Residual Mass in Aggressive Lymphoma—Does Size, Measured by Computed Tomography, Influence Clinical Outcome?

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Residual masses are frequently found in patients with aggressive lymphomas, following therapy. A study was undertaken to determine whether initial tumour size, changes during treatment, or size of the residual mass could provide prognostic information. Computed tomography (CT) examinations were carried out before, midway and after completion of chemotherapy in 37 patients with aggressive lymphoma with residual mass after treatment. The tumours were measured for both the greatest diameter sizes and area. The size of the residual mass correlated with the tumour size at diagnosis. Neither a large tumour size before treatment nor a large residual mass after treatment correlated with an increase in rate of relapse. The initial tumour reduction (measured after completion of half of the planned chemotherapy) was less pronounced in relapsing patients compared to relapse-free patients. Using a cut-off level of 70% tumour reduction (measured after completion of half of the planned chemotherapy), 66% of patients with a tumour reduction of $< 70\%$ relapsed, compared with 22% ($p < 0.05$) in those with more marked tumour regression.

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When treated with intensive chemotherapy, generalized aggressive lymphoma is a curable disease, with a long-term survival of 35–40% (1, 2). Detection of a residual mass in a patient who is otherwise in clinical complete remission (CR) is a common problem and represents a major dilemma for the physician (3–5). Some of these masses contain only fibrosis or necrotic tissue and the patients can be cured. Others, however, present residual masses that still have active tumour cells, which will result in a relapse if left untreated (6). In the radiographic follow-up it is virtually impossible to differentiate active lymphoma from fibrosis or necrotic tissue (7). In order to improve our knowledge of the clinical significance of residual masses, a retrospective analysis was carried out on all Swedish patients with residual masses, otherwise in clinical CR, participating in a randomized Nordic trial comparing two chemotherapy regimens, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and MACOP-B (methotrexate, cyclophosphamide, doxorubicin, vincristine, bleomycin, prednisone). The results of the study showed that there was no difference in treatment outcome between the two chemotherapy schedules (8).

MATERIAL AND METHODS

The study comprised CT examinations of 37 adult patients enrolled at a number of Swedish hospitals in a multicentre randomized trial, conducted in the Nordic countries between September 1989 and December 1994, in which two different chemotherapy schedules were compared: CHOP and MACOP-B (8). The patients were classified according to the updated Kiel classification (9) and retrospectively with the REAL (10) classification; initial staging was performed according to the Ann Arbor staging system (11). The key inclusion criteria for the trial were: previously untreated high-grade malignant non-Hodgkin's lymphoma according to the Kiel classification system (9), stage II–IV disease and ages between 18 and 67 years. According to the study protocol, all tumour sites were to be re-examined halfway through the therapy and within one month after termination of treatment. This halfway examination was conducted after 6–7 weeks for patients treated with MACOP-B and 12 weeks for patients treated with CHOP. All residual masses were documented in accordance with the study protocol and all Swedish patients with residual

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tumours > 1 cm at nodal site were potential candidates for the study. A further selection criterion included was the availability of pre- and post-treatment CT images. Seventy-six (30%) of 253 Swedish patients fulfilled the first three criteria but 39 patients had to be excluded because of either missing CT examinations (n = 32) or the poor quality of the examinations (n = 6) or radiotherapy to the rest tumour before the last CT examination was performed (n = 1). The characteristics of the 37 patients are presented in Table 1. The predominant histological subgroup was diffuse large B-cell lymphoma (REAL classification). Biopsies (cytology or core biopsies without remaining disease) of the residual mass were performed in 16 of the 37 patients. Three patients received radiotherapy shortly after the examination. The median follow-up time for surviving patients was 54 months (range 6 to 91 months). The three CT examinations performed according to the trial protocol were designated as CT 1 (before treatment), CT 2 (performed after halfway through the planned chemotherapy course) and CT 3 (performed after completion of chemotherapy).

In total, 115 CT examinations were evaluated retrospectively. The results of all three CT examinations were available for 33 patients, but those of the CT 2 examination were missing for the 4 remaining patients.

Image evaluation

The evaluation of the CT images started with measurement of the residual mass on CT 3, looking backwards for measurements of enlarged lymph nodes or lymphoma involvement at corresponding sites on CT 2 and CT 1 (see Fig. 1). When more than one residual mass was found on CT 3, the largest was selected for the study. Both the largest tumour diameter, in centimetres, and the tumour area (product of the largest diameter and the diameter perpendicular to it) in cm^2 were recorded. The tumour diameters (or areas) were then ranked from the smallest to the largest.

Statistical methods

The differences in tumour diameter and area between the relapse-free patient group and the relapsed patients were evaluated with the Mann-Whitney U test. Regression analyses were used to measure changes in tumour diameter and area during and after treatment. The Mann-Whitney U test was performed using Stat View II (Stat View™ 1986). Analyses for all patients and those treated with the MACOP-B regimen were performed separately. The reason for conducting separate analyses for MACOP-B was that this was the largest treatment subgroup (22 patients). For the Mann-Whitney U test, a significance level of 5% was used. For regression analyses, results are given as 95% confidence interval for regression coefficients. The mean rank values for tumour diameter and area before and after therapy and for the percentage size reductions between CT examinations during and after therapy were calculated.

RESULTS

The residual masses were found in the abdomen (57%), mediastinum (24%), peripheral lymph nodes (16%) and in the pelvis (3%). The largest diameter of the residual mass after treatment ranged between 1.2 and 10 cm (median 3 cm) and the largest area between 1.4 and 90 cm^2 (median 5 cm^2). The diameter of the corresponding tumour at diagnosis ranged between 2.3 and 20 cm (median 8 cm) and the area between 4 and 300 cm^2 (median 36 cm^2). A very strong correlation was seen between diameter and area at diagnosis and post-treatment ($p < 0.0001$ for both).

Table 1

Characteristics of the patients

	Relapse-free	Relapse (same site)	Relapse (different site)	All
Patients	22	8	7	37
Age years (mean)	56	53	55	
Stage				
I	1	1	–	2
II	12	2	2	16
III	5	2	2	9
IV	4	3	3	10
Histology (REAL)				
DLBL	20	6	6	32
ALC	–	1	1	2
UNS	2	1	–	3
Treatment				
MACOP-B	13	4	5	22
CHOP	9	4	2	15
Radiotherapy	1	–	2	3

Abbreviations: REAL = revised European–American classification of lymphoid neoplasms; DLBL = diffuse large B-cell lymphoma; ALC = anaplastic large cell lymphoma; UNS = high-grade lymphoma unclassifiable.

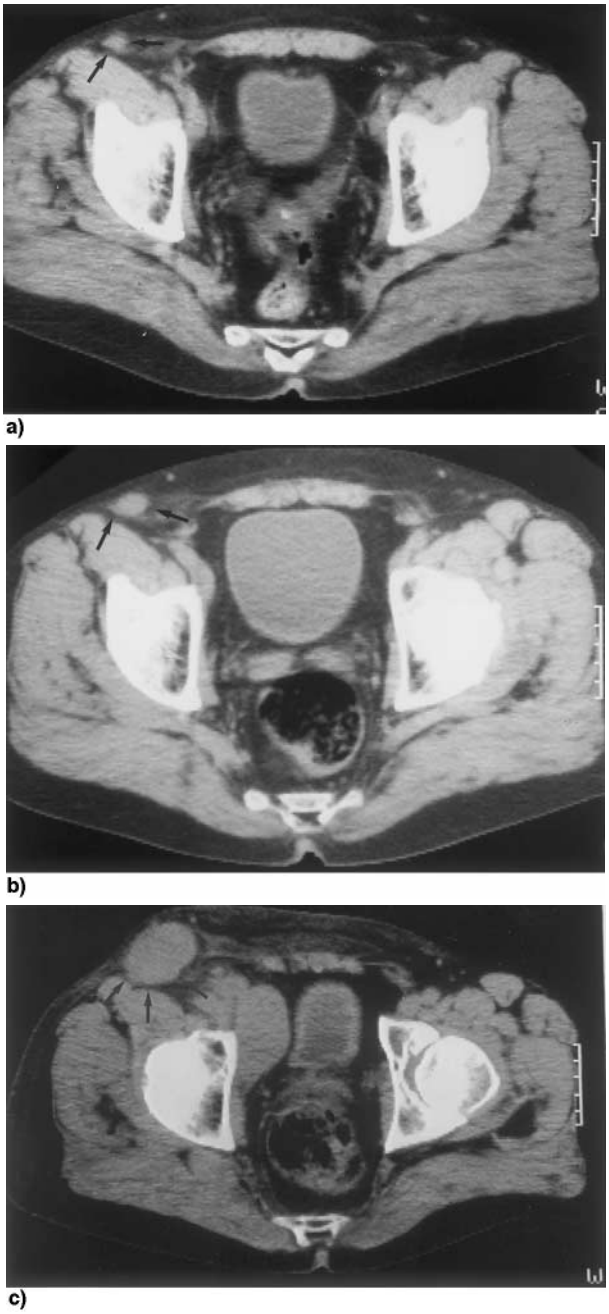

Fig. 1. Evaluation of the CT images in a patient with aggressive lymphoma before (CT 1), during (CT 2) and after (CT 3) therapy. a) CT 3 and b) CT 2 show a residual mass in the right groin (arrows) after completion and after half of the chemotherapy course, respectively. c) CT 1 shows an enlarged lymph node (arrows) before treatment, corresponding to the residual mass on CT 3 and CT 2. This patient also presented with enlarged lymph nodes in the pelvis at diagnosis.

Fifteen (41%) of the 37 patients relapsed, 8 patients at the site of the residual mass and 7 outside the residual mass. Neither a large tumour at diagnosis nor a large residual mass was associated with an increased relapse rate. Unexpectedly, the residual tumour mass and also the tumour size at diagnosis were significantly smaller in relapsed patients (mean diameter 3 cm; mean area 6.5 cm^2) compared with those who were disease-free (mean 3.7 cm; mean area 11.7 cm^2) (Table 2). When the recurrence rate among the patients in this study was compared with that of all the CR patients from the Swedish hospitals in the randomized trial without any persistent mass, no difference was found 15/37 (41%) vs. 43/96 (43%).

Tumour reduction (expressed as the percentage reduction between CT 1 and CT 2, and between CT 1 and CT 3) was calculated. The mean tumour reduction at CT 2 (halfway through therapy) was lower in patients who relapsed compared to those who did not relapse, but the differences were not statistically significant ($p = 0.13$ and 0.14 for diameter and area, respectively) as shown in Table 3. This was also true when the analyses were restricted to the 22 patients treated with MACOP-B (data not shown). Using a cut-off level of 70% tumour reduction between CT 1 and CT 2, 10/15 (66%) patients with a $< 70\%$ reduction relapsed, compared with 4/18 (22%) in those with $\geq 70\%$ reduction ($p < 0.05$). No such clear tendency was observed when the tumour reduction was measured between CT 1 and CT 3, i.e. from the start to the end of the treatment ($p = 0.28$ and 0.32 for tumour diameter and area, respectively), as shown in Table 3.

DISCUSSION

In order to achieve long-term disease-free survival in patients with aggressive lymphoma, it is important to induce a CR. However, defining complete recovery may be difficult in those patients who seem to respond very well to the treatment, with the disappearance of all clinical or biological abnormalities, but in whom radiological abnormalities persist. Residual masses detected after completion of therapy for aggressive lymphomas are quite common, especially in patients with a large tumour burden in the mediastinum and abdomen (3–5), which was also found in the present study.

We observed that the size of the residual mass could be predicted from the size of the tumour before therapy. This finding is in conformity with the finding by Surbone et al. (6) in their study of aggressive lymphomas and with the report by Nyman et al. (12), investigating residual mediastinal masses in Hodgkin's disease. We also found that neither a large tumour at diagnosis nor a large residual mass was associated with poor prognosis. In fact, in the present study we unexpectedly found that a larger residual mass was associated with a lower recurrence rate rather than a smaller mass. This is difficult to explain, and may be due to chance.

The early rate of regression of the tumour might be a predictor of recurrence. It has been reported that the time needed to reach CR as assessed by plain radiography and CT has prognostic significance (13). The first CT-docu-

Table 2

Mean rank value for tumour diameter and area, in the relapse-free and relapse groups, respectively

CT	Diameter Mean rank		p-value	Area Mean rank		p-value
	Relapse-free	Relapse		Relapse-free	Relapse	
CT 1	22.1	14.5	0.04	21.5	15.3	0.09
CT 3	22.1	14.4	0.03	21.1	16.0	0.16

CT 1 and CT 3 = CT examination before treatment and after completion of chemotherapy, respectively.

Table 3

Mean rank value of CT response rates, for diameter and area in the relapse-free and relapse groups. All 37 patients were included in the CT 1–CT 3 comparison and 33 patients in the CT 1–CT 2 comparison

CT	Diameter Mean rank		p-value	Area Mean rank		p-value
	Relapse-free	Relapse		Relapse-free	Relapse	
CT1–CT2	19.2	14.0	0.13	19.1	14.1	0.14
CT1–CT3	20.6	16.7	0.28	20.5	16.9	0.32

CT1-CT2 = tumour reduction between CT examination before and after half of chemotherapy.CT1-CT3 = tumour reduction between CT examination before and after completion of chemotherapy.

mented tumour reduction in this study was estimated halfway through therapy. Using a cut-off level of 70%, a more pronounced regression rate was associated with fewer relapses. A reduction of 70% for the diameter corresponds to a partial remission if the tumour is round ($0.7 \times 0.7 = 0.49$). However, using other cut-off points, or a non-parametric statistical analysis, the result did not reach formal statistical significance (Table 3). One must be aware of the small number of patients in our study, and a larger study is needed to clarify this question.

Magnetic resonance imaging (MRI) and CT scan are about commensurately useful for predicting the nature of residual masses (14, 15). Metabolic imaging allowing a functional rather than a morphological characterization may be of advantage. Some reports have proposed the utilization of ^{67}gallium scanning (^{67}Ga) (16, 17), which seems particularly effective for evaluating mediastinal masses. The excretion of ^{67}Ga in the bowel decreases the usefulness when studying abdominal masses. In the study by Janicek et al. (16), early restaging with ^{67}Ga distinguished the patients who remained disease-free from those who relapsed. Another metabolic method to interpret residual masses is positron emission tomography (PET) with 18-fluoro-deoxyglucose (FDG). The uptake of FDG by the tumour cells reflects the increased glycolytic activity of the malignant cell. An advantage with this method was recently reported, in the staging of lymphoma patients (18–20), but also in the post-treatment evaluation (21).

In advanced seminoma, residual masses represent the same type of clinical and radiological dilemma as the residual masses in lymphoma. Horwich et al. (22) conducted a retrospective study on 45 chemotherapy-treated patients with advanced seminoma and found that recurrences were not influenced by the size of the residual mass, a result similar to ours. Another result similar to ours, seen in non-seminomatous germ cell tumours, was that a rapid alpha-feto protein (AFP) decrease was associated with a significantly better survival (23). In conclusion, in aggressive lymphoma patients, the size of the residual mass may be predicted from the size of the tumour before treatment. Neither a large tumour size at diagnosis, nor a large residual mass after treatment correlated with relapse. A larger study is required to determine whether the early response rate of the tumour mass, as seen in this study, provides prognostic information.

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