Pergamon

European Journal of Cancer Vol. 32A, No. 3, pp. 470–479, 1996

Printed in Great Britain
0959-8049/96 $15.00+0.00

0959-8049(95)00607-9

Original Paper

The Follicular Non-Hodgkin's Lymphomas—I. The Possibility of Cure

J.W. Denham,[1] E. Denham,[1] K.B. Dear[2] and G.V. Hudson[3]

[1]Radiation Oncology Department, Newcastle Mater Misericordiae Hospital, Hunter Region Mail Centre, NSW 2310, Australia; [2]Department of Statistics, The University of Newcastle, Callaghan, NSW 2308, Australia; and [3]British National Lymphoma Investigation Offices, Middlesex Hospital, Mortimer Street, London W1, U.K.

The follicular lymphomas pursue an indolent course in many patients. Long-term follow-up in large series is therefore necessary to establish whether cure is taking place, and if so, at what stage in the dissemination of the disease process it becomes unlikely. The time to, and site of relapse, together with its impact on survival has been studied in 398 patients entered into the British National Lymphoma Investigation limited and disseminated disease trials between 1974 and 1980. Relapse data were compared with various models to obtain maximum likelihood estimates of the proportions permanently remaining relapse-free following treatment. Long-term relapse-free survival was observed in 54.8 ± 14.9% (95% CI) of patients at 15 years with Ann Arbor stage I disease, 29.2 ± 13.6% in patients with stage II disease, 18.1 ± 6.6% with stage III and 13.0 ±5.9% with IV disease. Relapse time-course data for all trial arms conform closely to lognormal distributions allowing maximum likelihood estimates of proportions remaining permanently relapse-free to be derived. Using this methodology, over a quarter of patients treated with involved radiotherapy alone or radiotherapy plus 6 months of chlorambucil in the limited disease (Ann Arbor stage I and II) trial are unlikely to relapse at any time in the future. Over 10% of patients treated in the disseminated disease trials with disease classified as Ann Arbor stage III are also statistically unlikely to relapse. The finding that a proportion of patients is statistically unlikely to experience a clinically obvious relapse is consistent with clinical cure. It is especially interesting that a small proportion of patients with disseminated disease and treated by chemotherapy have fallen into this category, but additional data are required to know at what point statistical cure becomes unlikely. Whether "clinical cure" is the same as "pathological cure" in this disease remains uncertain.

Key words: non-Hodgkin's lymphoma, follicular, nodular, radiotherapy, chemotherapy, cured subsets, long-term follow-up
Eur J Cancer, Vol. 32A, No. 3, pp. 470–479, 1996

INTRODUCTION

SEVERAL MAJOR advances in lymphoma management took place in the late 1960s and 1970s. The emergence of combination chemotherapy regimes of sufficient activity to cause complete remission in most types of non-Hodgkin's lymphoma (NHL) [1–4] as well as in Hodgkin's disease [5] was one of the most important. This, in turn, provided a rationale for the thorough staging of newly presenting patients [3, 6–15] which has contributed so much to our present understanding of the dissemination of the various lymphomatous processes. During this period, it also became clear that most NHLs have B-lymphocytic origins [16–23]. It quickly became obvious why malignancies with follicle centre cell origins such as the follicular NHLs were found to be disseminated so frequently throughout the B-lymphocytic domains of the reticulo-endothelial system and marrow at presentation [24–26].

The 1970s also brought disappointments. Although complete remission could be induced more readily in the low-grade NHLs, these remissions did not prove to be as durable as they did in patients with high-grade NHL [27–32]. Efforts to improve the durability of these remissions by intensifying

Correspondence to J.W. Denham.
Revised 2 Oct. 1995; accepted 13 Nov. 1995.

the induction regimens [1, 4] and by consolidating the remissions obtained with maintenance schedules were not as successful as had been hoped [34–39], and this led to the now widely held conclusion that the follicular lymphomas are not only frequently disseminated at presentation but are incurable [40–42]. Therefore, at many centres, chemotherapy is now applied in modest dosage for palliation of symptomatic disseminated disease and radiotherapy is used to palliate bulky but localised masses, much as it has been since the 1930s.

Despite this change in management emphasis, reports of durable remission following radiotherapy for ostensibly localised follicular lymphoma continue to be published [43–48]. The present report focuses on a very large series of patients with follicular lymphoma that were treated in the British National Lymphoma Investigation (BNLI) trials of the late 1970s which now have a minimum follow-up period of 12 years. It attempts to determine whether any of the patients entered into these trials may now be considered to be cured, and if so, at what stage in the advancement of disease process cure becomes unlikely.

PATIENTS AND METHODS

Patients

This report is based on 398 patients with follicular non-Hodgkin's who, after giving their consent and being staged according to the protocol outlined in Table 1, were entered from 38 institutions in the United Kingdom into three randomised controlled British National Lymphoma Investigation trials (Table 2)[36, 49] between January 1974 and October 1980. The analysis that forms the basis of this report commenced in October 1992 providing a minimum follow-up period of 12 years and a maximum of almost 19 years.

Histopathology

The histopathological appearances of pathological material from all of these patients have been reviewed by the authors by "British" classification of the NHLs [16, 50] (Drs Michael Bennett, Kristin Henry and Geoffrey Farrar-Brown) and have subsequently been re-reviewed by Dr Bennett (Table 3). The three follicular lymphoma subtypes of the British classification correspond closely to the three follicular lymphoma subtypes of the Working Formulation derived from the non-Hodgkin's lymphoma pathologic classification project sponsored by the National Cancer Institute of the U.S.A. [51]. Follicular (nodular) architectural pattern is the major criterion for classifying a lymphoma as follicular in both classifications. Both also allow for diffuse areas and for sclerosis. Where the classifications slightly differ is in the cytological criteria used for differentiating the three histological subtypes. For example, the British classification allows for more "large" cells in its predominantly small follicle cell subtype than the Working Formulation allows for in its corresponding subtype, that is the "predominantly small cleaved cell follicular" subtype. The implications are that a series classified according to the British scheme will contain a greater number of cases of the "predominantly small follicle" subtype than a series classified according to the Formulation. In addition it means that some of the British "small follicle cell" subgroup would be classified as "mixed small cleaved and large cell follicular" according to the Formulation. A further difference is that the British classification allows for a smaller percentage of large cells in cases which it chooses to call "predominantly large cell" follicular lymphoma than the Formulation does for its corresponding subtype, the "predominantly large cell" follicular lymphoma. Large cell follicular lymphomas therefore make up a smaller proportion of a series of lymphomas classified according to the British system than according to the Formulation. Some cases classified in the present report as "mixed small and large follicular" would undoubtedly be classified as predominantly large cell if the Formulation were used instead.

Table 1. Staging protocol for patients accrued into the British National Lymphoma Investigation trials

- History and examination
- ENT examination
- Nodal biopsy
- Weight
- Full blood count (including white cell differential and ESR)
- Liver function studies (including albumin and globulin levels)
- Chest X-ray, PA and lateral
- Mediastinal tomograms*
- Abdominal lymphangiogram
- Bone marrow
- Scintigraphy of liver and spleen*
- Ultrasound of liver, spleen and abdominal nodes*
- CT scanning abdomen and thorax*
- Liver biopsy*
- Laparotomy

*Optional, depending upon clinical indications and availability.

British National Lymphoma Investigation Trials overview

After staging, patients with Ann Arbor stage I and II disease were randomised to receive involved field radiotherapy alone (35 Gy/20 fractions/4 weeks) or the same radiotherapy followed by oral chlorambucil 0.2 mg/kg/day for 2 months then 0.1 mg/kg/day for a further 4 months. This trial is subsequently known in this report as "the localised disease trial". Patients with Ann Arbor stage III and IV disease were randomised to receive 2 years of oral chlorambucil 0.2 mg/kg/day until complete remission followed by 0.1 mg/kg/day until a total of 2 years of treatment had elapsed or to a minimum of six cycles of i.v. cyclophosphamide, vincristine and prednisone (COP) (i.e. six cycles if complete remission took place within the first three cycles, or three further cycles following complete remission in patients remitting after four or more cycles) (Table 2). In January 1977, this trial (subsequently known in this report as the "first disseminated disease trial") was discontinued when it became clear that patients receiving chlorambucil were faring inferiorly. It was felt at the time that this was owing to a defect in trial design that allowed patients not to "cross-over" to the altenative therapy once it had become clear that complete remission was unlikely to take place. An additional reason for the poor outcome in patients receiving chlorambucil in this trial may have been an imbalance in the number of patients over the age of 60 years between the trial options. These patients were subsequently shown to fare less well than younger patients, regardless of initial treatment option. The second disseminated disease trial, which commenced in May 1977, continued to compare initial treatment with oral chlorambucil for 2 years with six cycles of COP but incorporated a "cross-over" option. This trial also incorporated a second randomisation in completely responding patients to maintenance therapy with chlorambucil 0.1 mg/kg/day for 2 years or no further treatment. In the intervening period, patients were allocated treatment with a

Table 2. The British National Lymphoma Investigation (BNLI) Grade 1 trials (n = *number of patients with follicular lymphoma and considered in this report who were accrued into the various trial arms. A further 13 patients included in this report were treated with cyclophosphamide, vincristine and prednisone (COP) between the first and second disseminated disease trials)*

BNLI trials in low-grade NHL (1974–1980)
Limited disease trial (Ann Arbor stages I and II)
Involved field radiotherapy to 35 Gy ($n = 55$)
versus
Involved field radiotherapy to 35 Gy then chlorambucil 0.2 mg/kg/day orally for 8 weeks then chlorambucil 0.1 mg/kg/day orally for 16 weeks ($n = 50$)
Disseminated disease trials
First trial
Chlorambucil 0.2 mg/kg/day orally until complete remission and then for 8 weeks following this then chlorambucil 0.1 mg/kg/day orally until a total of 2 years had elapsed since starting treatment ($n = 50$)
versus
i.v. cycles of COP at intervals of 2–4 weeks until complete remission obtained then three further cycles following this to a minimum of six cycles administered ($n = 47$)
COP: Cyclophosphamide 600 mg/m^2 (max 1 g) i.v. days 1 and 8 Vincristine 1.4 mg/m^2 (max 2 mg) i.v. days 1 and 8 Prednisone 50 mg/m^2 (max 100 mg) orally days 1 to 8
Second trial
Chlorambucil ($n = 90$) versus COP ($n = 93$) as above. Patients not achieving complete remission within 3 months of starting therapy were switched to the opposite trial arm.
A second randomisation to chlorambucil 0.1 mg/kg/day orally until 2 years had elapsed after commencing treatment or no further treatment occurred in completely responding patients.

Table 3. Histologic classification of patients entered into the British National Lymphocyte Investigation grade 1 non-Hodgkin's lymphoma (NHL) trials. Grade 1 NHL histological subtypes according to Bennett and associates [50]

Follicular subtypes
Follicle cells predominantly small
Follicle cells mixed small and large
Follicle cells predominantly large
Diffuse subtypes
Lymphocytic, well differentiated
Lymphocytic, intermediate differentiation (small follicle lymphocyte)

minimum of six cycles of COP in the "Undrawn" disseminated disease trial. The patient numbers accrued into these trials are listed in Table 2.

Overview of the analytical methodology used

The present analysis was performed on data accumulated prior to randomisation, including basic demographic data, the staging investigations actually performed, Ann Arbor staging information, the distribution and bulkiness of nodal involvement, haematological indices (including haemoglobin, lymphocyte and platelet count) and biochemical indices (including serum albumin and total globulin levels) as well as data acquired during follow-up concerning site of and time to relapse and cause of and time to death.

To develop precise estimates of the proportion of patients who are unlikely to relapse following treatment and therefore may be considered "clinically" cured, a maximum likelihood estimates procedure of the type originally outlined by Boag [51] and developed subsequently by others [50, 53] was used. Several models, including mixtures of exponential distributions, were fitted with limited success. However, having established that the distribution of relapse time following treatment closely approximates a lognormal distribution for patients treated in all trial arms, it was then possible to estimate confidence intervals for the proportion that are ever likely to relapse if followed indefinitely.

Statistical methodology

The clinical data supplied by clinicians who participated in the BNLI trials were entered on to a PC-based temporal database package (MEDLOG) and analysed using some of the statistical options available on this database, which include Kaplan–Meier survival curve options [54], the log-rank test [55] for differences between curves, parametric and non-parametric tests for comparing variable value distributions between subgroups, multiple logistic and Cox proportional hazards regression analyses [56] and the additional data plotting and curve-fitting programmes offered on the SIGMA plot and STATA software packages. The GAUSS™ statistical programming language was used to apply the maximum likelihood estimates procedure to the relapse data. Survival estimates have been derived from the interval between the date of starting treatment to the date of death, or to the date last seen alive. Death has been assumed to result from lymphoma

unless the patient had been in first remission up to the time of death and the cause of death had been certified as being due to another (intercurrent) cause. Relapse-free survival was based on the time that relapse was first recorded from the date of starting treatment in patients who responded completely to therapy. The resulting relapse-free survival curves therefore commence at the percentage of patients who responded completely to initial therapy.

RESULTS

Overall, cause-specific and disease-free survival probability

Overall and cause-specific Kaplan–Meier survival curves were plotted using linear axes for the various trial arms in Figure 1. No significant differences emerged between the options tested in the localised disease trial (radiotherapy alone versus radiotherapy followed by chlorambucil). In the disseminated disease trials, a significant difference in overall survival ($P = 0.036$) and cause-specific survival ($P = 0.032$) in favour of the COP-treated arm in the first (old) trial disappeared altogether in the second (new) trial, in which patients failing to respond rapidly to their initially allocated treatment "crossed-over" to the alternative option.

Relapse-free survival curves in addition to cause-specific survival curves for the various trial arms were replotted on semilogarithmic axes in Figure 2 to provide an appreciation of the rate at which the events under examination took place (relapse and death due to lymphoma, respectively). The relapse-free survival curves for patients treated in the localised disease trial were clearly biphasic. The slope in both arms of this trial became distinctly shallower at approximately 5 years post treatment, patients were approximately 70% disease-free at 5 years when treated with chlorambucil in addition to radiotherapy, and approximately 45% if treated with radiotherapy alone, suggesting that it is subgroups of this size that experience lower rates of relapse. A statistically significant difference in relapse-free survival could not be detected between these two options ($P = 0.167$).

Further presentations of cause-specific and relapse-free survival according to Ann Arbor stage are shown in Figure 3. Relapse-free survival figures with 95% confidence intervals at 10 and 15 years for Ann Arbor stage I disease were 58.32 ± 14.1% and 54.8 ± 14.9%. The corresponding figures for stage II were 29.2 ± 13.6% and 29.2 ± 13.6%, for stage III 20.9% ± 6.7% and 18.0 ± 6.6% and for stage IV 13.0 ± 5.9% and 13 ± 5.9%. It should be noted that, although the classification separates cause-specific survival expectation poorly, the relapse-free survival probability curves for patients with I, II and IIIA disease separated the groups reasonably well. The relapse-free curves for Ann Arbor stage III and possibly IVA (in addition to the curves for stage I and II disease) were biphasic.

Factors influencing time and time-course of relapse

(*a*) *Factors influencing relapse.* Proportional hazards models were derived in completely responding patients to determine whether the biphasic nature of the relapse-free survival curves might simply be a result of the early relapse of patient subgroups characterised by the presence of known adverse non-stage and disease subtype-related variables. In fact, this did not prove to be the case. In none of the models shown in Table 4 did age, sex or histological subtype emerge as having a powerful and independent influence on relapse-free survival once complete remission had been obtained. In models that included Ann Arbor stage, this variable alone had a powerful and independent influence on relapse-free survival but this was in the limited disease trial only. In models in which stage-related variables such as number of lymph node sites involved, marrow involvement and presence of splenomegaly replaced Ann Arbor stage, the number of lymph node sites involved alone emerged as having a powerful and independent influ-

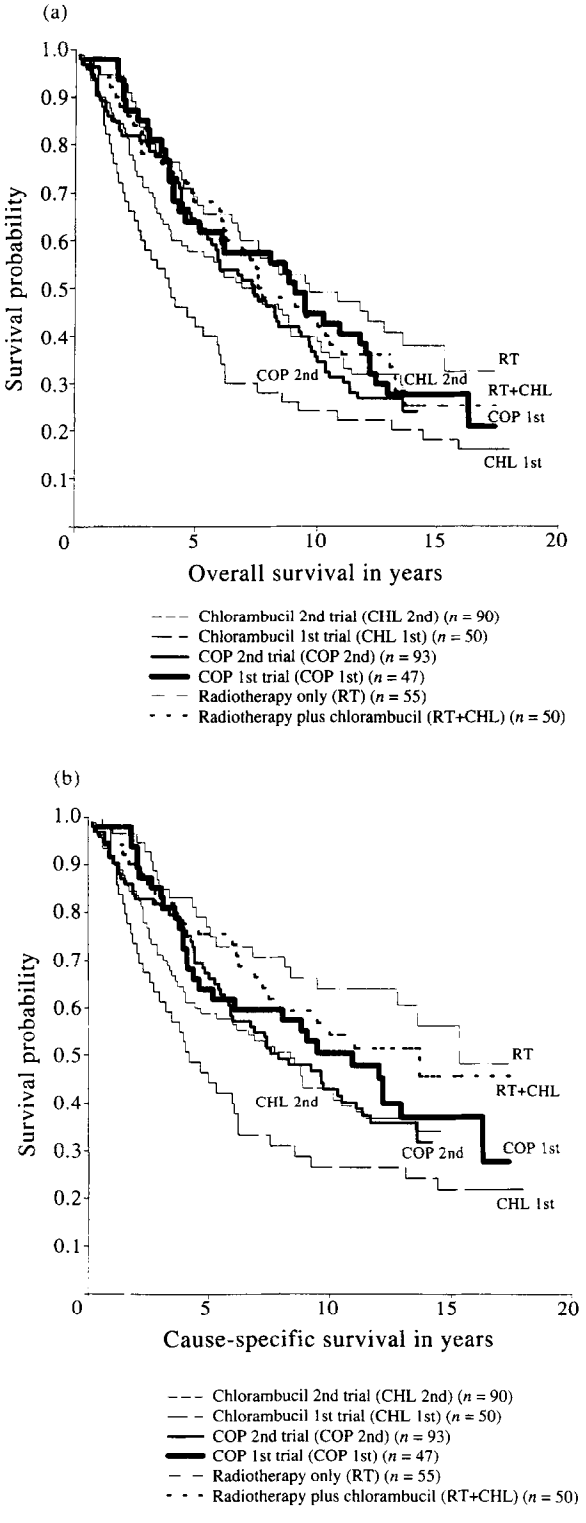

Figure 1. (a) Overall survival (taking into account all causes of death) and (b) cause-specific survival (taking into account deaths due to lymphoma only) for each trial arm.

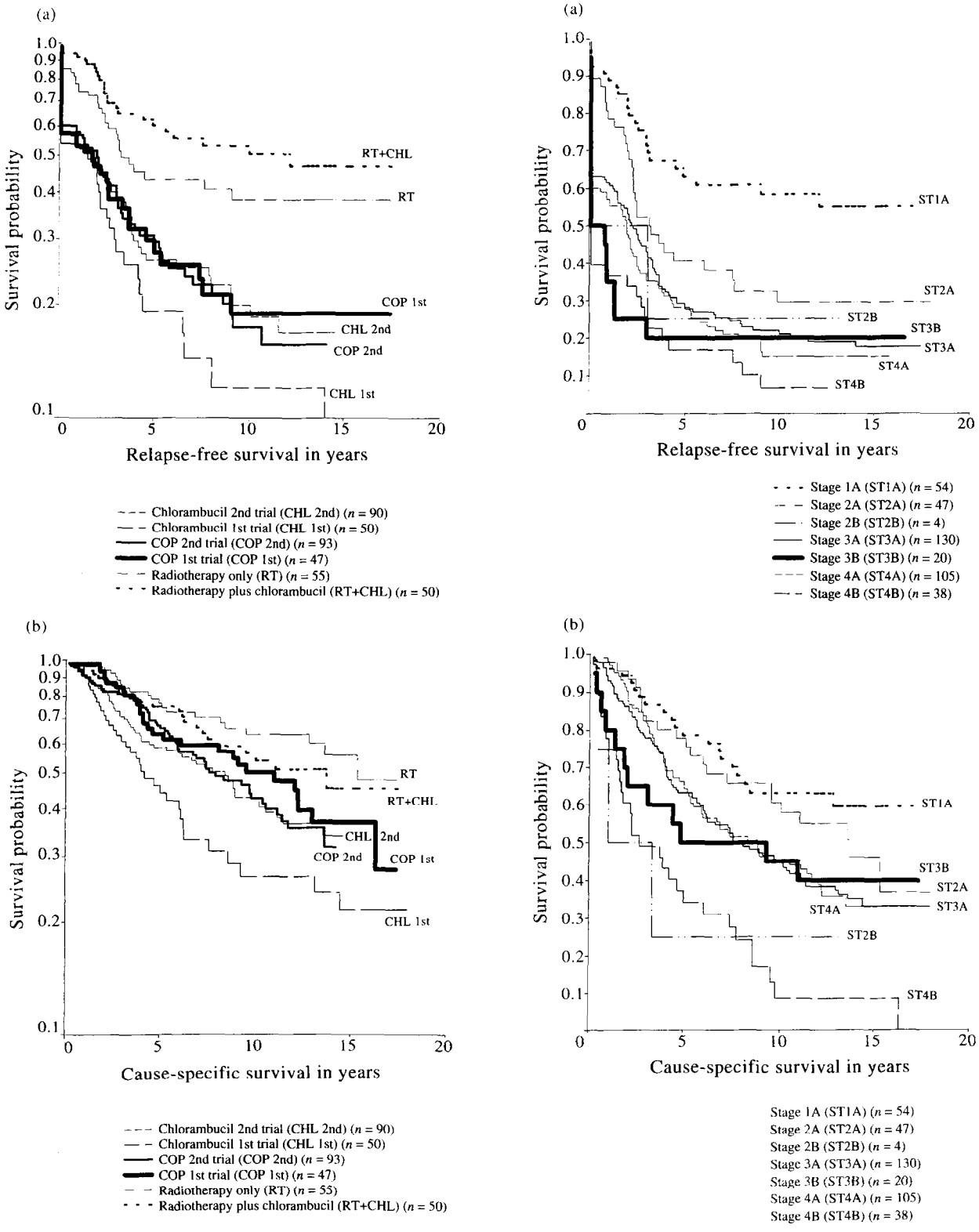

Figure 2. (a) Relapse-free and (b) cause-specific survival for each trial arm on a semilogarithmic plot.

Figure 3. (a) Relapse-free and (b) cause-specific survival according to Ann Arbor stage.

ence on relapse-free survival in both limited and disseminated disease trials.

In patients treated in the localised disease trial, time to relapse was found to be independent of the site of relapse. The time-course of adjacent nodal site, non-continuous nodal site and generalised relapses were very similar with peaks at 28 months following therapy. Patients receiving 6 months chlorambucil experienced a small but statistically non-significant delay in their time to relapse.

(*b*) *Time-course.* The distribution of relapse events following treatment for patients in every trial arm was found to approxi-

Table 4. Results from Cox proportional hazard models examining the relative influence of various patient-, disease subtype- and stage-related variables on relapse-free survival in patients who have gone into complete remission following therapy. Factors influencing probability of relapse in patients who responded completely following initial therapy

	Limited disease trial ($n = 105$)		Disseminated disease trials ($n = 293$)	
	Ann Arbor model*	Stage-related model*	Ann Arbor model*	Stage-related model*
Increasing age	1.01 (0.98–1.03) $P = 0.65$	1.01 (0.98–1.03) $P = 0.68$	1.01 (1.00–1.03) $P = 0.18$	1.01 (0.99–1.03) $P = 0.19$
Female sex	0.76 (0.41–1.42) $P = 0.39$	0.79 (0.41–1.50) $P = 0.47$	0.79 (0.55–1.14) $P = 0.21$	0.79 (0.54–1.15) $P = 0.22$
Histological subtype	1.16 (0.70–1.93) $P = 0.57$	1.16 (0.70–1.93) $P = 0.56$	0.98 (0.70–1.37) $P = 0.89$	1.09 (0.78–1.54) $P = 0.61$
Systemic symptoms absent	1.71 (0.23–12.86) $P = 0.60$	1.21 (0.15–10.15) $P = 0.86$	0.89 (0.53–1.51) $P = 0.67$	1.03 (0.60–1.76) $P = 0.91$
Ann Arbor stage	2.16 (1.17–3.97) $P = 0.01$	—	1.05 (0.73–1.53) $P = 0.78$	—
Increasing lymph node sites	—	1.79 (1.27–2.55) $P = 0.001$	—	1.17 (1.06–1.30) $P = 0.002$
Marrow not involved	—	—	—	0.80 (0.54–1.20) $P = 0.28$
Splenomegaly absent	—	1.40 (0.17–11.74) $P = 0.76$	—	0.87 (0.50–1.52) $P = 0.63$

*Hazard ratio (95% confidence intervals) P value.

mate a lognormal distribution very closely. Figures 4 and 5 provide examples of this fit and show how relapse distributes in time following treatment if relapse is assumed to distribute lognormally (as would seem to be the case). It should be noted that the majority of relapses took place within the first 5 years following treatment, with a peak shortly after 24 months from start of therapy for patients treated in both the limited and disseminated disease trials. The close fit of the relapse time-course data to lognormal distributions enables maximum likelihood estimates of the size of the subgroups that are statistically unlikely to experience a clinical relapse. A detailed breakdown is provided in Table 5. The proportion of patients from the whole treated group that are ever likely to fail (i.e. the proportion that fail to respond completely to therapy plus the proportion that are estimated to relapse if followed indefinitely) does not exceed two thirds of patients treated in the limited disease trials. The estimated proportions are 62% (95% CI: 48–75%) for patients treated with radiotherapy alone and 53% (95% CI: 38–71%) for patients treated with radiotherapy plus chlorambucil. The statistical probability that all patients will ultimately fail (i.e. that some are cured) is below 0.025 in both of these trial arms. The proportion of patients who are likely to fail in the disseminated disease trials is greater. However, Table 5 shows that it is highly unlikely for all patients with Ann Arbor stage III disease to ultimately fail ($P = 0.0001$). The proportion of patients likely to fail in this group is 82% (95% CI: 75–88%).

Anatomical patterns of relapse in patients with localised (Ann Arbor stage I and II) disease

(*a*) *Sites of relapse.* Table 6 provides details of site of first manifestation of relapse according to whether patients were randomised to radiotherapy alone or radiotherapy followed by 6 months of chlorambucil. The proportion of patients remaining at risk of relapse was slightly higher in the chlorambucil treated group because more of these patients experienced complete remission. However, no difference in the anatomical distributions of relapse could be detected between the groups. Sixty-five per cent (30/46) of relapses took place at nodal sites. While the majority of these took place in a nodal group adjacent to one of the originally affected groups, it is of interest that a significant minority of relapses (28%, 13/46) took place at nodal sites at some distance and separated from the originally affected nodal groups by at least one un-involved nodal group. (These have been termed non-contiguous relapses.) It will be noted that only a minority of first relapses were generalised (11/46, 24%). The site of one relapse was not clearly documented (and this has been termed an 'unknown' site in the table).

(*b*) *Nodal versus extranodal presentation.* Only 12 patients with Ann Arbor stage I and II disease could be classified as having an extranodal presentation. The parotid was involved in 6, the tonsil was involved in 3 and the thyroid in 3. Mixed and large cell histology was a feature in 8 patients which is a proportion that is considerably greater than is observed for nodal presentations in this series. Only 5 patients have relapsed to date which is a proportion that is similar to the proportion of patients with nodal presentations that relapsed. Disease-free and cause-specific survival curves for the 12 patients with extranodal disease were very similar to the corresponding curves for patients with nodal presentations (not shown).

DISCUSSION

The fact that the disease-free survival curve for any particular group of patients is biphasic does not necessarily mean that a subgroup of patients cured by treatment has emerged. It simply means that two populations of patients within that group exist—one that relapses quickly and the other at a

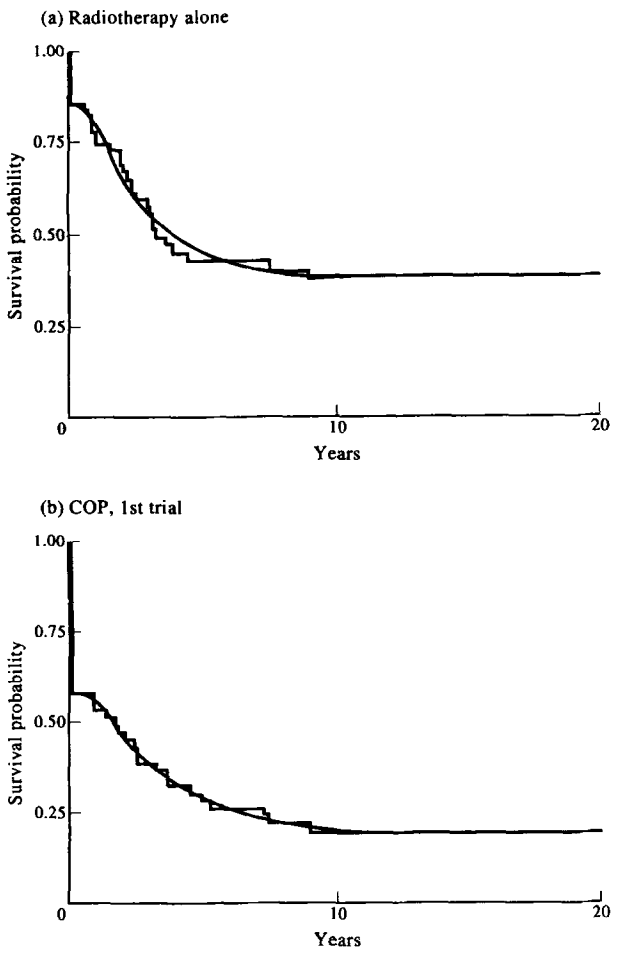

Figure 4. The approximation of Kaplan–Meier relapse-free survival plots for two of the trial arms to lognormal distributions.

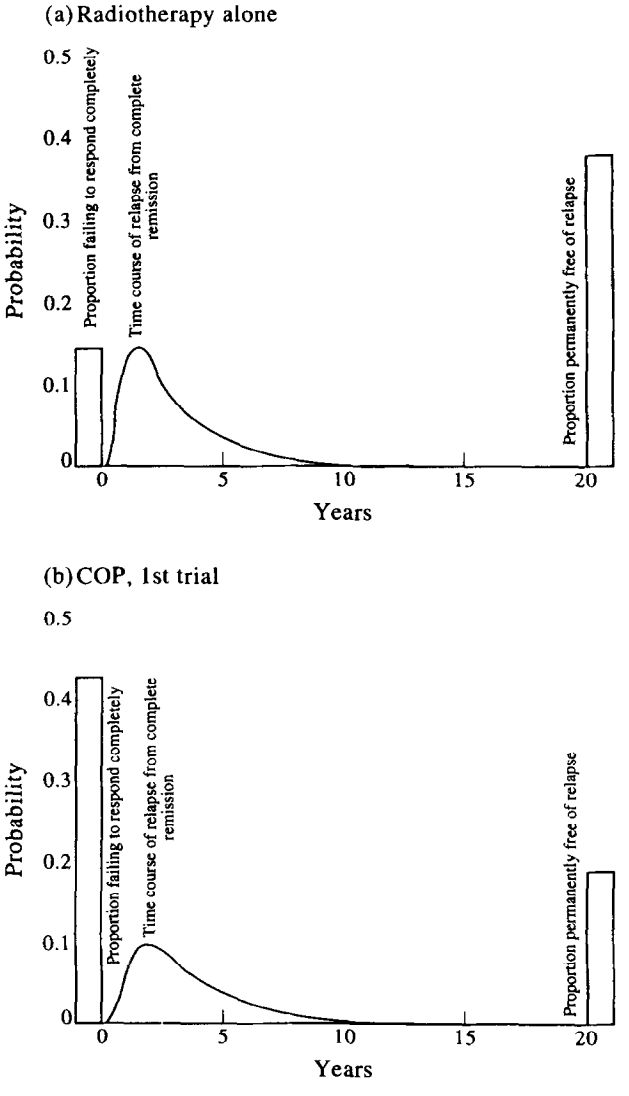

Figure 5. The temporal distribution of relapse for two trial arms illustrating maximum likelihood estimates for the proportion unlikely ever to relapse.

much lower rate. The two populations may not differ in their response to treatment, but the difference may be a result of the fact that there are subgroups of patients in whom the natural history of the disease evolves at a different rate. Many important prognostic factors have been identified for the follicular lymphomas besides the influence of treatment itself. Age is a particularly important one. Over the age of 60 years, patients more frequently fail to respond completely to treatment, and die more rapidly because of their disease [38, 57–60]. In attempting to define the influence of treatment itself on the biphasic nature of the disease-free survival curve, factors that have independently influenced prognosis, such as age, must be taken into account. The proportional hazards modelling performed on this series of patients suggested that, whereas histological subtypes and patient-related factors such as age and sex may have contributed in a minor degree to the biphasic nature of the disease-free curve, by far the greatest contributor in both limited disease and disseminated disease trials was a factor related to the advancement of the disease itself—the number of lymph node sites involved. Since relapse is more likely in patients with greater disease burdens prior to therapy, this type of information strongly suggests that it is the interplay between treatment itself and disease advancement that is responsible for the biphasic nature of the relapse-free survival curve.

There are two major difficulties in knowing whether a patient with follicular lymphoma remaining free of clinically obvious relapse is cured. It is well known, for example, that patients in clinical remission can have small numbers of circulating lymphocytes that exhibit the T14/18 translocations that are said to be pathogenomic of follicular lymphomas [61]. Patients treated in the trials analysed in this report have not been followed using polymerase chain reaction (PCR) techniques to identify abnormal circulating cells. Unfortunately, therefore, no comment can be offered as to the relevance of the finding to statistical clinical cure as described herein. In addition, it is well known that some patients may have paratrabecular infiltrates of "neoplastic" follicle cells in their marrows without obvious sign of disease elsewhere. A patient who is in clinical remission indefinitely and therefore is "clinically cured" may not necessary be "pathologically cured". No prospective investigation of this possibility has been conducted in patients treated in the trials analysed herein, but it is of interest that only 11 of 105 patients treated in the limited disease trials and who would now be considered understaged, developed generalised relapse. A further dif-

Table 5. Maximum likelihood estimates of the proportions of patients that remain permanently relapse-free following treatment, if lognormal relapse distribution is assumed

Group	Proportion	95% confidence intervals (%)	Relative likelihood* (%)
Limited disease trial			
Radiotherapy	38	25–52	0.0023
Radiotherapy plus chlorambucil	47	29–62	0.0233
Disseminated disease trials			
COP (first)	18	1–31	0.0305
Chlorambucil (first)	10	3–20	0.1427
COP (second)	14	3–23	0.0289
Chlorambucil (second)	15	0–25	0.0875
Ann Arbor stages			
Stages IA/B	55	37–69	0.0255
Stages IIA/B	28	16–43	0.0068
Stages IIIA/B	18	12–25	0.0001
Stages IVA/B	11	4–18	0.0334

*The "relative likelihood" values represent the probabilities that the proportions remaining permanently free of disease are zero.

Table 6. Sites of first relapse in patients treated in the limited disease trial

	Radiotherapy alone ($n = 55$)	Radiotherapy plus chlorambucil ($n = 50$)	Total ($n = 105$)
Incomplete response	8 (14.5%)	3 (6%)	11
Relapse (all sites)	24 (43.6%)	22 (44%)	46
Site of first relapse			
Original	1 (1.8%)	1 (2%)	2
Adjacent nodal	9 (16.4%)	10 (20%)	19
Non-contiguous nodal	8 (14.5%)	5 (10%)	13
Generalised	6 (10.9%)	5 (10%)	11
Unknown	0 (0%)	1 (2%)	1

ficulty in knowing where "clinical cure" is real cure is that the follicular lymphomas often pursue an extremely indolent course. Since patients afflicted are often in middle age or elderly, significant censorship occurs in any series of cases from death due to intercurrent causes and loss to follow-up. "Plateauing" of survival curves is not a particularly satisfactory method of inferring that a cured subset has emerged. A more statistically robust method is therefore necessary. It is in this situation that maximum likelihood estimation of the proportion of patients who are ever likely to relapse becomes useful. Relapse following treatment in every trial arm was found to approximate a lognormal distribution very closely. This made it possible to derive a statistical estimate of the size of the proportions of patients in each trial arm that are ever likely to relapse, and, of course, the proportion unlikely to relapse and therefore probably cured. From Table 5, it may be concluded that, while statistical "clinical cure" is taking place in over a quarter of patients treated in the limited disease trial, it may also be occurring in a small proportion of patients treated in the disseminated disease trials. What proportion of patients with limited stages of disease who will never experience clinical relapse, and at what stage of disease advancement "clinical cure" becomes unlikely, is far less easy to establish with certainty from the limited data that this series provides. Whereas 14 of 130 patients with Ann Arbor stage IIIA remain disease-free after the last recorded relapse at 14 years following treatment, only 3 of 105 with stage IVA disease remain relapse-free. More data would be required in this category to have a high degree of confidence that a small proportion of patients would never relapse.

Of course, it should be pointed out that the long-term relapse-free survival predictions for the early Ann Arbor stages in this series are consistent with the long-term relapse-free survival data from the Princess Margaret Hospital [44] and Stanford [46] series. In the Princess Margaret series, in which 248 patients with Ann Arbor clinical stages I and II disease were followed for a median time of 9 years, 53% of 190 patients treated with radiotherapy alone became long-term disease-free survivors. In the more rigorously staged Stanford series, a very similar proportion (54%) of 124 patients with Ann Arbor stages I and II disease became 10 year relapse-free survivors. If the substantial bodies of data from the EORTC [43] and elsewhere [60, 61] that also suggest that approximately 50% of patients with limited stage disease become long-term disease-free survivors, are added to the evidence provided by the Princess Margaret, Stanford and present series, a good case can be made for the appropriate staging of a newly presenting patient with follicular lymphoma and the provision of immediate treatment for patients with localised Ann Arbor stage I and II disease rather than a "wait and watch" policy.

Unfortunately, the number of patients in this series with isolated extranodal presentation is not great enough to know whether the natural history of such presentations differs substantially from the more usual nodal presentation. Relapse data from the 12 cases in this series who did have localised extranodal presentations (Ann Arbor stage IE or IIE) are very similar to the data for localised nodal (Ann Arbor stage I and II) presentations but little statistical confidence can be attached to this similarity. Unfortunately, therefore, a comment regarding the possibility of statistical cure in this group of patients cannot be made.

1. Luce JK, Gamble JF, Wilson HE, Monto RW, Isaaacs BL, Palmer RL. Combined cyclophosphamide, vincristine and prednisone therapy of malignant lymphoma. *Cancer* 1970, **28**, 306–317.
2. Bagley CM, De Vita VT, Berard CW, Canellos GP. Advanced lymphosarcoma: intensive cyclical combination chemotherapy with cyclophosphamide, vincristine and prednisone. *Ann Intern Med* 1972, **76**, 227–234.
3. KcKelvie EM, Gottlier JA, Wilson HE, *et al.* Hydroxydaunomycin (adriamycin) combination chemotherapy in malignant lymphoma. *Cancer* 1976, **38**, 1484–1493.
4. Anderson T, Bender RA, Fisher RI, De Vita VT, Chabner BA, Berard CW. Combination chemotherapy in non-Hodgkin's lymphoma: results of long term follow up. *Cancer Treat Rep* 1977, **61**, 1057–1066.
5. De Vita VT, Serpick AA, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Ann Intern Med* 1970, **73**, 881–895.
6. Glastein E, Guernsey JM, Rosenberg SA, Kaplan HS. The value of laparotomy and splenectomy in the staging of Hodgkin's disease. *Cancer* 1969, **24**, 709–718.
7. Hass AC, Brunk SF, Gulesserian HP, Givler RL. The value of exploratory laparotomy in malignant lymphoma. *Radiology* 1971, **101**, 157–165.
8. Bartlett NL, Rizeq M, Dorfman RF, Halpern J, Horning SJ. Follicular large-cell lymphoma: intermediate or low grade? *J Clin Oncol* 1994, **12**, 1349–1357.
9. Hanks GE, Terry LN, Bryan JA, Newsome JF. Contribution of diagnostic laparotomy to staging non-Hodgkin's lymphoma. *Cancer* 1972, **29**, 41–43.
10. Goffinet DR, Castellino RA, Kim H, Dorfman RF, Fuks Z, Rosenberg SA. Staging laparotomy in unselected previously untreated patients with non-Hodgkin's lymphomas. *Cancer* 1973, **32**, 672–686.
11. Ferguson DJ, Allen LW, Griem ML, Moran ME, Rappaport H, Ultmann JE. Surgical experience with staging laparotomy in 125 patients with lymphoma. *Arch Intern Med* 1973, **131**, 356–361.
12. Veronesi V, Musemeci R, Pizzett F, Gennari L, Bonnadonna G. The value of staging laparotomy in non-Hodgkin's lymphomas (with emphasis on the histiocytic type). *Cancer* 1974, **33**, 446–454.
13. Jelliffe AM. Diagnostic laparotomy in non-Hodgkin's lymphoma. *Br J Cancer* 1975, **31**, 248–251.
14. Moran EM, Ultmann JE, Ferguson DJ, Hoffer PB, Ranniger K, Rappaport H. Staging laparotomy in non-Hodgkin's lymphoma. *Br J Cancer* 1975, **31**, 228–236.
15. Lotz MJ, Chabner B, De Vita VT, Johnson RE, Berard CW. Pathologic staging of 100 consecutive untreated patients with non-Hodgkin's lymphoma. *Cancer* 1976, **37**, 266–270.
16. Collins RD, Lukes RJ. Studies on the possible derivation of some malignant lymphomas from follicular centre cells. *Am J Pathol* 1971, **62**, 63.
17. Lukes RJ, Collins RD. New observations on follicular lymphoma. *Gann Monogr Cancer Res* 1973, **15**, 209–215.
18. Lennert K. Follicular lymphoma. A tumour of the germinal centres. *Gann Monog Cancer Res* 1973, **15**, 217–231.
19. Bennett MH, Farrer-Brown G, Henry K. A classification of the non-Hodgkin's lymphomas. Presented at the workshop on classification of non-Hodgkin's lymphomas, University of Chicago. *Clin Radiol* 1973, **20**, 339–343.
20. Jaffe ES, Shevach EM, Frank MM, Berard CW, Green I. Nodular lymphoma—evidence for origin from follicular B lymphocytes. *N Engl J Med* 1974, **290**, 813–819.
21. Salmon SE, Seligmann M. B-cell neoplasia in man. *Lancet* 1974, **ii**, 1230–1233.
22. Jaffe ES, Shevach EM, Sussman EH. Membrane receptor sites for the identification of lymphoreticular cells in benign and malignant conditions. *Br J Cancer* 1975, **31**, 107–120.
23. Seligmann M, Brouet JC, Preud'Homme JL. Immunologic classification of non-Hodgkin's lymphomas: current status. *Cancer Treat Rep* 1977, **61**, 1179–1183.
24. Galton DAG, Catovsky D, Wiltshaw E. Clinical spectrum of lymphoproliferative disease. *Cancer* 1978, **42**, 901–910.
25. Weissman IL, Warnke R, Butcher EC, Rouse R, Levy R. The lymphoid system: its normal architecture and the potential for understanding the system through the study of lymphoproliferative diseases. *Hum Pathol* 1978, **9**, 25–45.
26. Warnke R, Levy R. Immunopathology of the follicular lymphomas—a model of 'B' lymphocyte homing. *N Engl J Med* 1978, **298**, 481–486.
27. Schein PS, Chabner BA, Canellos GP, Young RC, De Vita VT. Non-Hodgkin's lymphomas: patterns of relapse from complete remission after combination chemotherapy. *Cancer* 1975, **35**, 354–357.
28. De Vita VT, Canellos GP, Chabner BA, Schein PS, Hubbard SP, Young RC. Advanced diffuse histiocytic lymphoma a potentially curable disease. *Lancet* 1975, **i**, 248–250.
29. McKelvie EM, Moon TE. Curability of non-Hodgkin's lymphoma. *Cancer Treat Rep* 1977, **61**, 1185–1190.
30. Young RC, Anderson T, Bender RA. Nodular mixed lymphoma (NML). Another potentially curable non-Hodgkin's lymphoma. *Proc Am Soc Clin Oncol* 1977, **18**, 356.
31. Portlock CS, Glastein E. The non-Hodgkin's lymphomas: current concepts and management. *Ann Rev Med* 1978, **29**, 81–91.
32. Rosenberg SA. Non-Hodgkin's lymphoma—selection of treatment on basis of histologic type. *N Engl J Med* 1979, **301**, 924–928.
33. Ezdinli E, Costello WG, Fikri I, *et al.* Nodular mixed lymphocytic–histiocytic lymphoma. Response and survival. *Cancer* 1980, **45**, 261–267.
34. Muggia FM, Davis HH, Rosenweig M. Current cooperative trials in the non-Hodgkin's lymphomas. *Cancer Treat Rep* 1977, **61**, 1191–1197.
35. Nissen NI, Pajak T, Glidewell O, Blom H, Flaherty M, Hayes D. Overview of four clinical studies of chemotherapy for stage III and IV non-Hodgkin's lymphomas by the Cancer and Leukaemia Group B. *Cancer Treat Rep* 1977, **61**, 1097–1107.
36. Cabanillas F, Smith T, Bodey GP, Gutterman JV, Freireich EJ. Nodular malignant lymphomas: factors affecting complete response rate and survival. *Cancer* 1979, **44**, 1983–1989.
37. Dumont J, Asselain B, Weil M, *et al.* Evolution containe des lymphomes nodulaire. Devenir de 85 malades traites entre 1968 et 1975. *Nouv Presse Med* 1981, **10**, 2261–2265.
38. Rassiga A, Bartolucci A, Gams R, Durant J. Effect of chemotherapeutic regime on induction rate and survival in good risk non-Hodgkin's lymphoma. *Proc Am Soc Clin Oncol* 1981, **C719.**
39. Hayhoe FGH. Chemotherapy in the management of stage III/IV grade I non-Hodgkin's lymphomas. (Report No. 17). *Clin Radiol* 1981, **32**, 547–552.
40. Horning SJ, Rosenberg SA. The natural history of initially untreated low-grade non-Hodgkin's lymphomas. *N Engl J Med* 1984, **311**, 1471–1475.
41. Cheson PD, Wittes RE, Friedman MA. Low-grade non-Hodgkin's lymphomas revisited. *Cancer Treat Rep* 1986, **70**, 1051–1054.
42. O'Brien M, Easterbrook P, Powell J, *et al.* The natural history of low-grade non-Hodgkin's lymphoma and the impact of a no initial treatment policy on survival. *Q J Med* 1991, **292**, 651–660.
43. Paryani S, Hoppe RT, Cox R, Colby T, Rosenberg SA, Kaplan HS. Analysis of non-Hodgkin's lymphomas with nodular and favourable histologies, stages I and II. *Cancer* 1983, **52**, 2300–2307.
44. Gospodarowicz MK, Bush RS, Brown TC, Chau T. Prognostic factors in nodular lymphomas: a multivariate analysis based on the Princess Margaret Hospital experience. *Int J Radiat Oncol Biol Phys* 1984, **10**, 489–497.
45. Carde P, Burgers JM, van Glabbeke M, Hayat M, Cosset JM, Somers R. Combined radiotherapy–chemotherapy for early

stages non-Hodgkin's lymphoma, the 1975–1980 EORTC controlled lymphoma trial. *Radiother Oncol* 1984, **2**, 301–312.
46. Sutcliffe SB, Gospodarowicz MK, Bush RS, *et al.* Role of radiation therapy in non-Hodgkin's lymphoma. *Radiother Oncol* 1985, **4**, 211–223.
47. Hoppe RT. The role of radiation therapy in the management of the non-Hodgkin's lymphomas. *Cancer* 1985, **55**, 2176–2183.
48. Tubiana M, Carde P, Burgers JM, Cosset JM, van Glabbeke M, Somers R. Prognostic factors in non-Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys* 1986, **12**, 503–514.
49. Phillips DL. Radiotherapy in the treatment of localised non-Hodgkin's lymphoma (Report No. 16). *Clin Radiol* 1981, **32**, 543–546.
50. Rosenberg SA, Berard CW, Brown BW, *et al.* Study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. *Cancer* 1982, **49**, 2112–2135.
51. Boag JW. Maximum likelihood estimates of the proportion of patients cured by cancer therapy. *J R Stat Soc* 1949, **11**, 15–53.
52. Gamel JW, McLean IW, Rosenberg SA. Proportion cured and mean log survival time as functions of tumour size. *Stat Med* 1990, **9**, 999–1006.
53. Gordon NH. Application of the theory of finite mixtures for the estimation of 'cure' rates of treated cancer patients. *Stat Med* 1990, **9**, 397–407.
54. Kaplan EL, Meier P. Non-parametric estimation from incomplete observation. *J Am Stat Assoc* 1958, **53**, 457–481.
55. Peto R, Pike MC, Armitage P, *et al.* Design and analysis of randomised clinical trials requiring prolonged observations of each patient. II. Analysis and examples. *Br J Cancer* 1977, **35**, 1–39.
56. Cox DR. Regression models and life tables. *J R Stat Soc* 1972, **34**, 187–220.
57. Jones SE, Fuks Z, Bull M, *et al.* Non-Hodgkin's lymphomas: IV. Clinicopathologic correlation in 405 cases. *Cancer* 1973, **31**, 806–823.
58. Ciampi A, Bush RS, Gospodarowicz M, Till J. An approach to classifying prognostic factors related to survival experience for non-Hodgkin's lymphoma patients. *Cancer* 1981, **47**, 621–627.
59. Straus DJ, Gaynor JJ, Leiberman PH, Filippa DA, Koziner B, Clarkson BD. Non-Hodgkin's lymphomas: characteristics of long-term survivors following conservative treatment. *Am J Med* 1987, **82**, 247–256.
60. Bonnadonna G, Saccani-Jotti G. Prognostic factors and response to treatment in non-Hodgkin's lymphoma. *Anticancer Res* 1987, **7**, 685–694.
61. Ngan BY, Chen-Levy Z, Weiss LM, Warnke R, Cleary ML. Expression in non-Hodgkin's lymphoma of the BCL-2 protein associated with the T(14,18) chromosomal translocation. *N Engl J Med* 1988, **318**, 1638–1644.

Acknowledgements—The authors are grateful to the many past and present members of the British National Lymphoma Investigation who have participated in the trials organised by the BNLI but particularly to Dr A.M. Jelliffe, past Chairman. The authors are also grateful to Bryan Vaughan Hudson and other past and present staff members of the BNLI office. The BNLI is supported financially by the Lymphoma Research Trust, the Cancer Research Campaign, the Lisa Lear Fund and The Isle of Man Anti-Cancer Association. Its offices are supported by the Middlesex Hospital National Health Trust, London, U.K.