Survival of patients with breast cancer attending Bristol Cancer Help Centre

F. S. BAGENAL D. F. EASTON E. HARRIS C. E. D. CHILVERS
T. J. MCELWAIN

The Bristol Cancer Help Centre (BCHC) was set up in 1979 to offer various alternative therapies and treatments for patients with cancer. It attracted much public interest and a high demand for its services—and profound medical scepticism. In a study beginning in 1986 of 334 women with breast cancer attending the centre for the first time between June, 1986, and October, 1987, information about the diagnosis was obtained from case notes. Controls were a sample of 461 women with breast cancer attending a specialist cancer hospital or two district general hospitals. The same information was obtained for the control group as for the BCHC group. All patients have been followed up to June, 1988. 85% of patients with breast cancer attending the BCHC were aged under 55 at diagnosis. More than half had experienced recurrence of their disease before entry. For patients metastasis-free at entry, metastasis-free survival in the BCHC group was significantly poorer than in the controls (relapse rate ratio 2·85). Survival in relapsed cases was significantly inferior to that in the control group (hazard ratio 1·81). For cases metastasis-free at entry to the BCHC there was a significant difference in survival between cases and controls, confirming the difference in metastasis-free survival. There was no significant difference in survival or disease-free survival between the cancer hospital controls and other controls.

Lancet 1990; **336**: 606–10.

Introduction

Interest in and use of alternative medicines and practices for the treatment of cancer has been growing for several years despite lack of any scientific evidence for anti-tumour effects. Most cancer specialists are not happy to recommend "alternative" therapy, although some take the view that it is at least harmless. Countries differ in their attitudes to alternative medicine in state health services. For instance, in France complementary medicine attracts the subsidy accorded to allopathic medicines[1] while in the UK complementary medicines are not available on National Health Service prescriptions although doctors may recommend practitioners of alternative therapies so long as they themselves retain overall responsibility for the patient. Clearly what is needed is a scientific evaluation of the efficacy of the regimens now being used by increasing numbers of people.

Alternative cancer regimens tend to be based on three notions—that "detoxification" leads to a better quality of life and possible cancer regression (this being the basis of the many diets supposed to have an anti-tumour effect); that the immune system can be stimulated and that this will lead to an anti-tumour effect; and that a holistic approach, seeking a harmonious balance between the patient's mind, body, and spirit, will be beneficial.

The Bristol Cancer Help Centre (BCHC) was set up in 1979 to offer alternative treatments for patients with cancer. The stringent "Bristol diet" of raw and partly cooked vegetables with proteins from soya and pulses attracted much public interest and a high demand for the services of the centre—and deep medical scepticism.[2] The ideology of the BCHC is that the cancer patient can contribute to the healing process in a positive, active way. The diet, though still a central part of the treatments on offer, has become more palatable and adherence to it is now tailored to the individual's needs and state of health rather than to his or her willpower. The centre also offers counselling, "healing", and alternative therapies claimed to enhance quality of life and help to develop a positive attitude to cancer. Patients may initially attend the BCHC for a week-long course or for a single day.

This study began in June, 1986. BCHC staff and patients felt a need to validate scientifically the results they felt had been achieved. They invited a team of doctors and scientists (T. J. McE., Lord McColl, Sir Walter Bodmer, C. E. D. C., and Dr Peter Maguire) to discuss how this could be done. Two studies were proposed, this one and one that evaluated quality of life. Both the staff and the patients at the centre and the patients' consultants have cooperated fully. The study is restricted to women with breast cancer attending the centre for the first time; one-third of all BCHC clients have a diagnosis of breast cancer.

Patients and methods

Cases

BCHC patients are designated "cases". Eligible cases conformed to the following criteria: attending for the first time as either a daily or weekly patient at the BCHC; diagnosed in the UK and since Jan 1, 1979; age under 70 at diagnosis; and having a single invasive primary cancer of the breast. Women with bilateral synchronous tumours were ineligible, though patients with subsequent, recurrent tumours in either breast were eligible.

Eligible patients were selected from the lists of those attending the BCHC daily or weekly between June 1, 1986 and Oct 31, 1987. They were interviewed at the BCHC and consent was obtained for access to their notes. Copies of the registration forms used at the BCHC were then sent to the Institute of Cancer Research where details of disease and treatment, the names of the treating consultants, and the use of alternative treatments were abstracted. These consultants were asked to supply the hospital notes, from which full clinical data were collected on the diagnosis, treatment, and history up to the date of first attendance at the BCHC. 81% of

ADDRESSES: **Section of Epidemiology, Institute of Cancer Research, Sutton, Surrey SM2 5NG, UK** (Prof C. E. D. Chilvers, MSc*, F. S. Bagenal, BSc, D. F. Easton, MA), **Bristol Cancer Help Centre, Grove House, Cornwallis Grove, Clifton, Bristol** (E Harris, MSc); **and Section of Medicine, Institute of Cancer Research and Royal Marsden Hospital, Sutton, Surrey** (Prof T J McElwain, FRCP) Correspondence to Ms F. S Bagenal

* Present address Department of Public Health Medicine and Epidemiology, University of Nottingham Medical School, Queen's Medical Centre, Nottingham

cases had been diagnosed from 1984 onwards and 69% were aged less than 50 at diagnosis.

Controls

To be eligible a control had to conform to the same criteria as the cases but must not have attended the BCHC. Controls were drawn from the Royal Marsden Hospital RMH (a specialist cancer hospital) and two district general hospitals (DGH). At RMH controls were identified in the breast cancer database. They were selected by age (up to 50, 50 and over) and year of diagnosis (1979–83, 1984 onwards). A random sample of hospital numbers was drawn for the four strata defined in this way with sampling fractions such that roughly equal numbers of controls and cases were drawn. Notes were obtained as for the cases. Crawley Hospital was selected as a typical DGH, and a random list was drawn up that reflected the age and date of diagnosis distributions at the BCHC. Case notes were obtained as before. Because there were insufficient controls for patients diagnosed from 1984 onwards and under 50 at diagnosis, a listing of all controls fitting these criteria was generated by the Thames Cancer Registry for a second DGH (Royal Surrey County Hospital, Guildford), and all were included.

Follow-up

Cases were followed up annually. Clinical details of recurrence and treatment since a defined date (date of last follow-up or initial data collection at BCHC) were entered onto a form sent to treating consultants. Should a case have abandoned conventional treatment her general practitioner was sent the form to complete. Cases were sent an annual questionnaire asking about use of alternative therapies and diets. Cases and controls were followed up to June 1, 1988. Cases and controls lost to follow-up were flagged in the NHS Central Register. Dates of death of cases or controls known to have died but with unknown date of death were supplied by the central register.

Computerisation of records and quality control

Data on the forms for consent and BCHC registration, the clinical form completed on receipt of the hospital notes, and the clinical follow-up and death forms were entered onto computer via the COMPACT package.[3] This package has a facility for entering both single forms (eg, initial patient data) and multiple follow-up forms and has an output facility designed to give easy access to latest follow-up information or first occurrence of any event plus user-defined checks to prevent illogicalities in dates and in related variables such as staging. Extensive checking with original data was done.

Survival analysis

Our main aim was to compare survival and metastasis-free survival in patients treated at the BCHC and in the controls. There are two main potential sources of bias in this non-randomised study. The BCHC and control groups may differ with respect to known prognostic factors such as T and N stage. To allow for possible imbalances we have used Cox regression,[4] in which the risk of death (or recurrence) can be related to several prognostic factors simultaneously; each factor is assumed to act multiplicatively, and the effect of each factor (including BCHC attendance) is expressed in terms of a death rate ratio (or hazard ratio).

The second difficulty is that patients enter the BCHC from a few weeks to several years after diagnosis and are only "at risk" from the date of entry to the BCHC. The controls, however, are followed up from their date of diagnosis. The principal method used was to analyse treatment group as a time-dependent covariate, which is unknown for cases up to the time of BCHC entry. This allows a more efficient analysis of relapse-free survival and of overall survival in patients with metastatic disease at BCHC entry. It is not, however, straightforward to analyse overall survival in cases initially disease-free in this way, because they must be compared with control patients relapse-free after the same interval from diagnosis. This entails different BCHC patients being compared with a different, but overlapping, subset of controls. The second method is to begin the analysis at a fixed time after diagnosis, the "landmark" method. Individuals presenting at BCHC after that time are excluded. Since most women presenting at the BCHC without metastatic disease do so within 1 year of diagnosis (see below) this time point has been used in the landmark analyses. This technique can be used for the analysis of both relapse-free survival, and overall survival in patients without metastatic disease at entry. For the analysis of survival in patients with metastatis at entry, analysis is started one year after the date of metastasis. This straightforward method of analysis allows simple survival curves to be produced, but is inefficient because individuals relapsing (or dying) within 1 year of diagnosis, and individuals in the BCHC group not presenting at the BCHC within 1 year of diagnosis do not contribute. The third type of analysis was one in which cases and controls have been individually matched. For cases metastasis-free at BCHC entry, controls were matched on T stage, N stage, age at diagnosis (under 35, 35–44, 45–54, 55+), and year of diagnosis. The control with the date of diagnosis nearest to that of the case was chosen. For cases relapsed at BCHC entry, controls were matched on year of relapse and time from primary diagnosis to relapse (0, <2 years, 2–4 years, 4 years+), and the control with the nearest date of relapse to that of the case was chosen.

A further potential bias relates to the recorded date of relapse. A relapse will usually be diagnosed using tests carried out as a result of symptoms (such as bone pain) and some time will elapse between first symptoms and the definitive date of relapse (usually no more

TABLE I—FORMATION OF BCHC STUDY GROUP

Consent to study	No	Ineligible because of	No
Attending	459	Previous cancer	1
Missed by interviewer	17	Bilateral	6
Refused to take part	29	Diagnosed pre-1979	23
Not known	6	Diagnosed abroad	3
		In-situ cancer only	15
Total consenting to study	407 (88·7%)	Age over 70	7
Consultant refused	5	Other*	13
Total potentially eligible	402 (87·6%)	Total ineligible	68
		Total in study	334

*Revoked consent 1, insufficient information 3, notes untraceable 2, consultant refusal to sent notes 2, refused treatment, no pathology 5

TABLE II—CHARACTERISTICS OF BCHC SAMPLE

	No (%*)
Age	
<45	176 (52·7)
45–54	110 (32·9)
55–64	42 (12·6)
65–69	6 (1·8)
Current smoker (yes/no)	23 (6·9)/310 (93·1)
Reported family history of cancer (yes/no)	228 (68·3)/106 (31·7)
Reported mother with cancer (yes/no)	70 (21 0)/264 (79·0)
Alternative therapies used at entry	
Any	134 (40 9)
Diet	75 (22·9)
Healing	60 (18·3)
Homoeopathy	22 (6·7)
Iscador (mistletoe extract)	16 (4·9)
Acupuncture	10 (3·1)
Reflexology	5 (1·5)
Meditation	4 (1·2)
Yoga	2 (0·6)
Other	34 (10·4)
Disease status at entry to BCHC	
Recurrence-free	148 (44·3)
Local recurrence only	47 (14·1)
Metastatic disease	139 (41 6)

*Answers not recorded for all patients, hence varying denominators

than 2–3 weeks). Some cases may attend the BCHC because of symptoms of relapse (perhaps instead of going to their doctor), although relapse had not been diagnosed at that time. Such cases would seriously bias the analysis of relapse-free survival, and to avoid this possibility, the date of entry for cases is taken to be 3 months after their actual BCHC entry. Thus cases relapsing in this 3-month period are taken to be "relapsed cases" rather than relapse-free cases.

Results

Response rates

459 cases were identified at the BCHC between June, 1986, and October, 1987. For various reasons 57 of these potentially eligible patients did not take part. Of the remaining 402, 68 were found to be ineligible once the notes were received, leaving 334 (table I). 244 RMH controls and 217 DGH controls were included. For all the controls access to the notes was allowed.

Follow-up

For cases, consultant response to the first year of follow-up (ie, consultants who returned the follow-up completed) was 98%, the remaining 5 reflecting loss or unavailability of case notes. 1 case and 1 control have been lost to follow-up and have been flagged by the NHS Central Register. 6 cases and 1 control have emigrated and the date of these events is awaited from the central register. Cases and controls have been followed up until June 1, 1988, for this analysis. All controls have been followed up until this date but information is unavailable for 3 cases.

Bristol cases

86% of patients with breast cancer attending the BCHC were aged under 55 at diagnosis (table II). 7% were current smokers at entry; of the 310 who said they did not smoke 201 (65%) had never smoked and 109 had given up. Of the ex-smokers 101 (93%) had smoked for 5 or more years. 68% reported a close relative with cancer, 21% having a mother with cancer. 41% were using some alternative therapy at the time of their first visit to the BCHC. By the first visit to the BCHC, 56% had experienced disease recurrence (local in 14%, metastatic in 42%).

Cases attending the BCHC for the first time during a one year period were selected and return visits within a year were counted. 83 (43%) of the 195 day visitors, and 32 (30%) of the 107 attending for the first time for a one week course returned at least once within the year.

Comparison of cases and controls

Even though controls were broadly divided by age into less than and greater than 50 stratification in 10-year age bands revealed that 86% of cases were aged less than 55 compared with 73% of controls (table III). This difference in age is reflected in menopausal status, more cases (65%) than controls (54%) being premenopausal. Cases and controls were similar with respect to history of oophorectomy, but 10% of cases and 15% of controls had had a hysterectomy.

All cases and controls were TNM staged, and initially cases and controls were not matched on stage of disease. The only differences between RMH and DGH controls was in respect of T and N stage at diagnosis (table III), RMH controls being more likely to be T3–4 and less likely to be T1 than the other controls and more likely to be node positive. Clinical staging was similar in the cases and controls, being stage I in 56% and 56%, respectively, stage II in 16% and 20%, stage III in 25% and 22%, and stage IV in 3% and 2%.

Surgical treatment of the primary disease tended to be more extensive for cases than that for controls, mastectomy being more common in the cases (43% *vs* 36%).

Metastasis-free survival

Metastatic disease developed in 46 BCHC patients who had been metastasis-free at entry. Of these, 13 were within 3 months of BCHC entry. Our analysis began 3 months from BCHC entry (see Methods), leaving 33 relapses to be analysed. Among 471 controls 134 relapses have occurred. Relapse-free survival is slightly poorer in RMH controls than in the DGH controls (hazard ratio after adjusting for other prognostic factors 1·32; NS). The Cox regression analysis, with BCHC attendance as a time-dependent covariate, is shown in table IV. After allowance for T and N

TABLE III—COMPARISON OF CASES AND CONTROLS

—	Cases (n=334)	Controls RMH (n=244)	Controls DGH (n=217)	Controls All (n=461)	p*
Age:					<0·001
≤45	176	82	85	167	
45–54	110	84	84	168	
55–64	42	58	46	104	
65–69	6	20	2	22	
Menopausal status					0·001
Pre	202	118	112	230	
Peri	29	15	16	31	
Post	81	98	71	169	
NK	22	13	18	31	
Oophorectomy:					NS
Yes	5	9	4	13	
No	322	234	206	440	
NK	7	1	7	8	
Hysterectomy.					0·05
Yes	33	38	31	69	
No	293	205	183	388	
NK	8	1	3	4	
Side of tumour:					NS
Left	175	129	100	229	
Right	159	115	117	232	
Stage at diagnosis:					
T1	99	48†	61	109	NS§
T2	146	134	111	245	
T3–4	83	62	35	97	
Tx	6	0	10	10	
N0	232	140‡	155	295	0·08§
N1	90	87	53	140	
N2–3	12	17	9	26	
M0	325	240	212	452	NS
M1	9	4	5	9	
Stage·					NS§
I	187	123	133	256	
II	53	54	39	93	
III	85	63	40	103	
IV	9	4	5	9	
Surgical treatment of primary:					0·07
Biopsy only	26	7	18	25	
Wide local excision	156	138	118	256	
Mastectomy	142	87	77	164	
Aspiration only	10	12	4	16	
Radiotherapy					NS
Yes	222	174	153	327	
No	111	68	62	130	
NK	1	2	2	4	
Adjuvant therapy·					NS
Yes	143	101	102	203	
No	191	143	115	258	

*χ^2 tests (degrees of freedom 1, 2, or 3) for homogeneity or difference in trends
†Test for difference in trends between RMH and other controls (p<0·05)
‡Test for difference in trends between RMH and other controls (p<0·01)
§Homogeneity or difference in trends

TABLE IV—COX REGRESSION ANALYSIS OF METASTASIS-FREE SURVIVAL

Variable	Coefficient	SE	RR*
BCHC	1·05	0·25	2·85
T2	0·44	0·26	1·55
T3	1·20	0·30	3 32
T4	1·41	0 37	4·08
N1/N2	0·40	0·19	1·50
Age 45+ at diagnosis	0·06	0·18	1·06
Diagnosed 1984 or later	−0·75	0·21	0·47

*Relative risk, control group, T1, N0, age at diagnosis below 45, and diagnosis before 1984 having RRs of 1 00

stage, year of diagnosis and age at diagnosis, metastasis-free survival in the BCHC group is significantly poorer than in the control group (relapse rate ratio 2·85, $p < 0·001$). In the matched analysis, 126 cases relapse-free at BCHC entry were successfully matched with controls; their relapse-free survival is shown in the figure. 21 cases have relapsed compared with only 6 controls (table V; log-rank test $\chi^2 = 8·31$, $p = 0·004$), confirming the Cox regression analysis.

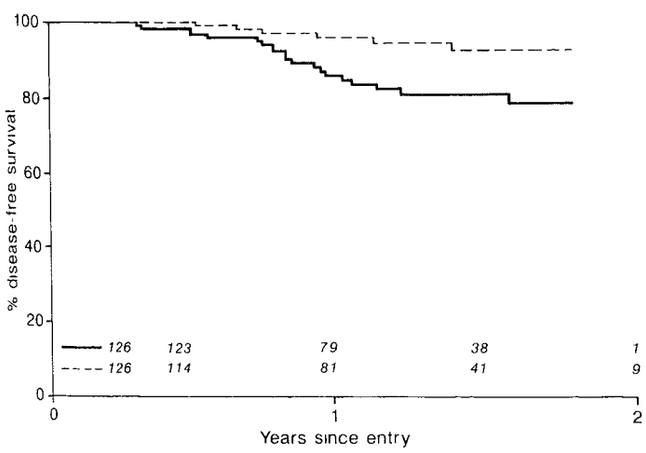
When the landmark method is used the difference in relapse-free survival between cases and controls is smaller and non-significant (relapse rate ratio 1·52; NS). This analysis however utilised only 11 of the relapses in the BCHC group.

Overall survival, relapsed patients

104 patients in the BCHC group had died by June 1, 1988, 89 deaths being in patients who had already relapsed before BCHC entry. The 5 deaths within 3 months of BCHC entry have been excluded from the analysis. On Cox regression analysis (time-dependent covariate method) survival in the BCHC group is significantly inferior (hazard ratio 1·81, $p < 0·001$), after allowing for other prognostic factors (table VI). In the matched analysis the effect is smaller and non-significant (relapse rate ratio = 1·26, table V) and the landmark method shows little difference between the two groups. There is no significant difference between RMH and DGH controls.

Overall survival, patients relapse-free at BCHC entry

Cox regression is not appropriate here. Matched analysis suggests a significant difference between cases and controls



Relapse-free survival in cases (———) and matched controls (----).

Numbers on x axis indicate patients at risk

TABLE V—LOG RANK ANALYSIS OF SURVIVAL AND DISEASE-FREE SURVIVAL BASED ON MATCHED ANALYSIS

Group	No	Events		p*
		Obs	Exp	
Relapse-free survival				
BCHC	126	21	13·52	0·004
Control	126	6	13 48	
Overall survival (with metastasis)				
BCHC	92	55	47 90	NS
Control	92	73	80·10	
Overall survival (initially disease-free)				
BCHC	126	8	4·13	0·01
Control	126	2	5 87	

*Log-rank χ^2 test

TABLE VI—COX REGRESSION ANALYSIS OF SURVIVAL IN METASTATIC PATIENTS

Variable	Coefficient	SE	RR*
BCHC	0·59	0·26	1·81
T2	0 23	0·29	1·25
T3	0·19	0·33	1·21
T4	0·21	0·44	1 24
N1/N2	−0 07	0·22	0·93
Age 45+ at diagnosis	−0 05	0·21	0·95
Diagnosed 1984 or later	−0·12	0 26	0·89
Disease-free interval 1–3 yr	−0·19	0·25	0·83
Disease-free interval 3 yr or more	−0 18	0 36	0 83

*Relative risk, control group, T1, N0, age at diagnosis below 45, diagnosis before 1984, and disease-free interval less than 1 year having RRs of 1 00

(hazard ratio 5·69, $p = 0·01$; table V) but by the landmark method the difference is only marginally significant ($p = 0·07$). There is no evidence of a difference between RMH and DGH controls.

Discussion

These results suggest that women with breast cancer attending the BCHC fare worse than those receiving conventional treatment only. Delays in the diagnosis of relapse as a result of attendance at the BCHC is an unlikely explanation because relapse would normally be confirmed within a few weeks and patients relapsing within the first 3 months of going to the BCHC are excluded. Inspection of hospital case notes suggests that it is unlikely that patients suspecting a relapse went to the BCHC rather than to their own doctor. An alternative possibility is that patients attending the centre, coming as they do from DGHs, may be less intensively investigated for relapse than patients attending RMH. However, DGH controls and RMH controls show no difference in disease-free survival. "Upstaging", the tendency to classify patients into a higher stage as a result of more intensive investigations, is also unlikely because all participants were staged by one of us (F. B.) on UICC criteria.[5]

The difference in survival amongst patients with metastatic disease could be the result of a difference in severity of disease at time of entry to the BCHC, and this requires further investigation. The least biased comparison will probably be that between overall survival of BCHC attenders without a relapse at their first visit to BCHC and similar controls, but numbers of deaths are small.

7 cases (2%) attending the BCHC had a second histologically confirmed primary breast cancer whereas no

controls had a confirmed second primary. Since these cases may have poor survival, the principal analyses censored follow-up at the date of the second primary. However, analyses not excluding patients with a secondary primary made little difference to the results. Cox regression should be the most efficient analysis in metastatic cases, but is trickier for the analysis of overall survival because cases metastasis-free at BCHC entry must be compared with controls who are disease-free after the same period. Matched analysis can be used for all these endpoints but it is less efficient because individual matches sometimes could not be found.

When alternative or unconventional therapies are being compared with orthodox treatments randomisation is the ideal—as was done, for instance, in trials of spinal manipulation for low back pain,[6] acupuncture for spinal pain,[7] and hypnotherapy for irritable bowel syndrome[8]—but a randomised study design was not acceptable to the BCHC. Comparability of the control and BCHC groups is thus important to interpretation of these results. RMH is a cancer hospital but the similarity of relapse rates between the two control groups confirms that patients attending the RMH are not a selected group. Patients with breast cancer attending BCHC are atypical in that 85% of them were under 55 years of age at diagnosis (for England and Wales the comparable figure in 1984 was 29%[9]). However, menopausal status is not a strong prognostic factor for breast cancer[10] and the BCHC group was not grossly dissimilar to the controls with respect to the important factors of T and N stage.

We do not yet know why patients choose to visit the BCHC. Experience of cancer in a close relative might motivate a search for an alternative model of healing. Or the apparent failure of conventional therapy in their own case may prompt a commitment to try a different regimen. Before their first visit the cases had not, however, rejected conventional treatment: they were just as likely to have had surgery and/or radiotherapy. A commitment to a healthy lifestyle may explain the preference for a regimen based upon a specific diet. Only 7% of cases were current smokers and 33% had given up smoking. Nationally, amongst women aged 20 and over, 34% currently smoke and only 14% are ex-smokers.[11] 41% of cases were using alternative therapies at the first BCHC visit, such as diet or "healing".

The substitution of the BCHC regimen for conventional therapy is clearly not an issue since few patients had rejected conventional therapy. However, psychological differences between attenders and non-attenders have not been addressed in our study, and these may be important.[12] While it is possible that BCHC attenders may, in some subtle way, have worse disease than our control series, the possibility that some aspect of the BCHC regimen is responsible for their decreased survival must be faced. For example, does radical adherence to a stringent diet shorten life in patients whose survival is already threatened by cancer? Our study certainly shows that patients choosing to attend the BCHC do not gain any substantial survival benefit. Whether quality of life is enhanced is yet to be answered. Other alternative practitioners should have the courage to submit their work to this type of stringent assessment.

We thank the BCHC patients and staff and the consultants who responded so generously and promptly; Prof P. S. Boulter, Dr A. Folkes, Dr A. Y. Rostom, Dr C. A. Topham, Dr W. F. White, and Dr J. Brient (Guildford), Mr J. C. Ball, Mr S. J. Janvrin, and Mr J. Neely (Crawley) and Dr Trevor Powles and Dr Sue Ashley (RMH) for help in assembling control groups; the medical records staff and medical secretaries at the Royal Marsden, Crawley, and Guildford Hospitals, especially Ann Strudwick, for helping in retrieving notes; staff at the Thames Cancer Registry; Lindsay Johnson, Karen Moser, Margaret Snigorska, Ruth Gell, Ruth Marriott, and Peta Heatley for clerical and secretarial assistance; and Judith Bliss and Nigel Rawson for computing advice. This study was funded by the Cancer Research Campaign and the Imperial Cancer Research Fund.

REFERENCES

1. Editorial. Europe looks at complementary medicine. *Br Med J* 1989; **299:** 1121.
2. Crawford MS. Cancer help in Bristol. *Lancet* 1984; ii: 582.
3. Chilvers CED, Fayers PM, Freedman LS, et al. COMPACT computer package. *Stat Med* 1988; **7:** 1165–70.
4. Cox DR. Regression models and life-tables. *J Roy Stat Soc B* 1972; **34:** 187–220.
5. International Union against Cancer. TNM classification of malignant tumours. Geneva: IUAC, 1968.
6. Doran DML, Newell DJ. Manipulation in treatment of low back pain: a multicentre study. *Br Med J* 1975; ii: 161–64.
7. Gunn CC, Milbrandt WE, Little AS, et al. Dry needling of muscle motor points for chronic low back pain. *Spine* 1980; **35:** 279–91.
8. Whorwell PJ, Prior A, Faragher EB. Controlled trial of hypnotherapy in the treatment of severe refractory irritable-bowel syndrome. *Lancet* 1984; ii: 1232–34.
9. Office of Population Censuses and Surveys. Cancer statistics registrations. Series MBI no 16. London. OPCS, 1984.
10. Pocock SJ, Gore SM, Kerr GR. Long term survival analysis: the curability of breast cancer. *Stat Med* 1982; **1:** 93–104.
11. Office of Population Censuses and Surveys. General household survey 1984. London: HM Stationery Office, 1986.
12. Greer S. Cancer and the mind. *Br J Psychiatry* 1983; **143:** 535–43.

VIEWPOINT

Assisted death

INSTITUTE OF MEDICAL ETHICS WORKING PARTY ON THE ETHICS OF PROLONGING LIFE AND ASSISTING DEATH*

The Institute of Medical Ethics has frequently been urged to address the following issue:

> The lives of an increasing number of patients, predominantly but by no means all elderly, are now being prolonged by modern medicine in states of coma, severe incapacity, or pain they consider unrelievable and from which they seek release. Doctors in charge of such patients have to decide not only whether they are morally bound to continue with life-prolonging treatment, but also, if no such treatment is being given, whether and in what circumstances it is ethical to hasten their deaths by administration of narcotic drugs.

In response the Institute set up a working party to investigate and report on the ethics of prolonging life and assisting death. The individuals invited to serve had been nominated with the intention of securing a broad spectrum of ethical viewpoints on the subject.

---

*Chairman: Mr Geoffrey Drain. Members: Miss Sheila Adam, Prof Thomas Arie, Sir John Batten, Miss Irene Bloomfield, Dr Colin Brewer, Prof Alex Campbell, Fr Brendan Callaghan SJ, Dr Donald Evans, Prof Charles Fletcher, Dr Gillian Ford, Prof Roger Higgs, Prof Bryan Jennett, Dr Elliot Shinebourne, the Very Revd Edward Shotter, Prof James Williamson, and Mrs Lynne Young (the late Paul Sieghart was a member and took part in the discussion of earlier drafts of this paper). Secretary: Dr Kenneth Boyd. Hon research assistant: Miss Ursula Gallagher.

LETTERS to the EDITOR

Bristol Cancer Help Centre

SIR,—Most of the discussion of the report by Ms Bagenal and her colleagues (Sept 8, p 606) on the survival of breast cancer patients attending the Bristol Cancer Help Centre (BCHC) has focused on possible explanations for the apparently poorer survival and relapse-free survival of women attending the centre. Less attention has been paid to possible weaknesses in the study design and the interpretation of the statistical analysis. The analysis was complex, and the published description so concise that details of the methods are not always clear.

The impression given is that there was little obvious difference between the prognostic features of "cases" and "controls". There were only minor differences between the two groups at primary diagnosis, except for age and menopausal status, but data on metastasis indicate major differences. Before entry to the BCHC, 139/334 (42%) of the cases already had metastatic disease, whereas only 134/461 (29%) of the controls relapsed at any time during follow-up, even though the two groups were matched roughly on time of primary diagnosis. Thus, the previous disease history of cases when they entered the Bristol centre was considerably worse than that of the controls at the same time after primary diagnosis. This could be explained by a greater tendency for women who had relapsed to seek complementary therapy. In this case, the survival comparisons made in the study may still be valid providing it can be assumed that relapse-free women on entry to the BCHC were comparable in their disease prognosis with controls who had been relapse-free for a similar time from primary diagnosis; and that women with metastatic disease on entry to the BCHC were comparable with control women who had relapsed at a similar time. The above data raise doubts over the reasonableness of this assumption.

Another odd finding, not much discussed, is that 7 cases but no controls had a second histologically confirmed primary breast cancer. This also suggests that patients attending the BCHC may have been self-selected from those with a poorer prognosis.

A further peculiarity is that in the matched analysis of survival in metastatic cases (table V), in which women attending the BCHC were stated to have a higher death rate than controls (rate ratio 1·26), there were considerably more deaths in the controls than in the cases (73 compared with 55). The apparent discrepancy arises from the greater number of expected deaths in the control group (80·1 compared with 47·9). We assume that survival in this analysis was measured from time of entry to the BCHC for each case, and from an equivalent time after relapse for her matched control, although this is not made clear. If our assumption is correct, the reported difference in expected deaths is surprising in view of the equal size of the two groups (92 in each), and the fact that they were matched on year of relpase.

The three methodological approaches used in the analysis did not always give similar results. In the survivial analysis of metastatic cases, for example, only the Cox regression showed a significant difference between cases and controls, although the reported p value ($<0·001$) seems surprisingly small given the results in table VI (coefficient for BCHC 0·59 [SE 0·26]). The matched survival analysis and the "landmark" method both showed smaller, non-significant differences between the groups. The difference between the rate ratios estimated in the Cox regression (1·81) and the simpler matched analysis (1·26) is surprising given that most metastatic cases were in both analyses, and that the additional variables adjusted for in the Cox regression did not appear from table VI to be strong confounders. Bagenal et al emphasise the results of the Cox regression and play down the two simpler methods. Even though Cox regression makes full use of the data available, it does involve additional assumptions about the multiplicative combination of factor effects.

Further analysis is unlikely to resolve the possible lack of comparability of the case and control groups which stems from the use of an observational study design. This can only be done through randomised controlled trials. Practitioners of complementary medicine tend to resist the randomised trial, arguing that the patient's motivation in freely selecting the therapy is essential to its efficacy. However, this is a strong argument against observational design, since motivated individuals often differ substantially from others in their risk of disease. The random allocation of patients to two groups, one of which is offered the option of complementary therapy, is to be preferred. The design of such trials to evaluate complementary therapy is not straightforward and the uptake of the therapy among those to whom it is offered and those to whom it is not will dilute any effect, but any difference observed can confidently be attributed to the therapy. Bagenal et al note that this is the ideal approach, and it is unfortunate that the BCHC rejected randomisation.

A possible outcome of this controversy is that practitioners of complementary medicine are so alarmed by the possibility of adverse results that the welcome trend towards careful evaluation of the impact of complementary therapies comes to a premature end. Another possible outcome is an acceptance that randomised trials offer the best chance of giving these therapies a fair evaluation. The second option provides the most fruitful way forward.

R. J. HAYES
P. G. SMITH
L. CARPENTER

London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK

SIR,—Publication of the interim report of the study comparing survival of women with breast cancer attending the Bristol Cancer Help Centre (BCHC) with NHS controls was followed by substantial and not infrequently sensational mass media coverage. Much of the reporting was inaccurate since it propagated the theme that attendance at BCHC worsened the prognosis of breast cancer (eg, "'doubled risk' at cancer unit" *Guardian* front page, Sept 6). The mass media need sensation to make a living but I was most concerned that both the Imperial Cancer Research Fund (that in part funded the study) press release and remarks made by some of the authors on television seemed to lend further credence to this unsubstantiated conclusion (*Br Med J*, Sept 15, p 510). Such a conclusion belongs to the realm of speculation, not science,[1] and can be refuted by a systematic analysis of the study. Even at the time of publication, as I pointed out (Sept 15, p 683), it was clear that the design of the study and the lack of data on significant variables (eg, compliance, site and extent of metastases, and psychosocial factors) rendered it inconclusive. Since then further serious flaws have emerged.

(1) Analysis of BCHC case notes of 32 of the 33 women who relapsed (1 set of notes missing) reveals that:

(*a*) 47% had had local recurrences before attending BCHC (10 on one occasion, 4 twice, 1 thrice) and in addition 3 had persistent disease despite treatment. This contrasts sharply with the 14% of the total case sample who had had local recurrences before attending Bristol. Local recurrences were apparently not taken into account

when comparing cases and controls: this is a fundamental error that the research team are now aware of, and I await their revised statistics with interest.

(*b*) 1 of the 32 was recorded as having had a positive bone scan before attendance but was classed as "disease-free". The researchers are investigating this case also.

(*c*) 2 women who apparently had supraclavicular and cervical lymph-node involvement before attendance at BCHC were also classed as disease-free. Clearly such women are more at risk of relapse but this is not controlled for in the report.

(*d*) Similar proportions (44%) of the case and control groups received adjuvant therapy; however, the type is not indicated. This is relevant since the case group were significantly younger on average (52% aged less than 45) so chemotherapy would have been the adjuvant therapy of choice for most of them.[2] Our case notes, however, indicate the reverse was the case (chemotherapy 16%, tamoxifen 28%). It is plausible that the Surrey based controls received more appropriate adjuvant therapy because most of them attended the Royal Marsden Hospital or a specialist breast unit at Guildford, and this could significantly change the relapse rate ratio. The type of adjuvant therapy must be controlled for before relapse rate ratios can be calculated reliably.

(*e*) The cases, despite being significantly younger, had a higher rate of mastectomy. This strongly suggests down-staging in the case group. This theory is supported by our case notes showing the rate of mastectomy in the relapsed cases was 72% compared with 25% in a randomly selected sample of 32 non-relapsed cases (mean ages 42·7 and 45·9 years, respectively).

Some of our case notes rely solely upon information gleaned from the patients themselves, and therefore those figures would have to be checked with the hospital case notes. However, this caveat does not significantly detract from the overall force of my argument. The discussion section of the report speculates whether the Bristol women may have been more ill "in some subtle way". All the indications are that the difference was not subtle but gross; like was not being compared with like.

(2) Another factor strongly suggesting systematic bias is the magnitude of the disparity between survival and relapse rate. The results are "intrinsically implausible", as Dr James and Dr Reed have noted (Sept 22, p 744). No known treatment of women with breast cancer could produce such results in a follow-up of no more than 2 years.

(3) The lack of documentation of compliance after attending BCHC is further compounded by the failure to ensure that the controls were not using complementary or self-help therapies. However, more than half the controls were patients of the Royal Marsden Hospital, which offers complementary therapies similar to those used at BCHC. A survey by M. Slevin (reported in a Marie Curie Cancer Care Symposium on Oct 16, 1990) showed that 17% of patients attending one London oncology unit used complementary therapies of their own volition (this figure excludes counselling and attendance at support groups). At London's Hammersmith Hospital (K. Sikora, unpublished) 10 of 100 cancer patients were using complementary therapies but 33% had used them for other conditions (the survey was done before the links with Bristol). One can fairly safely assume that these figures would be greater still for the control group, largely middle class and consisting solely of women with breast cancer. (Women with breast cancer constitute 40% of our total case load and our clientele is strongly skewed to the white middle classes.) A significant proportion of the "controls" would therefore have been using complementary therapies and should have been eliminated from the study. How can one draw any conclusions from a study which has shown neither that the cases took the treatment nor that the controls did not?

The report concludes that any survival advantage gained through attending BCHC can be ruled out. Such an assertion can only be based on a 5 or preferably a 10 year follow-up. Spiegel's randomised prospective study[3] of a psychosocial intervention for women with metastatic breast cancer showed a near-doubling of survival for the cases—but the survival advantage only began to emerge after the first eighteen months of the study.

The study is seriously flawed and entirely inconclusive, yet it has been publicised as demonstrating that attendance at BCHC worsens prognosis. The consequences have been far-reaching. Many cancer patients have been very distressed by the publicity, some concluding that activities such as relaxation or visualisation may have seriously damaged their health; a cancer help centre at Hastings was denied charitable status because it was going to offer complementary therapies; and the number of patients attending the BCHC has dropped substantially. The BCHC would invite an independent expert panel of doctors and scientists (acceptable to BCHC and Ms Bagenal and her colleagues) to review the study and indicate what conclusions, if any, can be validly drawn from it.

Bristol Cancer Help Centre,
Grove House,
Cornwallis Grove,
Bristol BS8 4PG, UK

T. A. B. SHEARD

1. Angell M. The interpretation of epidemiologic studies. *N Engl J Med* 1990; **323**: 823–25
2. Early Breast Cancer Trials Collaborative Group. Effects of adjuvant tamoxifen and cytotoxic chemotherapy in early breast cancer: an overview of 61 randomised trials among 28 896 women. *N Engl J Med* 1988; **319**: 1681–92.
3. Spiegel D, Bloom JR, Kraemer HC, Gottheil E. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet* 1989; ii: 888–91

**These letters have been shown to Professor Chilvers and her colleagues, whose reply to them and to earlier correspondence follows.—ED. L.

SIR,—We broadly agree with much of the comment generated by our report on breast cancer patients attending the Bristol Cancer Help Centre (BCHC), which indicated that they had higher risks of recurrence and mortality than similar patients receiving conventional treatment elsewhere. The main points raised by your correspondents (and others who have commented privately) are that inferences based on unrandomised studies of cancer therapy are intrinsically unreliable, that some of our methods of analysis were not clearly described, and that we might not have adjusted or matched adequately for differences between BCHC and control patients.

We did not claim, and do not believe, that our findings consititute strong evidence that some aspect of BCHC management was the direct cause of the observed difference in outcome. Differences in survival between similarly treated patients at different centres often relate to differences in patient self-selection, exclusion criteria, and clinical staging. Such biases are a recognised hazard of non-randomised treatment studies[1] and underlie the generally accepted principle that randomisation is the only way to obtain completely reliable evidence on therapeutic comparisons. We do not, however, agree with Dr Monro and Dr Payne (Sept 22, p 743), who seem to imply that questions that cannot be studied by randomisation should not be studied at all. We were unable to do a randomised trial because the BCHC felt that it would be unethical and because it was thought that few patients attending the BCHC would consent to being randomised; it was agreed that an observational study should at least indicate whether there was strong evidence of improved survival. All of us, like Dr Sheard of the BCHC (Sept 15, p 683), expected when the study was planned that there would be little or no difference in outcome. When a clear difference emerged the possibility that some aspect of the BCHC regimen might be responsible had to be discussed. Our comment "for example, does radical adherence to a stringent diet shorten life in patients whose survival is already threatened by cancer?" was not intended to imply a well-established scientific conclusion. We pointed out that there were other interpretations of our results, including the possibility that BCHC patients might have worse disease or receive less effective conventional treatment, or that psychological differences might affect prognosis. As far as psychological differences are concerned, two projects were originally planned to run in parallel—this survival study and a study comparing psychological state both before and after attendance at the BCHC against that of control patients. Unfortunately, the second study (by a different group of investigators) has not yet progressed beyond the pilot stage. These data would be useful, both for their own sake and to put our findings into context. As Dr Wright observes (Sept 22, p 743) quality of life may be as important as quantity.

Adequate adjustment for potential differences in prognostic factors is crucial in a non-randomised study, and several

NUMBER OF EVENTS (N) AND WOMAN-YEARS (WY) IN SUCCESSIVE PERIODS (i) FROM DIAGNOSIS, (ii) FROM LOCAL RECURRENCE, (iii) FROM DISTANT RECURRENCE

Time variable in Cox analysis (yr)	Analysis and corresponding time variable											
	(i) Time from diagnosis to distant recurrence, censored at local recurrence				(ii) Time from local recurrence to distant recurrence				(iii) Time from distant recurrence to death			
	BCHC		Control		BCHC		Control		BCHC		Control	
	N	WY	N	WY	N	WY	N	WY	N	WY	N	WY
0–	4	55·65	35	424·60·	2	10·15	13	28·65	30	53·66	51	104·92
1–	12	67·90	33	332·20	13	12·41	3	14·90	37	56·61	25	54·76
2–	1	9·97	17	213·39	0	2·58	1	8·85	7	16·27	16	28·36
3–	0	1·40	12	122·65	1	0·51	0	7·54	7	5·04	4	13·49
4+	0	1·33	7	143·10	0	1·08	2	9·42	5	3·36	4	11·17
Total	17	136·26	104	1235·93	16	26·72	19	69·35	86	134·94	100	212·70
Overall rate ratio (BCHC:control)	1·48				2·19				1·36			
Unadjusted Cox rate ratio (BCHC:control)	1·60 (p = 0·11)				7·47 (p = 0·003)				1·66 (p = 0·02)			
*Adjusted Cox rate ratio (BCHC:control)	1·79 (p = 0·07)				10·72 (p = 0·001)				1·81 (p = 0·02)			

*Analyses (ii) and (iii) are adjusted for time from diagnosis to local (ii) or distant (iii) recurrence (0, < 3, 3 + yr) All analyses are adjusted for T, N, age, and period of diagnosis as before.

correspondents suggest factors that might be important. Initial prognostic factors such as T and N stages were adjusted for by conventional methods, but factors that change after diagnosis, and may differ between cases and controls, are more difficult to allow for. In our analysis of time to first distant metastasis we did not take account of local recurrence, which is prognostic, especially for patients treated by mastectomy. This may be important, since BCHC patients may attend as a result of local recurrence. This could in principle be adjusted for by individual matching of cases and controls, but a very large pool of controls would be needed to provide a close match for all cases. An alternative is to censor both cases and controls at the time of local recurrence, and to analyse time from local recurrence to distant recurrence separately. These analyses, adjusted for disease-free interval, and a reanalysis of survival after distant recurrence in the same format, are shown in the table. Cox regression analysis, in which event-rates are compared at each time point, is a procedure that rather obscures the underlying data, and our analyses are further complicated by the fact that BCHC patients enter at various times after diagnosis. We have therefore tabulated the actual recurrence and survival data against the time variable used in the Cox regression for all three analyses (table).

The overall rate ratio (ORR), calculated directly from the total events and woman-years in the table, is lower than the corresponding unadjusted Cox rate ratio (RR) for the analysis of survival following distant recurrence (analysis [iii]: ORR = 1·36, Cox RR = 1·66), and grossly lower for distant recurrence after local recurrence (analysis [ii]: ORR = 2·19, Cox RR = 7·47). This inconsistency in analysis (ii) is partly due to the fact that the high early recurrence rate among controls occurred during a period when few BCHC cases were under observation, and therefore had little influence on the regression results. It should also be noted that there are few events in analysis (ii). The Cox method is optimum provided the risk ratio is constant, but the data in the table suggest departures from this assumption. In these circumstances, the "best estimate" is not well-defined. The regression estimates are further increased by adjustment for other factors (see adjusted Cox RR in table). Our conclusion that the observed BCHC recurrence and death rates are consistently higher than those of control patients, however the data are analysed, is confirmed, and the overall difference, combining the three analyses, remains highly significant, but the data shown in the table suggest that the Cox regression results may have given exaggerated estimates in this instance. Moreover, the Cox regression estimate of the distant recurrence rate censored at local recurrence (analysis [i]: adjusted Cox RR = 1·79, p = 0·07) is lower than our previous overall estimate ignoring local recurrence (adjusted RR = 2·85, p < 0·01), and this reduction suggests that the difference between BCHC patients and controls may also have been inflated by selective self-referral.

Although we disagree with Monro and Payne that young age at diagnosis indicates a poor prognosis (see ref 10 in our Sept 8 paper), we adjusted for age in all our analyses. Dr Heyse-Moore (Sept 22, p 743) suggests that detailed information on psychological status and patient management at Bristol might reveal differential effects of different aspects of BCHC management. The BCHC does not collect data on psychological status, but information on different components of the regimen are available. We are also collecting data on adherence to the Bristol regimen, and future analyses will include this and a comparison of daily and weekly attenders. Dr James and Dr Reed (Sept 22, p 744) suggest that we should have given equal weight to the survival analyses we carried out. We preferred the results based on Cox regression because the alternative "landmark" method and matched analyses omitted patients (those entering BCHC more than a year since diagnosis or distant relapse and those that we could not match exactly with a control, respectively).

We would also like to clarify two points alluded to by Dr Hayes and his colleagues (this issue). First, the significance level for the comparison of survival in metastatic patients by Cox regression was p = 0·02, as is clear from the ratio of the coefficient (0·59) to its standard error (0·26) in our table V. (All statistical tests were two-sided.) Second, in the matched analysis of patients with metastatic disease, controls with date of metastasis nearest to that of the cases were chosen, but not necessarily in the same year. This accounts for the longer follow-up in controls and the difference in expected numbers noted by Hayes et al. Matching on year of metastasis reduces the number of matched pairs available for analysis, but hardly alters the relative risk estimate.

Dr Sheard (this issue) raises concerns about individual clinical records held by BCHC on 3 women. We considered hospital case notes (rather than the BCHC notes) to be the more accurate source of information, and this source was used for both the BCHC case group and the control group. In response to Sheard's point about hormonal and chemotherapy we note that among women diagnosed under age 50 24% of BCHC cases and 31% of controls received hormonal therapy (tamoxifen, aminoglutethamide) and 12% of cases and 14% of controls had chemotherapy. For women aged 50 and over at diagnosis, 48% of cases and 38% of controls received hormonal therapy, and 5% and 2%, respectively, received chemotherapy. Even if the controls had received more appropriate adjuvant therapy the effects would be small.[2]

The Royal Marsden Hospital does now offer counselling, and psychotherapy where needed, in a systematic way. This is a recent development and would not have been available to the patients (diagnosed 1979-87) in our control series. Staff at the Royal Marsden do not consider the currently offered psychological

support by qualified psychotherapists to be similar to that offered at the BCHC.

We regret that our paper has created the widespread impression that the BCHC regimen directly caused the differences that we observed in recurrence and survival. This was never stated. In our view it is much more likely that the differences could be explained by increased severity of disease in BCHC attenders. Further data will be collected during the remaining two years for which this study is funded. The important conclusion to be drawn from our study is not that the BCHC regimen is harmful, but rather that there is as yet no evidence of anti-tumour effect. Ultimately the only definitive way to evaluate complementary therapeutic methods will be by means of randomised, controlled trials, and we welcome news that such studies are being planned.

Department of Community Medicine and Epidemiology, University of Nottingham, Queen's Medical Centre, Nottingham NG7 2UH, UK — C. E. D. CHILVERS

Section of Epidemiology, Institute of Cancer Research, Sutton, Surrey — D. F. EASTON, F. S. BAGENAL

Bristol Cancer Help Centre — E. HARRIS

Section of Medicine, Institute of Cancer Research and Royal Marsden Hospital, Sutton — T. J. MCELWAIN

1. Peto J, Easton D. Cancer treatment trials: past failures, current progress and future prospects. *Cancer Surveys* 1989; **8:** 513–33.
2. Early Breast Cancer Trialists' Collaborative Group. Effects of adjuvant tamoxifen and of cytotoxic therapy in early breast cancer. *N Engl J Med* 1988; **319:** 1681–92.

SIR,—This study was jointly supported by the Cancer Research Campaign and the Imperial Cancer Research Fund to obtain an objective evaluation of the therapies the centre offers, following an approach from the centre and with their full cooperation. The study was assigned to the Institute of Cancer Research.

It is clearly very difficult without randomisation to obtain unbiassed evidence of the effects of the Bristol Cancer Help Centre therapies. Our own evaluation is that the study's results can be explained by the fact that women going to Bristol had more severe disease than control women. In particular, they had a much higher rate of local recurrence.

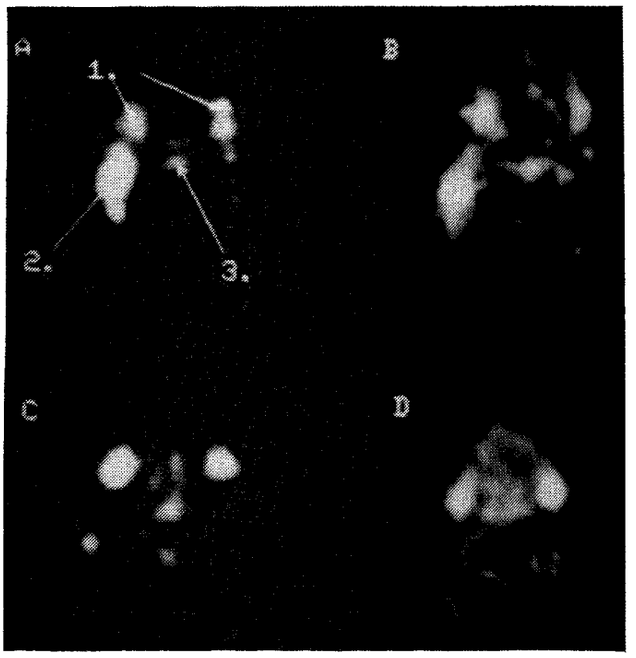
That patients are attracted to complementary medicine when they feel their outlook is unpromising is a useful observation to emerge from the study.

Imperial Cancer Research Fund, London WC2A 3PX, UK — WALTER BODMER, Director of research

PET and [^{11}C]methionine in assessment of response in non-Hodgkin lymphoma

SIR,—Failure to identify complete responses may have serious consequences in patients being treated for non-Hodgkin lymphoma. L-[methyl-^{11}C]methionine uptake has occasionally been used in the evaluation of malignant brain and lung tumours with positron emission tomography (PET),[1-3] but little is known about the accumulation in lymphomas.

A 56-year-old man was admitted to this hospital in March, 1989, with a 10 × 5 cm tumour in his right neck and tumours up to 1·5 cm on the left side of his neck. Biopsy revealed centrocytic-centroblastic intermediate grade malignant lymphoma, and lymphoma was found also in inguinal lymph nodes (Ann Arbor stage IIIB). [^{11}C]methionine imaging with PET demonstrated high radioactivity in the neck tumour, and weak accumulation in the submandibular salivary glands and the bone marow of the cervical vertebrae. There was also some accumulation in the small tumours on the left side of the neck (figure).



[^{11}C]methionine PET scans in patients with neck lymphoma.

(A) Intermediate grade lymphoma before chemotherapy: uptake in submandibular salivary glands (1), tumour in right neck (2), bone marrow (3), and also uptake in small tumours in left neck.

(B) After 3 months' chemotherapy.

(C) Some accumulation remaining in right neck after 6 months' chemotherapy.

(D) After chemotherapy and radiotherapy there is no abnormal accumulation.

After 3 months of chemotherapy with a combination of methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B) there was no palpable tumour in the neck, but a PET-scan demonstrated radioactivity in the neck at the tumour site to the right. Because of incomplete regression also in the inguinal nodes MACOP-B was continued.

After 6 months of chemotherapy the patient was clinically in complete remission. However, the increased uptake of [^{11}C]methionine in the right neck at the tumour site persisted. At this time computerised tomography and ultrasonography only showed lymph nodes less than 1 cm in diameter under the right sternocleidomastoid muscle; ultrasound-guided fine-needle biopsy yielded normal cells in the neck.

Because of the [^{11}C]methionine uptake the patient was thought to have residual lymphoma, and consolidation radiotherapy was given to the right neck. A fourth [^{11}C]methionine PET scan was done in December, 1989, and no uptake was seen in the tumour area. The patient had no evidence of disease in September, 1990.

It is difficult to distinguish viable tumour from normal or scar tissue with X-ray studies or with ultrasound after cytotoxic chemotherapy. PET may be a new way of detecting viable malignant tissue.[4] [^{11}C]methionine PET imaging needs to be further investigated in the evaluation of treatment responses in lymphoma.

Department of Oncology and Radiotherapy, Turku University Central Hospital, 20520 Turku Finland; and Turku Medical Cyclotron-PET Centre, Department of Nuclear Medicine, Turku University Central Hospital — SIRKKU LESKINEN-KALLIO, HEIKKI MINN, HEIKKI JOENSUU

1. Bustany P, Chatel M, Darcel F, Sgouropoulos P, Soussaline F, Syrota A. Brain tumor protein synthesis and histological grades: a study by positron emission tomography (PET) with C11-L-methionine. *J Neuro-Oncol* 1986; **3:** 397–404.
2. Mosskin M, von Holst H, Bergström M, et al. Positron emission tomography with ^{11}C-methionine and computed tomography of intracranial tumours compared with histopathologic examination of multiple biopsies. *Acta Radiol* 1987; **28:** 673–81
3. Fujiwara T, Matsuzawa T, Kubota K, et al. Relationship between histologic type of lung cancer and carbon-11-L-methionine uptake with positron emission tomography. *J Nucl Med* 1989; **30:** 33–37.
4. Strass LG, Clorius JH, Schlag P, et al Recurrence of colorectal tumors: PET evaluation. *Radiology* 1989; **170:** 329–32.