. We divided causes of infant deaths into five groups using Woolf's classification[15]—congenital, bronchitis and pneumonia, infectious diseases, diarrhoea, and others.

We compared adult mortality (1959-78) with infant mortality (1921-5) in the four main geographical groups used by the Registrar General since 1911—that is, county boroughs (larger towns), London boroughs, urban areas (metropolitan boroughs and urban districts) within counties, and rural areas. These groups divide England and Wales into 212 local authority areas, comprising 80 county boroughs, 15 London boroughs, 59 urban areas, and 58 rural areas.[13]

We used correlation coefficients, regression analysis, and scatter plots to examine the relation between different causes of adult and infant deaths. The coefficients are influenced by the numbers of deaths as well as by the strength of the relation. During 1921-5 there were 291 082 infant deaths, 127 796 in the first month of life (neonatal) and 163 286 thereafter (postneonatal). Death was attributed to bronchitis and pneumonia in 61 770.

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