Malignant lymphomas: results and observations from St George’s Hospital

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Summary
With both Hodgkin’s and non-Hodgkin’s lymphoma, the results documented compare well with reference series. Hence the advantages of a modest clinic need not be at the cost of recovery or of survival.

A major factor attenuating the scale of therapy in Hodgkin’s disease is the risk of inducing second malignancies. Four such complications have been observed amongst 27 patients with Hodgkin’s disease.

Amongst the patients with non-Hodgkin’s lymphoma better results were noted than the designation ‘poor prognosis histology’ had led the authors to expect. These findings suggest that the concept of histologically based prognosis may be over-subscribed and that contemporary therapeutic strategies can be extremely effective in this group.

Introduction
A Combined Lymphoma Clinic was inaugurated at St George’s Hospital, London, in 1973 through collaboration of physicians, radiotherapists and haematologists. The authors feel it may now be instructive to document the results and observations in a small clinic with certain advantages for both the patient and the clinician.

Materials and methods
The study was based on 27 cases of Hodgkin’s disease (HD) and 36 cases of non-Hodgkin’s lymphoma (NHL) managed in the Combined Lymphoma Clinic at St George’s Hospital in the period April 1973–January 1980. Eight of the patients with HD and 4 of those with NHL were diagnosed before April 1973.

Hodgkin’s disease
Of the 27 patients, 21 were male and 6 female, a greater male preponderance (3:5:1) than is usually the case (Smithers, 1973). The mean age was 42 years (range 15–77). The distribution was bimodal with a distinct paucity of cases (only one) in the 30–40 years age group.

Histological material was classified according to the Rye nomenclature (Lukes et al., 1966), and the following distribution was found: lymphocyte predominant (LP) 2, mixed cellularity (MC) 11, nodular sclerosis (NS) 10, lymphocyte depleted (LD) 3, and unclassified 1. Four of the 6 women in the series had the NS subtype and the other 2 the MC subtype.

The Ann Arbor Staging Classification (Carbone et al., 1971) was used. Nineteen patients were submitted to laparotomy and 8 were clinically staged. Of the latter, 6 were clinically advanced (Stages IIIB or IV) and 2 were not fit for surgery (IB and IIA). Table 1 shows the relationship of histology to stage at the time of presentation. With the exception of the NS group there appears to be correlation between histology and stage. NS was represented by all stages, and of the 10 patients in this group 6 had mediastinal involvement. Only one other patient (MC) in this series had mediastinal disease.

Treatment followed conventional lines (Rosenberg, 1978). Patients with pathological Stage I and II disease were treated with wide field radiotherapy—mantle or inverted Y. Patients with pathological Stage IIIA disease were given total nodal irradiation. Combination chemotherapy with MOPP (mustine, vincristine, procarbazine, prednisolone), MVPP (mustine, vinblastine, procarbazine, prednisolone), or CHLPP (chlorambucil, vinblastine, procarbazine, prednisolone) was reserved for patients with Stage IIIB and IV disease and for those who failed to respond to or who relapsed after initial radiotherapy. Three patients with advanced disease including mediastinal involvement were treated with both chemotherapy and radiotherapy.
Non-Hodgkin’s lymphoma

There were 19 males and 17 females. The mean age was 60 years (range 20–86). The Rappaport system of histological classification was used (Rappaport, 1966). Table 2 shows the relationship of histology to clinical stage at presentation. It is generally accepted that nodular well differentiated lymphocytic (NWDL), nodular poorly differentiated lymphocytic (NPDL), diffuse well differentiated lymphocytic (DWDL) and nodular mixed (NM) lymphomas have a favourable prognosis, while diffuse poorly differentiated lymphocytic (DPDL), diffuse mixed (DM), nodular histiocytic (NH) and diffuse histiocytic (DH) lymphomas are associated with poor prognosis (Jones et al., 1973). In this series the majority of patients with ‘favourable’ histology were in advanced stage at presentation, whereas a significant proportion of patients with ‘unfavourable’ histology presented with early stage disease.

Treatment of patients with ‘favourable’ histology was given only when clinically necessary, consisting of either local radiotherapy or single drug chemotherapy, typically chlorambucil. In contrast, disease of ‘unfavourable’ histology was treated intensively from the time of diagnosis with extended field radiotherapy and/or combination chemotherapy with COP (cyclophosphamid, vincristine, prednisolone) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone).

Statistical analysis

In the analyses, duration of survival was measured from time of diagnosis and duration of remission from time when complete clinical remission was achieved. Survival curves were calculated by means of the life-table method; levels of significance were based on the logrank test (Peto et al., 1977). Only one patient with HD was lost to follow-up.

Results

Hodgkin’s disease

Survival. The 5-year survival rates were 74% overall, 90% for Stages I+II and 56% for Stages III+IV (Fig. 1(a)). The difference between Stages I+II and Stages III+IV was significant (P<0-02). Survival ranged from 2 months to >10 years. Figure 1(b) shows survival in relation to histology. The difference between MC and NS was not significant (P>0-5). Although there were no deaths related to the disease in the LP and LD groups the numbers are too small for any meaningful conclusion.

Remission. Complete clinical remission occurred in all patients except 2 who died of unrelated cause before remission could be achieved. The duration of first remission ranged from 9 months to >6 years; there was no significant difference between early and late stage disease or the various histological groups.

Relapse. Nine relapses were observed among the 25 patients who achieved remission. Of these 9, 4 (44%) had occurred within the first year, 6 (67%) by the end of the second year, 7 (78%) by the end of the third year and 8 (89%) by the end of the fourth year. The remaining relapse occurred after 28 years.

<table>
<thead>
<tr>
<th>Stage</th>
<th>NWDL</th>
<th>DWDL</th>
<th>NPDL</th>
<th>NM</th>
<th>DPDL</th>
<th>DM</th>
<th>NH</th>
<th>DH</th>
<th>Others</th>
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NWDL = nodular well differentiated lymphocytic; DWDL = diffuse well differentiated lymphocytic; NPDL = nodular poorly differentiated lymphocytic; NM = nodular mixed; DPDL = diffuse poorly differentiated lymphocytic; DM = diffuse mixed; NH = nodular histiocytic; DH = diffuse histiocytic.

Fig. 1. Hodgkin’s disease: life-table estimate of duration of survival in relation to (a) pathological stage (P<0.2) and (b) histology (P>0.5). (●) (▲) and (○) represent patients still surviving.
of complete remission. Survival after relapse ranged from 6 months to more than 9-5 years. In 4 patients death occurred between 6 and 30 months after relapse. The other 5 patients are alive, second remission ranging from 30 months to 9-5 years so far.

Causes of death. Figure 2 shows the cause of death and length of survival in 9 patients who have died. Two infec tive deaths during remission may be attributable partly to treatment (chemotherapy in patient 3, and previous splenectomy in patient 6). Three deaths were caused by second malignancies. One patient died of a myocardial infarction and another of renal failure before remission could be achieved. Two died of uncontrolled disease.

Second malignancies. Four patients developed second malignancies following therapy for HD (Table 3). Two developed adenocarcinoma of the lung. In one patient, the second tumour appeared 9 months after the start of chemotherapy and 3 months after mantle radiotherapy; the other patient had received only total nodal radiotherapy 72 months earlier. Two patients developed acute leukaemia.

![Fig. 2. Hodgkin's disease (HD): cause of death and length of survival in 9 patients. □, mixed cellularity; ■, nodular sclerosis; ●, lymphocyte depleted. ALL = acute lymphoblastic leukaemia; AMonL = acute monocytic leukaemia.](image)

TABLE 3. Hodgkin's disease: development of second malignancies after therapy in 4 patients

<table>
<thead>
<tr>
<th>Second malignancy</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Treatment</th>
<th>Time (months) from start of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Adenocarcinoma lung</td>
<td>46</td>
<td>F</td>
<td>MVPP→RT</td>
<td>9→3</td>
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<td>2 Adenocarcinoma lung</td>
<td>36</td>
<td>M</td>
<td>RT</td>
<td>72</td>
</tr>
<tr>
<td>3 ALL</td>
<td>52</td>
<td>M</td>
<td>RT→ChlVPP</td>
<td>60→28</td>
</tr>
<tr>
<td>4 AMonL</td>
<td>56</td>
<td>M</td>
<td>RT→RT</td>
<td>360→18</td>
</tr>
</tbody>
</table>

ALL = acute lymphoblastic leukaemia; AMonL = acute monocytic leukaemia. ChlVPP = chlorambucil, vinblastine, procarbazine, prednisolone; MVPP = mustine, vinblastine, procarbazine, prednisolone; RT = radiotherapy.

In one of these, acute lymphoblastic leukaemia (ALL) occurred 60 months after total nodal radiotherapy and 28 months after the start of 6 courses of ChlVPP for recurrence. The other patient developed acute monocytic leukaemia (AMonL) following low dose irradiation to the cervical, axillary and inguinal regions for HD 30 years earlier; review of the original histological sections showed NS. Following this treatment he remained in complete remission for 28 years. When he relapsed with cervical node involvement of MC histology he was given mantle radiotherapy. His second remission lasted 18 months and was terminated by the development of AMonL with no evidence of HD at post mortem.

Non-Hodgkin's lymphoma

Survival. This ranged from 2 months to more than 10 years. The 5 years survival probability was 40% overall (72% Stages I+II and 29% Stages III+IV) as shown in Fig. 3(a). The apparent difference between Stages I+II and Stages III+IV was not statistically significant (P>0.3) because of the small
Discussion

The results documented here are those of a small, recently established lymphoma clinic. Although the numbers are not large enough to allow for major conclusions, comparison of the results in the HD group with those of 3 much larger series (Kaplan and Rosenberg, 1975; DeVita et al., 1976; Aisenberg and Qazi, 1976) shows no major disparities. If allowance is made for the exclusion of patients over the age of 66 years from the series of Aisenberg and Qazi (1976) the 5-year survival rates are comparable (Table 4). There was a clear relationship between stage and survival, but histology was of less predictive value.

The majority of relapses occurred within the first 2 years, an observation which is in agreement with that of Spittle et al. (1973). However, the adverse influence of a primary relapse on prognosis as shown by that study is less apparent in the data of the present series. The difference probably reflects the effectiveness of combination chemotherapy in improving salvage in this group.

The occurrence of second malignancies in patients treated for HD has been well documented (Arseneau et al., 1972; Canellos et al., 1975). In another large series (Coleman et al., 1977), the actuarial estimate of the incidence of acute non-lymphoblastic leukaemia at 7 years was 3.9% for patients treated with irradiation and chemotherapy. More recently, it has been shown that much of the oncogenic potential of the treatment resides in the MOPP chemotherapy regimen, as neither solid tumours nor leukaemia occurred in patients who received the ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) regimen (Valagussa et al., 1980). Second malignancies have been observed developing from 9 to 360 months after the start of treatment for HD in 4 patients. In one patient the development of adenocarcinoma of the bronchus may have been coincidental, judging from the short interval between treatment and the appearance of the second malignancy. All 4 patients had received radiotherapy in conventional doses. In addition, 2 patients had received chemotherapy similar to the standard MOPP regimen. These findings are disconcerting and call into question the wisdom of recent trends towards more intensive combined modality therapy in early stage disease. The benefits of such an approach in terms of fewer recurrences must be balanced against the risks of inducing a second malignancy.
Observations amongst the non-Hodgkin's lymphomas confirm that the majority present clinically at a relatively late stage (Roseberg, 1977) and that early stage disease is more often of 'unfavourable' histology (Chabner et al., 1976). In contrast to other commentators (Jones et al., 1973), the present data suggest that histology is an unreliable index of survival, whereas clinical staging does relate to prognosis. In therapy the authors have generally adhered to the conventions of administering specific treatment for 'favourable' histology NHL only where this seemed clinically appropriate, whereas patients with disease of 'unfavourable' histology have been given intensive therapy from the time of diagnosis. Longer survivals were noted for patients with histiocytic lymphoma than for those with lymphocytic lymphoma. It is possible that this is a chance finding, but it may be that reputedly 'unfavourable' histology is an oversubscribed determinant. Contemporary therapeutic strategies which are well within the
capacity of even small clinics can be extremely effective in this group.

These results demonstrate that patients treated in a small lymphoma clinic fare no worse. This is contrary to the current dogma that large centres treating large numbers of patients are essential. The convenience for the patient and relatives of attending a local hospital is probably the single most important advantage. There are also the un-doubted benefits associated with an unhurried consultation; it is easier for the clinician to develop a rapport with the patient. Finally, closer contact with colleagues facilitates speedy referral to and from other disciplines.

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References


