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Tumour Burden as the Main Indicator of Prognosis in Hodgkin's Disease

Lena Specht

A method of estimating the total tumour burden in patients with Hodgkin's disease was devised, combining the number of involved regions with the tumour size in each region. Further, a method of estimating the total tumour cell burden was devised, combining the estimate of the total macroscopic tumour burden with an estimate of the concentration of tumour cells in the tumour tissue. The prognostic signficance of the total tumour burden was examined in multivariate studies of 300 patients in pathological stages I and II treated in the Danish National Hodgkin Study and 506 patients in all stages treated at the Finsen Institute, Copenhagen, Denmark, during a 15-year period. The total tumour burden turned out to be the most important prognostic factor in Hodgkin's disease. Most of the hitherto known prognostic factors were shown to be correlated with the total tumour burden and to lack independent prognostic significance.
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INTRODUCTION

THE ANN ARBOR staging system for Hodgkin's disease [1] was introduced in 1971 and has since been universally accepted, thus facilitating comparisons of clinical data and treatment results from different institutions around the world. In recent years, however, it has become increasingly evident that the Ann Arbor staging system is not sufficient in the prognostic evaluation of patients, primarily because clinical experience has shown that groups of patients with widely differing prognoses exist within the individual Ann Arbor stages. Numerous studies have therefore investigated prognostic factors within the general framework of the Ann Arbor staging system with the aim of improving the prognostic evaluation of patients. Factors such as the anatomic extent of disease within stages, the volume of disease in individual regions, the anatomical localisation of disease, systemic symptoms, histopathological features, age, sex, and haematological, biochemical and immunological indicators have all been shown to possess prognostic significance [2]. Many of these prognostic factors are correlated, however, and in multivariate analysis only a few retain independent significance.

The fact that numerous studies had shown that various indicators of the extent of disease and the volume of disease in individual regions are very important for prognosis prompted the search for a method of estimating the total tumour burden present in the body, and a series of studies examining the prognostic significance of the total tumour burden thus estimated [3–8].

METHOD OF EVALUATION OF THE TOTAL TUMOUR BURDEN

To obtain a rough estimate of the total tumour burden of a given patient a relatively simple method based on information already available after ordinary staging procedures was developed. The method combines the number of involved regions with the tumour size in each region.

The lymph node regions defined in the Ann Arbor classification were used [9]. Some of these regions are very large in the sense that they contain very large numbers of lymph nodes. In order to reach a fair estimate of the total amount of tumour of a given patient, the individual lymph node regions should be roughly the same size. Therefore, it was necessary to subdivide the largest of the regions of the Ann Arbor classification, namely the neck, the mediastinum, the inguinofemoral region and the para-aortic region (see Fig. 1).

For each involved lymph node region a measure of the amount

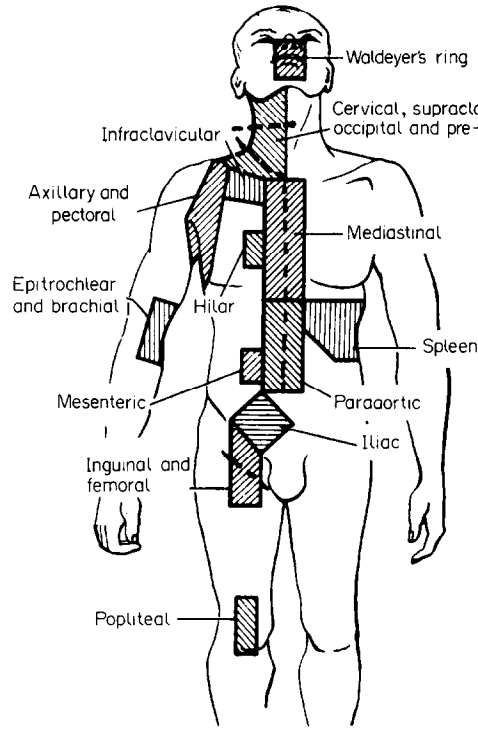

Fig. 1. Diagram of the anatomic definition of separate lymph node regions (reprinted, by permission, from Kaplan and Rosenberg [10]). The proposed subdivisions of the largest regions (as indicated in the present text) are marked with stippled lines.

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of tumour was obtained by measuring the largest diameter. Peripheral lymph nodes were measured by ordinary physical examination and the amount of tumour was graded as either small, medium or large, depending on the largest diameter of the involved lymph node or lymph node conglomerate (see Table 1). Mediastinal involvement was evaluated from ordinary postero-anterior chest X-ray. Grading of the size of mediastinal involvement was performed in the way generally employed in clinical practice, namely by measuring the mediastinal mass ratio (maximum width of mediastinum/maximum intrathoracic diameter; see Table 1). As each side of the mediastinum cannot be evaluated separately, both sides were regarded as having the same grade. Involved pulmonary hilar lymph nodes were evaluated from PA and lateral chest X-rays and graded as small, medium or large according to largest hilar diameter (see Table 1).

Thus, for peripheral and intrathoracic lymph nodes it is possible to get a rough measure of the amount of tumour in each region. By giving 'points' (= grade) according to the amount of tumour in each region, and then for each patient adding together all the points from peripheral and intrathoracic lymph node regions, a rough and yet fairly detailed estimate of the patient's total peripheral and intrathoracic tumour burden may be obtained (see Table 1).

Retroperitoneal lymph nodes were evaluated by lymphangiography. From lymphographic pictures it is impossible to measure the total amount of tumour in each region. Instead, the average size of abnormal lymph nodes was evaluated and graded, according to the average of their largest diameters, into small, medium or large (see Table 2). By adding the 'points' (= grade) that each patient obtained from the average size of abnormal lymph nodes in each lymphographic region, a rough measure of the patient's total retroperitoneal tumour burden was obtained. As this measure was based on the average size of lymph nodes in a region and not on the total amount of tumour in a region, the measure of the retroperitoneal tumour burden could not be added to the measure of the peripheral and intrathoracic tumour burden. These two measures had to be entered as separate variables in the analyses.

Table 1. Evaluation of peripheral and intrathoracic tumour burden

Grading of involvement in peripheral nodal regions	
Small (grade 1):	largest diameter $\leq$ 2 cm
Medium (grade 2):	2 cm $<$ largest diameter $\leq$ 5 cm
Large (grade 3):	largest diameter $>$ 5 cm
Grading of mediastinal involvement*	
Small (grade 1):	MMR $\leq$ 0.25
Medium (grade 2):	0.25 $<$ MMR $\leq$ 0.33
Large (grade 3):	MMR $>$ 0.33
Grading of hilar involvement	
Small (grade 1):	largest diameter $\leq$ 5 cm
Medium (grade 2):	5 cm $<$ largest diameter $\leq$ 7 cm
Large (grade 3):	largest diameter $>$ 7 cm
Estimate of total peripheral and intrathoracic tumour burden	
Tumour burden =	sum of grades of peripheral nodal regions + 2 $\times$ grade of mediastinum + sum of grades of hilar involvement

*Mediastinal mass ratio (MMR) = maximum width of mediastinal mass divided by maximum intrathoracic diameter.

Table 2. Evaluation of retroperitoneal tumour burden

Grading of lymphographically involved nodes	
Small (grade 1):	average diameter $\leq$ 2 cm
Medium (grade 2):	2 cm $<$ average diameter $\leq$ 5 cm
Large (grade 3):	average diameter $>$ 5 cm
Estimate of retroperitoneal tumour burden	
Tumour burden =	sum of grades of retroperitoneal regions

The spleen is often involved in Hodgkin's disease. Unfortunately, the only method of evaluating the presence and amount of disease in the spleen is to perform a splenectomy. At present, splenectomies are only performed in selected patients with Hodgkin's disease. Consequently, the amount of tumour in the spleen cannot be measured in the majority of patients and it was therefore left out of the present method of estimating the total tumour burden.

In disseminated (stage IV) disease it is not possible to quantitate the amount of tumour outside the lymphatic system on the basis of information obtained from routine staging procedures. The only measure of extranodal tumour mass which is readily available is the no. of involved extranodal organs. The amount of tumour in each of these may, however, vary considerably. At present there is thus no accurate way of assessing the total tumour burden in disseminated disease. The best possible approximation would seem to be a combination of the estimate of the total tumour burden in lymph node areas and the no. of involved extranodal organs.

Statistical methods

Survival was estimated by the product-limit method [11], and comparisons in univariate analyses were performed by the logrank test (for trend if appropriate) [12]. In order to determine the independent contribution of each factor to prognosis, multivariate analyses were undertaken using the method developed by Cox [13]. The proportionality assumption underlying the Cox model was checked for each factor by stratifying according to levels of the factor and checking graphically whether the estimated baseline intensities were proportional [14].

STUDIES OF THE PROGNOSTIC SIGNIFICANCE OF THE TOTAL TUMOUR BURDEN

Stage I–II

A total of 300 patients with Hodgkin's disease in pathological stages I and II were treated in the randomised Danish National Hodgkin Study with either total (or, in some cases, subtotal) nodal irradiation or mantle field irradiation plus six cycles of MOPP. With regard to disease-free survival, multivariate analysis showed that the only factors with independent prognostic significance were treatment modality and total tumour burden, and to a lesser extent sex [3, 4, 8]. Other well-known prognostic factors, such as the no. of involved regions, mediastinal size, stage, systemic symptoms, and erythrocyte sedimentation rate (ESR), were correlated with the total tumour burden but without independent prognostic significance. With regard to mortality from Hodgkin's disease, the total tumour burden was also by far the most important prognostic factor, whereas treatment modality had no significance.

Stage III

A total of 143 patients in stage III were treated with either radiotherapy, chemotherapy or both at the Finsen Institute, Copenhagen, Denmark, from 1969 to 1983. With regard to disease-free survival, the only factor of independent prognostic significance in multivariate analysis, apart from treatment modality, was the total tumour burden [5]. The retroperitoneal part of the total tumour burden was somewhat more important than the peripheral and intrathoracic part. Neither substage (whether defined according to Desser *et al.* [15] or according to Rodgers *et al.* [16]), histologic subtype, systemic symptoms, number of involved regions, mediastinal size, ESR, sex, nor age possessed independent significance. With regard to overall survival (including all causes of death) the only factor with independent prognostic significance apart from age was the retroperitoneal tumour burden, whereas the influence of the peripheral and intrathoracic tumour burden did not reach statistical significance.

Stage IV

A total of 104 patients in stage IV were treated with combination chemotherapy with or without additional irradiation at the Finsen Institute from 1969 to 1983. The prognostic significance of clinical data and haematological and biochemical indicators was examined in multivariate analysis [6]. The most important factors were shown to be lymphocytopenia and bone marrow involvement for disease-free and overall survival, respectively. With regard to mortality from Hodgkin's disease both factors were significant. Both of these factors were shown to be correlated with the retroperitoneal tumour burden and with the number of involved lymph node regions, and bone marrow involvement was also correlated with the number of involved extranodal organs. Both factors, therefore, are likely to reflect to some extent the total tumour burden. As mentioned above, disseminated extranodal disease cannot be measured, and therefore the total tumour burden in stage IV cannot be estimated accurately. Consequently, the evidence for the prognostic importance of tumour burden in stage IV remains indirect.

All stages together

A multivariate analysis including all the 506 patients treated at the Finsen Institute from 1969 to 1983 established that the only factors with independent influence on mortality from Hodgkin's disease were the patient's age and the total tumour burden, estimated as a combination of three variables, namely the peripheral and intrathoracic nodal tumour burden, the retroperitoneal nodal tumour burden, and the no. of involved extranodal sites [7]. The influence of age should probably be ascribed to the fact that a few, mostly elderly patients, could not be given adequate treatment for relapse because of concurrent medical problems.

TUMOUR CELL BURDEN

Based on these findings, the hypothesis was formed that the great prognostic impact of the macroscopic tumour burden might have a direct bearing on the topic of histopathological classification, and that the prognostically important histopathological feature might in fact be, quite simply, the concentration of tumour cells in the involved lymph node tissue. Theoretically, it seemed likely that the total no. of tumour cells in the body would be the true determinant of prognosis. It was assumed that the best possible estimate of the total tumour cell burden would be a combination of the total macroscopic tumour burden and the concentration of tumour cells in the tumour tissue.

Table 3. Evaluation of tumour cell concentration in sections

Grading of tumour cell concentration	
Low (grade 1)	1 – 5*
Medium (grade 2)	6 – 25*
High (grade 3)	> 25*

*Tumour cells per high-power field.

From all the 300 patients in pathological stages I and II described above, who were treated in the randomised Danish National Hodgkin Study, initial biopsy material was available for histopathological revision. The concentration of tumour cells in sections was estimated by counting the no. of Hodgkin's cells and Reed–Sternberg cells per high-power field at a ×400 magnification [8]. These estimates of the tumour cell concentration were graded into 3 grades: low, medium and high tumour cell concentrations (see Table 3). The tumour cell concentration was demonstrated to be a better prognostic factor than the Rye classification [17] and the grading proposed by the British National Lymphoma Investigation [18]. However, if the macroscopic tumour burden was taken into account, both the tumour cell concentration and the other classification systems lost their prognostic impact. Most significantly, however, a combination of the macroscopic tumour burden and the tumour cell concentration, yielding an estimate of the total tumour cell burden present in the patient, was shown to be significantly better as a prognostic factor than the macroscopic tumour burden alone [8].

DISCUSSION

The results of these studies thus confirmed the hypothesis that the total tumour burden, or even better, the total tumour cell burden, is the most important prognostic factor in Hodgkin's disease. Most of the hitherto known prognostic factors were shown to be correlated with the total tumour burden and to lack independent prognostic significance when the total tumour burden was taken into account. The estimate of the total tumour burden is admittedly fairly approximate, and ultimately inaccurate. But it seems reasonable to assume that this estimate, imperfect though it may be, offers an approximate measure of the true amount of tumour cells in the patient. The fact that this estimate has been shown to be the most important prognostic factor in Hodgkin's disease, rendering most of the hitherto known important factors insignificant, would seem to indicate that the number of tumour cells in the body is of paramount importance in determining the ultimate outcome for the patient with Hodgkin's disease.

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Evaluation of a Breast Cancer Screening Programme—The DOM Project

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In several studies it has been shown that breast cancer screening by means of mammography reduces breast cancer mortality. To ensure that when organising a service screening programme the aim is reached, it is necessary to control and monitor the process. This is possible by several methods. In this study, disease-free intervals and survival rates were used as monitoring tools. The DOM project, a breast cancer screening programme for women aged 50–64 years old at intake, started at the end of 1974. All breast cancer cases diagnosed between 1973 and 1989 were followed up to 1991. It is clear that disease-free interval and survival rates are proper predictors of the effects of screening on breast cancer mortality.
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INTRODUCTION

MORTALITY REDUCTION as shown in randomised controlled trials [1–6], is the ultimate proof of the effectiveness of a breast cancer screening programme. However, when starting a new programme it is not acceptable to the population to be divided into a study and a control group. Moreover, it is more effective to monitor a population by being aware of signals that the expected effect will or will not be reached, so ways of monitoring have to be found. Monitoring has to be distinguished from quality control. Quality control deals with the test, both technical aspects and performance, in order to correct or improve it when necessary [7, 8]. Monitoring focusses on events that cannot easily be influenced, such as participation rate of women, changes in methods of treatment, incidence rates, etc. [9]. Up to now little attention has been paid to the influence of the screening programme itself on survival of the breast cancer cases. Survival alone cannot be proof of the effectiveness of screening, but in order to reduce mortality rate, increase of the survival rate is necessary (as screening is secondary and not primary prevention). So questions arise: 'Are screening activities reflected in survival rates?' and, 'Will longer survival and better survival rates be predicted by disease-free interval rates?'

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MATERIALS AND METHODS

At the end of 1974 the DOM project, a population-based breast cancer screening programme was started in Utrecht, The Netherlands. All women born between 1911 and 1925, being between 50 and 64 years old at the start of the project, were invited; 72% participated (14697 women). The programme had a cohort design, which implied that only women having participated in the previous screening round were invited for the following screening. From 1974 to 1984 five screening rounds were performed, with different time intervals between two successive screening rounds [10, 11]. As a consequence of this design the screening activities in Utrecht were variable (Table 1).

At the start of the screening programme a breast cancer registry (including 1973) was established. Data from the population registry of Utrecht were collected making it possible to