Q J Med 1998; **91**:131–139

Hodgkin's disease: a population-adjusted clinical epidemiology study (PACE) of management at presentation

P.R.A. TAYLOR[1], B. ANGUS[2], J.P. OWEN[3] and S.J. PROCTOR[1] on behalf of the Northern Region Lymphoma Group*

From the Departments of [1]Haematology, [2]Histopathology, and [3]Radiology, Royal Victoria Infirmary, Newcastle upon Tyne, UK

Received 8 September 1997 and in revised form 5 December 1997

Summary

Between January 1991 and December 1993, all newly-diagnosed patients with Hodgkin's disease in the Northern Health Region (population 3.08 million) were entered into a prospective population-based (PACE) study to assess the accuracy of staging at diagnosis, and to evaluate treatment and outcome. On histological review, 202 patients were confirmed to have Hodgkin's disease, an incidence of 2.2 per 100 000 per annum. Radiological review revealed that only 12% of patients were staged to recognized guidelines. In early-stage disease, treatment outcome was comparable to published results in Stage IA disease, but disappointing for Stage IIA. This was partly due to inadequate or inaccurate staging. In-built audit in the process was followed by the introduction and implementation of improved guidelines. Of younger patients (15–55 years) with 'poor-risk disease', 75% of the eligible population were entered into the appropriate randomized controlled trial. This intensive treatment has led to improved survival in this group over that which might be expected on four-drug therapy. The results of the randomized trial are not discussed as it is currently ongoing. This combined research/audit programme has resulted in greater standardization of care across a whole region, and confirms that the PACE (population-adjusted clinical epidemiology) approach facilitates the flow of information from research into practice and vice versa.

Introduction

Hodgkin's disease is a rare malignancy, accounting for 1 in 4 of all lymphoma cases. It is one of the 'curable' cancers with well-described protocols for investigation and management. In most health-care systems, it is likely that the specialist physician who first sees the patient will organize all the investigations and treatment. While large centres may see substantial numbers of cases from a given geographical area, many patients are seen and treated by other physicians in adjacent smaller hospitals, and thus data reported by larger centres may be unrepresentative of the wider population.

In the Northern Region Lymphoma Group (part of the Scotland and Newcastle Lymphoma Group, SNLG), population-based studies have been in operation for over a decade.[1–3] To evaluate the overall state of Hodgkin's disease management in our population, a prospective multidisciplinary study was constructed to assess the accuracy of diagnosis and staging, and to review clinical management. A secondary aim of the study was to assess whether such a clinical research/medical audit approach would enhance recruitment to the existing SNLG randomized study in operation for patients with poor-risk Hodgkin's disease. This strategy follows the PACE (population-adjusted clinical epidemiology) approach recently described by our group,[4] aimed at making research immediately clinically relevant

Address correspondence to Professor S.J. Proctor, Department of Haematology, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP

* See Acknowledgements for the list of Group members.

and, therefore, allowing findings to move seamlessly into practice. We report on the first 3 years of this programme.

Methods

Between 1 January 1991 and 31 December 1993, all patients with Hodgkin's disease presenting in the Northern Health Region of England (population 3.08 million) were registered. This was made possible by the co-operation of regional pathologists, haematologists, and medical and clinical oncologists, who all registered patients. Although this led to some duplication, on cross-checking with Cancer Registries, no additional cases were revealed. The date of diagnosis was taken as the date of the original, unreviewed, pathological report.

Histopathology

Regular (fortnightly) multidisciplinary lymphoma review meetings are held centrally, and these facilitate rapid, central review of histopathological material by one of us. The meetings are open to all interested physicians and pathologists in the Region. The diagnosis of Hodgkin's disease was confirmed, and interpretation assisted, by the use of immunohistochemistry on paraffin sections where considered appropriate. The standard panel of antibodies used for immunohistochemistry was L26 (CD20, Dako), MBI (CD45RA Novocastra), MT1 (CD43 Novocastra), CD3 (Dako), CD15 (Novocastra) BerH2 (CD30, Dako). For immunostaining of paraffin sections a standard avidin-biotin peroxidase technique was employed. Subtypes were allocated according to the RYE classification.[5]

Staging procedures

Recommended staging procedures at diagnosis included a detailed history and examination, full blood count with differential white cell count, and a comprehensive biochemical profile (Figure 1). A bone-marrow aspirate and trephine was recommended in patients with Stage III/IV disease or in the presence of an abnormal full blood count or systemic 'B' symptoms. On review of the presentation details, information was collected on whether or not a bone-marrow examination was performed as part of the initial staging and the results were recorded.

Radiology

Recommended radiological staging for patients with Hodgkin's disease included CT scan of thorax, abdomen and pelvis and chest radiograph. With the co-operation of other radiological colleagues throughout the Region, all analogue images such as chest and skeletal radiographs and CT 'hard copy', as well as CT optical disc data, (where available) were reviewed centrally. (JPO and colleagues). The time from diagnosis to the first CT scans and other radiological assessments was recorded and all protocols used in the examinations were assessed to see if they conformed to Cotswold/Royal College of Radiologist Guidelines.[6,7] These guidelines recommend that 10 mm contiguous sections through the chest, abdomen and pelvis should be performed and that if there is any doubt regarding the presence of disease, then the examination should be repeated using intravenous contrast medium. Reports by the original radiologists were compared to those of the reviewer and also to the physician's interpretation of the original report. Patients were 'restaged' when necessary, and both the original and revised staging were recorded.

Clinical details

Full presenting details were obtained from the hospital notes of all confirmed cases of newly diagnosed HD. Information collected included the pattern of nodal presentation, the presence or absence of extranodal disease and B symptoms, the full blood count and biochemistry profile. From this information the patient's prognostic index was calculated (see Figure 1). Patients were allocated a clinical stage using the Ann Arbor classification.[8]

Treatment

In our Region, since the late 1980s, the SNLG prognostic index has been in use for therapy decisions, in preference to classical Ann Arbor staging alone.[9] Treatment guidelines in use during the time of this study are shown in Figure 2, and details of trial HD3 are shown in Figure 3. Full treatment details were collected and an assessment was made as to whether or not this corresponded to agreed Regional guidelines. Reasons for non-compliance were requested from the physician in charge of treatment and documented. Patients aged <15 years were under the care of specialists in a Paediatric Cancer unit, and were excluded from the treatment analysis.

Clinical audit

Each year, starting in July 1992, data from the study was fed back to all participants (clinical, pathological, radiological) in order that adjustments in practice might result. Thus a 'rolling' audit was linked to the research programme.

HODGKIN'S DISEASE INDEX

To calculate the index, patient's age, clinical stage, absolute lymphocyte count, haemoglobin and bulk disease are required.

The index (I) + 1.5858 - 0.0363 Age + 0.0005 (Age^2)
+ 0.0683 CS - 0.086 LC - 0.0587 Hb
+ additional factor if bulk disease is present*

Age is entered as an absolute figure in the equation

Clinical stage entered according to the key (Ann Arbor Classification)

IA,IIA,IIIA	=	1
IB,IIB	=	2
IIIB	=	3
IV	=	4

Absolute lymphocyte count is entered as a score

< 1.0 x 10^9/l	=	1
1.0-1.5 x 10^9/l	=	2
1.5-2.0 x 10^9/l	=	3
>2.0 x 10^9/l	=	4

Haemoglobin (Hb) in g/dl is entered as an absolute figure in equation

* Bulk disease (> 10cms) - index score, add 0.3

Patients with index 0.5 have risk of death from progressive HD of 60 - 70% in 4 years. Such patients are being entered on a trial protocol in first remission.

This index is not for use in patients < 15 years of age.

Figure 1. Scotland and Newcastle Lymphoma Group; numerical prognostic index used to identify patients with 'poor-risk disease'.

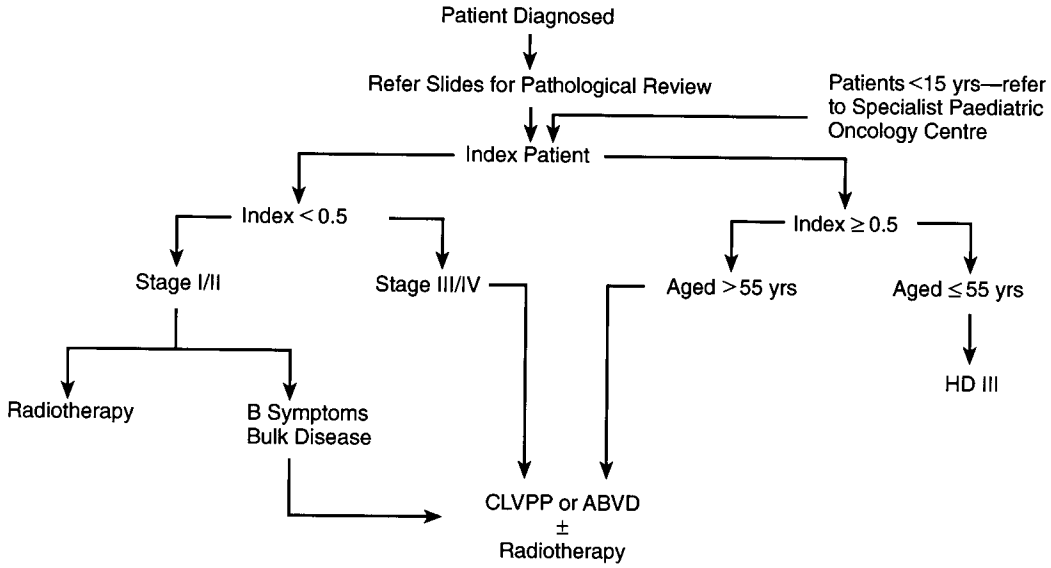

Figure 2. Regional guidelines for the treatment of Hodgkin's disease 1991–1993.

Results

The Northern Health Region contains a population of 3.08 million and in the 3 years 1991–1993, 213 patients were notified to the register as new cases of Hodgkin's disease. Of these, 11 patients were not eligible for inclusion in this study cohort; eight were excluded because they were either relapsed cases or had been diagnosed outside the region; only three patients were found not to have Hodgkin's disease. Two patients included in the cohort were originally diagnosed as non-Hodgkin's lymphoma and had been treated for this prior to the diagnosis of Hodgkin's disease being made. Thus 202 patients

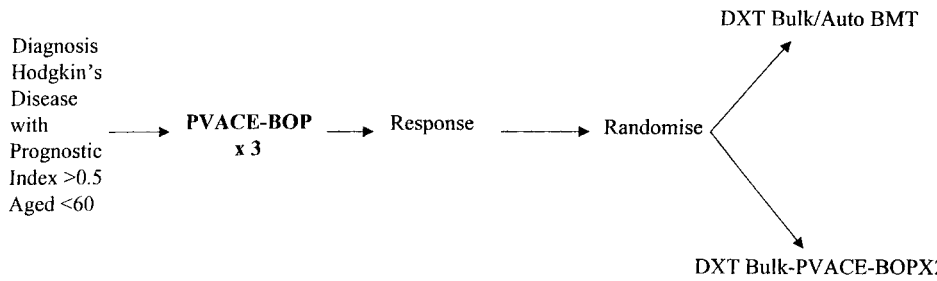

Figure 3. PVACEBOP (prednisolone, vinblastine, adriamycin, chlorambucil, etoposide, bleomycin, vincristine, procarbazine) is a continuous 28-day cycle similar in dose intensity to Stanford V (reference 23).

were confirmed to have newly-presenting Hodgkin's disease, a crude incidence of 2.2 per 100 000 per annum. There were 121 males, and 81 females, with a median age of 39 years (range 7–85). The peak incidence was in the third and fourth decades (Figure 4). It is noteworthy that 21% of patients were aged 56 years or more at diagnosis. An analysis of the hospital where initial treatment took place, revealed that 72% of patients were treated in non-teaching (non-University) hospitals.

Pathology

After central review, the histological subtypes were nodular sclerosing (60%), mixed cellularity (18%), lymphocyte-depleted (2%) and lymphocyte-predom-

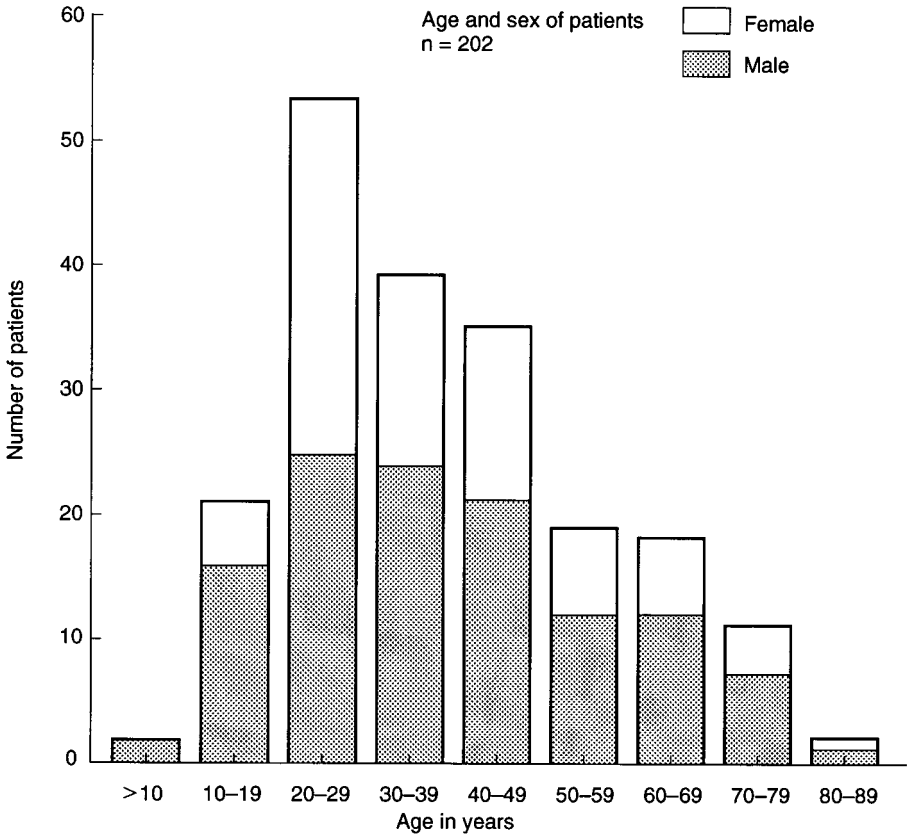

Figure 4. Distribution, by age and sex, of patients diagnosed with Hodgkin's disease, 1991–1993.

inant (17%). In five patients, it was impossible to define a subtype, as the specimen was inadequate or (in two of these) the diagnosis had been made on a bone-marrow biopsy.

Staging

An analysis of the results of review of the original radiological material are shown in Table 1 and Figure 5. A significant number of patients were not CT scanned before treatment. Of those who were scanned, 15% of the chest and abdominal/pelvic CTs were undertaken more than 8 weeks after diagnosis. Many different CT protocols had been used, and the majority did not comply with RCR/Cotswold guidelines. Only 24/202 (12%) of patients were staged exactly according to guidelines.

Following review of the scans, the initial reports and the initial staging which had been allocated by the physician in charge of treatment, 14% were found to have been incorrectly staged. In four, this was due to a misinterpretation of the original radiological report by the physician. Of the 29 patients restaged on review, 20 had their staging altered such that chemotherapy would have been indicated as the treatment of choice rather than radiotherapy alone. Of these 20 patients, 10 had been spared inappropriate treatment by the application of the HD index.

Following the first audit meeting in July 1992, when an initial report of these findings was presented, an improvement was observed in the number of studies done to protocol. In the subsequent 18 months, CTs of chest improved from 42 to 57%, and of the abdomen from 11 to 25%; in the same period, the number of patients staged to guidelines rose from 6/140 (4%) to 18/93 (19%). Radiologists were also encouraged to change the style of their reporting to incorporate a 'summary' line at the end of the report to minimize the chances of individual misinterpretation.

Bone-marrow examination

Bone-marrow biopsies (a more controversial feature of the staging procedure) were done in 61% of patients. In only 18 of these patients (15%) was evidence of bone marrow infiltration found, i.e. 85% were negative. If the procedure had been limited to those patients with abnormal full blood counts and/or B symptoms, none of the 18 patients with a 'positive' marrow would have been missed, and 40% of the remainder would have been spared an unpleasant

Table 1 Imaging procedures in 220 patients

	Not done prior to treatment *n* (%)	Number of different protocols used	Not complying with RCR/Cotswold guidelines (%)
CT chest	54 (27)	14	53
CT abdomen and pelvis	46 (23)	20	83
Chest X-ray	75 (37)		

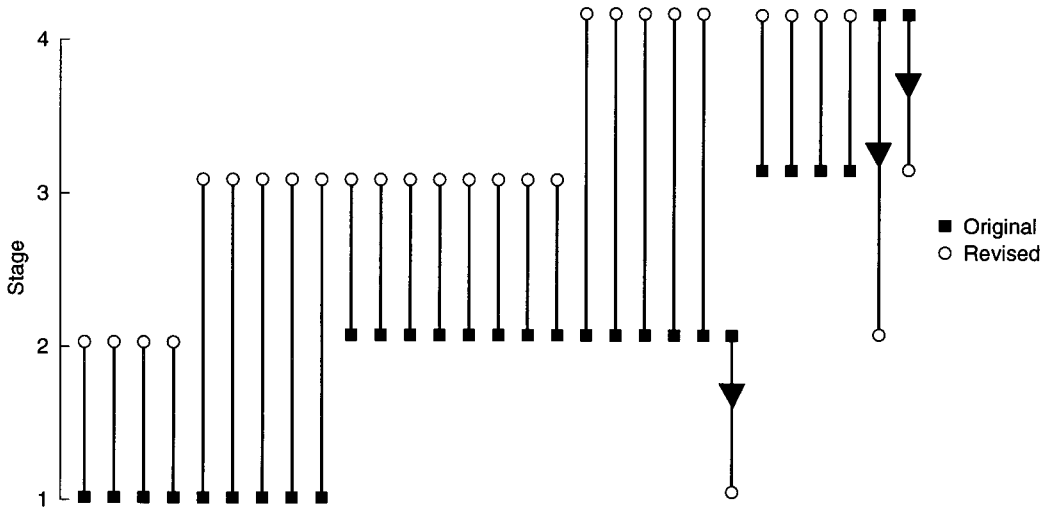

Figure 5. Staging following central review of original staging material: 29 patients had their initial staging revised.

procedure which, if sedation or general anaesthetic is used, is not without risk.

Treatment

The SNLG prognostic index, which is used in the Region to help determine therapy, was applied to all adult patients (Tables 2 and 3). This index (Figure 1), which includes stage, is used to help identify those patients requiring intensive chemotherapy but also, conversely, to identify those patients with advanced stage disease who are expected to benefit from more conventional four-drug regimens.[9]

In Tables 2 and 3, patients are divided into younger (15–55 years) and older (>55 years). The tables demonstrate the stages cross-referenced to the SNLG index, which places patients into good, intermediate and poor risk categories. In the younger group, (Table 2), 34/70 of the Stage III/IV patients did not have a 'poor' index, i.e. were in a category which indicated they could be spared, newer, intensive treatments and would be predicted to respond well to the more traditional four-drug treatment schedules. Those with a poor index (regardless of stage) and who were considered able to tolerate an intensive regimen were eligible for the current SNLG HD3 trial, and as seen in Figure 5, 80% of those eligible for the Regional trial were offered this study, with the majority of the remainder being given similar intensive treatment off-study. The overall survival figures available at this time, with a median follow-up of 4 years, indicate a marked improvement for these 'poor' index patients compared to that predicted, such that they now have a similar survival pattern to that seen in the more favourable prognostic groups. On the other hand, the patients with advanced-stage disease who were not eligible for the trial and who were generally treated with well-established four-drug regimens, do not appear to have been disadvantaged in survival terms. (Table 2).

In the older patients (>55 years), who were not eligible for HD3 because a pilot study had indicated they would be unable to tolerate it, the index remains valid; whilst the majority of higher stage patients have a poor index, the index identifies those with less advanced stage who have a poor prognosis. (Table 3).

Discussion

The aim of this study was to try and identify all new patients with Hodgkin's disease presenting in the Northern Health Region, and to assess the accuracy of the diagnosis and staging in these patients; patients would also be followed-up, and treatment and outcome monitored so that the impact of the introduction of a numerical prognostic index for clinical decision-making could be evaluated.

We observed the predicted number of cases of Hodgkin's disease for our population,[10] with the expected excess of males and a peak incidence in the third and fourth decade. However, we did note a higher than expected incidence of the lymphocyte-predominant subtype. It must be conceded, however, that the assignment of cases of HD to specific subtypes is notoriously subjective.[11] The percentage we observed is in accord with some early studies[5] where the LP classification accounted for 16.7% of cases. Both diffuse and nodular subtypes were included in that study, as in our own. More recent investigations have found a much lower incidence

Table 2 Hodgkin's disease cohort categorized by classical staging and SNLG prognostic index: younger patients (15–55 years)

Prognostic index	Sex (M/F)	Age (years) median (range)	Stage				5-year actuarial overall survival
			1	2	3	4	
Good	52/29	30(17–55)	23	37	18	3	87%
Intermediate	14/12	36(17–55)	3	10	9	4	78%
Poor	26/21	31	0	12	9	27	75%

Table 3 Hodgkin's disease cohort categorized by classical staging and SNLG prognostic index: older patients (>55 years)

Prognostic index	Sex (M/F)	Age (years) median (range)	Stage				5-year actuarial overall survival
			1	2	3	4	
Good	4/4	61(56–63)	2	6	0	0	75%
Intermediate	2/2	59	0	2	2	0	66%
Poor	18/11	67	5	6	7	11	34%

of LP HD, (2.7% and 4.1%),[12,13] but in these cases much stricter criteria had been applied. Review of these 1991/1993 cases within the context of the European Task Force, LPHD study,[14] reallocated 2 of the 30 cases designated LPHD as classical Hodgkin's disease, and thus the true incidence of LPHD in this study is probably 12% which compares with an instance of 13% of patients on the SNLG computer database registered at the same time in Scotland (J. White, personal communication).

Clear guidelines exist for the radiological staging of Hodgkin's disease,[6,7] and yet the review of the staging procedures produced some disturbing findings. All the patients had been allocated a 'stage' by the physician in charge of their treatment, yet a surprising number (nearly 25%) had had neither CTs of the chest or abdomen nor a chest X-ray prior to the start of treatment. Further, of the CTs, only 47% of the examinations of the chest and 17% of those of the abdomen complied with the guidelines published by the Royal College of Radiologists or suggested at the Cotswold Meeting.[6,7] At the July 1992 audit meeting held to discuss the first year's results, it became apparent that the majority of physicians reading CT scan reports were unaware that these examinations were done to many different protocols and that a CT scan of chest performed under the direction of one radiologist was not, necessarily, strictly comparable to one done by a colleague, even in the same institution. Reading a report which states 'no sign of disease', few physicians look to see which protocol has been used (or whether, for instance, the lungs have been viewed separately).

Thus, of our cohort of over 200 patients, the majority had not been optimally staged by radiological means. This lack of accuracy in staging perhaps accounts, in some measure, for the fact that the results from single-institution treatment trials reported in the literature are seldom as successful when applied to populations of unselected patients. Our data would suggest that when multicentre trials or studies are being designed in which CT scans form an essential part of staging, the protocols to be used by the radiologists should be specified in some detail, and well publicized to all participants, so that patients staged in one hospital are strictly comparable to those staged in another.

Despite recommendations to the contrary,[15] many patients with normal full blood counts and no B symptoms, continued to have bone-marrow biopsies performed. This is an unpleasant procedure for the patient and, if sedation is used, not without risk.[16] If the published guidelines had been followed, 55 patients would have been spared this procedure. It would perhaps be more valuable if fewer routine biopsies were performed, and in those patients where it is indicated, to do bilateral trephines; it has been shown that performing bilateral biopsies increases the number of positive results.[17] New Regional guidelines for the indications for performing bone-marrow biopsies in these patients have now been accepted.

The third aim of the study was to monitor the treatment and outcome of all the patients with Hodgkin's disease. The six patients aged <15 years are excluded from the treatment analysis. All other patients were treated by haematologists and/or clinical/medical oncologists, with regional guidelines available (see Figure 2). An analysis of the compliance with treatment guidelines for early stage disease (IA and IIA) showed that whilst 73% of stage IA patients were treated to guidelines, only 45% of Stage IIA were so treated. Treatment outcome was found to be comparable to published results for Stage IA disease, but was disappointing for Stage IIA, partly due to inadequate and inaccurate staging.

Patients with more advanced disease, prognostic index >0.5, who were aged <56 years were eligible for the current HD3 (SNLG) trial if they had a poor index; of those eligible, 75% entered the study (Figure 6). It was felt that the existence of this 'cohort' study and the regular (twice monthly) multidisciplinary lymphoma meetings aided recruitment. The use of the index also led to 10/20 patients who had been 'understaged' and who would have therefore been undertreated, being given appropriate therapy.

The index was also applied to the older group of patients. It is well known that age in itself is a significant prognostic factor in Hodgkin's disease,[18–20] but unfortunately older patients are unable to tolerate the intensive drug regimes used in younger people. Twenty-one per cent of the total cohort were aged >55 years. Because they could not tolerate this more intensive treatment, the index was seldom used to influence treatment in these patients and results were similar to those recorded elsewhere. However, more recently a novel treatment protocol for these patients was introduced, and is currently being assessed.

Conclusions

Despite well-recognized guidelines on staging in Hodgkin's disease, physicians continue to perform bone marrow biopsies on patients where it is not indicated. There was wide variation in the protocols used for radiological staging. Some patients were not referred to the radiologists for staging at all prior to treatment, and less than half of the CT scans were done to recognized guidelines. Dialogue needs to be maintained between physicians and radiologists and results such as these discussed so that the staging

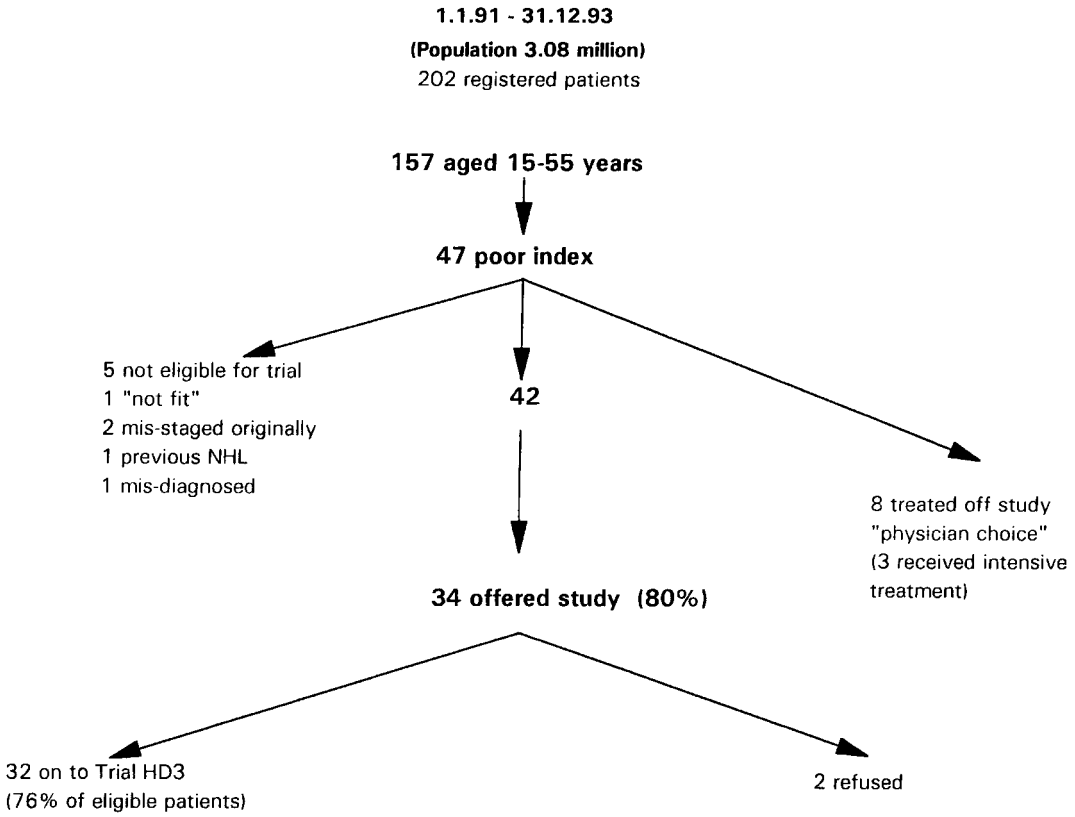

Figure 6. An analysis of treatment given to patients aged 15–55 with 'poor risk' Hodgkin's disease, to determine how many eligible patients were offered trial HD3.

of patients with Hodgkin's disease and other malignancies is standardized. When apparent stage of disease influences treatment, such staging must be dependable. The level of recruitment to our 'poor prognosis' study (75% of those eligible) suggests that multidisciplinary collaborative studies can improve patient care in all areas of management and provide representative populations of patients for the randomized trial process.

Recently the Consort initiative[21] decreed that clinical trial reporting should count and categorize patients not included in the study. Others[22] have concluded that such characterization is often impossible and probably pointless, since stratification in modern randomized trials is more rigorous. We feel however, that being able to assess accurately the impact that a particular randomized trial will have on outcome in the total population of patients with a particular disease is critical, and that this can only be done by placing the trial in context, i.e. by collecting information on exclusions.[4] We have demonstrated that this is not only possible but also that by having such a structure in place, recruitment of a homogenous patient population to the randomized trial is improved, and the true impact of a novel treatment intervention on disease outcome can be assessed.

Acknowledgements

We are extremely grateful to the Radiology Departments of the collaborating hospitals for generously allowing us to review the radiological images of their patients. Special thanks to Linda Smith for her exceptional skills in designing and maintaining the computer database for the data analysis, to Linda Burn for assistance with collecting clinical information, and to Jennifer Wilkinson for secretarial help.

The Northern Region Lymphoma Group are: M. Abela, G. Baird, A. Branson, N. Browning, P. Carey, R. Cartner, J. Chandler, C. Chapman, P. Condie, P.J. Dawes, M. Dewar, R. Finney, M. Galloway, D. Goff, P. Hamilton, A. Hendrick, G.H. Jackson, M. Keenan, P. Kesteven, A. Lennard, H. Lucraft, I. Neilly, H. O'Brien, M. Reid, D. Ritchie, J. Roberts, A. Rathmell, P. Saunders, D. Stainsby, G. Summerfield, H. Tinegate, J. Wallis, N. West, P. Williamson, K. Windebank, A. Youart.

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