RADIOLOGIC TECHNIQUES IN STAGING MALIGNANT LYMPHOMA

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Chapter 1

Introduction and outline of investigation

1.1 Introduction

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1.1 INTRODUCTION

Malignant lymphoma is the collective name for primary malignant tumors of lymphoid tissue. Two main categories are distinguished: Hodgkin disease (HD) and the non-Hodgkin lymphoma's (NHL).
HD and NHL not only differ in histopathologic structure, but also in the way of clinical presentation, course of disease, responsiveness to therapy and overall survival.
The malignant lymphomas were responsible for 3% of first hospital admissions due to malignant neoplasms in the Netherlands in 1983. NHL constituted the largest group with 2% (7 cases per 100.000 inhabitants) and HD was diagnosed in 1% (3.2 cases per 100.000 inhabitants). Registrated mortality due to NHL was 726 cases in 1983, or 2.3% of all cancer deaths. Mortality due to HD was 137 cases, or 0.4% of all cancer deaths (1).

In view of the differences between HD and NHL, a separate discussion of the radiologic tribute to the staging and management of these diseases is desirable and justified. Earlier radiologic literature - especially on computed tomography - frequently presents combined findings in HD and NHL. In the present study, however, the distinction between the two diseases is maintained whenever appropriate.

1.2 GENERAL INFORMATION

1.2.1 Hodgkin disease (HD).

HD was first described in 1832 by Thomas Hodgkin, whose name was actually linked to the disease by Sir Samuel Wilks in 1865 (2). One hundred years later Lukes et al. developed a pathologic classification, which was accepted in its final form as the standard histopathologic classification at the Rye conference (3,4). The diagnostic cell-component is the Reed-Sternberg cell, which is a large, binucleated cell. In association with similar mononuclear cells, this cell is assumed to represent the neoplastic cell component of the disease.
The Rye classification distinguishes the following types of HD:

1. Lymphocytic predominance (LP): 10 to 15% of adult HD-cases. This type typically manifests itself with an early stage in young, asymptomatic males, and has the most favourable prognosis. Histologically, abundant small lymphocytes and/or histiocytes dominate the picture, and Reed-Sternberg cells may be scarce.

2. Nodular sclerosis (NS): 20 to 50% of adult HD-cases. This type has a female predominance, with a peak incidence in adolescence and early adulthood. The prognosis is very good when diagnosed at an early stage. Histologically, nodules of lymphoid tissue, encircled by bands of collagen tissue are to be seen. Both the degree of sclerosis and the cellular composition including the Reed-Sternberg cell show numerous variations in manifestation.

3. Mixed cellularity (MC): 20 to 40% of adult HD-cases. These patients often show systemic symptoms. Prognosis is less favourable than for the above-mentioned forms. Histologically, a highly cellular, pleomorphic stroma is to be seen, with numerous Reed-Sternberg cells,

mononuclear Hodgkin cells, eosinophils, plasmacells and fibroblasts.

4. Lymphocyte_depletion_(LD): 5 to 15% of adult HD-cases. This generally occurs in older, symptomatic patients with stage III or IV at initial diagnosis, and has an unfavourable prognosis.
   Histologically, a diffuse or reticular fibrotic stroma is to be seen, with few lymphocytes, and usually abundant Reed-Sternberg cells.

With modern radiotherapy and chemotherapy, the present 5-year and 10-year survival rates for patients with HD have improved. They now range from 90% and 79% respectively for stage I disease, to 57% and 40% respectively for stage IV disease (5).

1.2.2 Non-Hodgkin lymphoma (NHL).

Non-Hodgkin lymphoma is a heterogeneous group of neoplasms that vary in clinical presentation, course, prognosis and radiological manifestations. In earlier nomenclature, the terms lymphosarcoma, reticulum-cell sarcoma, and giant follicular lymphoma (Brill-Symmers disease) were used up to the sixties. Since then, various histopathologic classifications were developed of which the Rappaport, Lukes & Collins and the Kiel/Lennert classifications are the most familiar.
None of these classifications was definitely superior, and after an extensive assessment of histologic material by experienced pathologists and comparison of the results the so-called "Working Formulation of non-Hodgkin lymphoma for clinical usage" was developed (6). By using this formula, it became possible to "translate" one system into an other, making it possible to compare data from different centers. The "Working Formulation" distinguishes the malignant lymphomas into categories of low, intermediate and high grades of malignancy, relating to the clinical

Table I

CLASSIFICATIONS of NON-HODGKIN's LYMPHOMAS

A Working Formulation of Non-Hodgkin's Lymphomas for Clinical Usage
(equivalent or related terms in the Kiel classification are shown)

Working Formulation	Kiel equivalent or related terms
Low grade	
A. Malignant lymphoma, Small lymphocytic, consistent with CLL	ML lymphocytic, CLL
plasmacytoid	ML lymphoplasmacytic/lymphoplasmacytoid
B. Malignant lymphoma, follicular, Predominantly small cleaved cell, diffuse areas, sclerosis	ML centroblastic-centrocytic (small), follicular ± diffuse
C. Malignant lymphoma, follicular, Mixed, small cleaved and large cell, diffuse areas, sclerosis	ML centroblastic-centrocytic (small), follicular ± diffuse
Intermediate grade	
D. Malignant lymphoma, follicular, Predominantly large cell, diffuse areas, sclerosis	ML centroblastic-centrocytic (large), follicular ± diffuse
E. Malignant lymphoma, diffuse, Small cleaved cell, sclerosis	ML centrocytic (small)
F. Malignant lymphoma, diffuse, Mixed, small and large cell	ML centroblastic-centrocytic (small), diffuse
sclerosis	ML lymphoplasmacytic/-cytoid, polymorphic
epithelioid cell component	
G. Malignant lymphoma, diffuse, Large cell	ML centroblastic-centrocytic (large), diffuse
cleaved cell	ML centrocytic (large)
noncleaved cell	ML centroblastic
sclerosis	
High grade	
H. Malignant lymphoma, Large cell, immunoblastic	ML immunoblastic
plasmacytoid	
clear cell	
polymorphous	T-zone lymphoma
epithelioid cell component	Lymphoepithelioid cell lymphoma
I. Malignant lymphoma, Lymphoblastic, convoluted cell	ML lymphoblastic, convoluted cell type
nonconvoluted cell	ML lymphoblastic, unclassified
J. Malignant lymphoma, Small noncleaved cell, Burkitt's, follicular areas	ML lymphoblastic, Burkitt type and other B-lymphoblastic
Miscellaneous	
Composite	—
Mycosis fungoides	Mycosis fungoides
Histiocytic	—
Extramedullary plasmacytoma	ML plasmacytic
Unclassifiable	—
Other	—

behaviour (table I). In the Netherlands, the Kiel/Lennert classification is usually preferred.
According to data from the National Cancer Institute (7), the overall 5-year survival in 1984 for NHL was 48%.This figure varies from 85-100% in favourable histologies in stages I and II, to 25-50% for unfavourable histologies in stages III and IV (8).

1.3 STAGING

Once the histopathological diagnosis of HD or NHL is made -usually by a biopsy from a peripheral lymph-node region- the patient must undergo a series of staging examinations to determine the spread of disease through the body.
HD and NHL differ in the manner and extent of disease, diagnosed at initial examination.
Whereas HD apparently shows an orderly spread of disease by contiguity and in a relatively predictable manner (9), NHL usually is more disseminated at the time of initial diagnosis, and more frequently shows organ involvement (table II; ref. 10).

Table II: Anatomic sites involved at presentation (%).

	HD	NHL
thoracic nodes	65	25
lung parenchyma	10	4
pleural effusion	10	7
para-aortic nodes	34	55
mesenteric nodes	<5	51
spleen	34	33
liver	6	14
G-I tract	0	8
urinary tract	0	3

The description of disease extent in HD occurs according to the Ann Arbor classification (11; table III). This system is also applicable to NHL.

Table III: Ann Arbor Staging classification

Stage I : Involvement of a single lymph-node region (I) or of a single extralymphatic organ or site (I_E).
Stage II : Involvement of two or more lymph-node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and of one or more lymph-node regions on the same side of the diaphragm (II_E).
Stage III: Involvement of lymph-node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (III_S) or by localized involvement of an extralymphatic organ or site (III_E) or both (III_{SE}).
Stage IV : Diffuse or disseminated involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement.
The absence or presence of fever (>38°), night sweats, and/or unexplained loss of 10% or more of body weight in the 6 months preceding admission are to be denoted in all cases by the suffix letters A or B respectively.

A distinction is made between the clinical stage (CS) and the pathological stage (PS).
The former is based on data from the initial biopsy site, patient history, physical examination, laboratory tests, radiologic and radioisotope studies, and bone marrow examination. A liver biopsy is performed when the patient at this time has not yet proven generalized disease or B-symptoms.
The definition of PS is based on evidence from staging laparotomy, which includes splenectomy, and multiple biopsies of lymph nodes, liver and bone marrow.
Staging laparotomy was introduced in the late sixties at Stanford Medical School for patients with HD and NHL. It soon became obvious that the clinically determined stage of disease underestimated the actual extent of disease in 30-40% of patients (5). The method was widely accepted and applied, but in later years, due to more modern views on classification and treatment, the indications for

laparotomy became more specific.
Nowadays, indications for staging laparotomy are only given in selected patients, and - especially in NHL -, are only rarely present.

1.4 IMAGING PROCEDURES

1.4.1 Radiologic procedures

Chest radiography and tomography, computed tomography (CT) of the chest and abdomen, and lymphography of the infradiaphragmatic nodes are the subjects of discussion in the following chapters. The reader is referred to the specific chapters.
Before the advent of CT, intravenous urography (IVU) was used to gain an impression of the retroperitoneal lymph nodes by visualizing the course of the ureters. At the same time, the renal parenchyma could be evaluated, which is rarely involved with NHL. Also, inferior vena cavography was performed at times to evaluate potential enlargement of retroperitoneal lymph nodes which escaped visualization with lymphography. Nowadays these techniques are not used anymore for routine staging.

1.4.2 Radionuclide studies

Gallium 67 citrate or Technetium 99 microcolloid studies are used in certain institutions for detection of lymphoma sites in the body. In general, these examinations will not obviate the need for other radiologic imaging techniques and it is therefore not performed routinely in the St. Radboud Hospital.
Isotope scanning can be of use for determination of size of liver and spleen, and for the possible presence of large lesions. Since the introduction of CT, the examinations have only been rarely done.
Bone scanning can give indications of the presence of osseous lesions, but since the technique has a relatively low specificity it is not routinely used during initial staging.

1.4.3 Ultrasonography

Modern real-time ultrasound techniques have the potential to visualize enlarged lymph nodes, and lymphomatous deposits in liver and spleen. Ultrasound imaging is most successful in the upper abdomen. The caudally situated para-aortic and parailiac nodes, and the mesenteric nodes are more difficult to visualize, unless they are markedly enlarged. Generally, ultrasonography does not obviate the need for an abdominal CT scan or lymphogram. Ultrasonography can be of value in the case of equivocal CT findings in the upper abdomen especially in slender adults and children. It can also be of use in the follow-up of large abdominal masses to monitor the effects of therapy. In the St. Radboud Hospital ultrasonography is at present used for staging children with malignant lymphoma, and not for adult patients. The technique was only sporadically applied in the patient groups that were the subjects of the present studies.

1.4.4 Magnetic Resonance Imaging (MRI)

This newly applied technique is based on the use of magnetic fields and radiofrequency signals in imaging certain atoms (usually protons), without the use of ionizing radiation. With MRI, it is possible to visualize body regions in freely chosen planes, which occasionally facilitates localization of disease. The diagnostic performance is at the moment inferior to CT, but techniques are rapidly improving. Series comparing CT and MRI findings, or MRI and histologic findings in lymphoma patients are not yet available in medical literature. MRI may contribute to the development of tissue characterization in vivo, but data have still to be generated.

1.5 THE PRESENT STUDY

The choice of optimal therapy for patients with malignant lymphoma calls for an accurate determination of disease

extent to avoid over- or undertreatment.
Radiologic examinations are non-invasive methods which can show a multitude of potential sites of involvement. The various techniques applied determine to a large extent the so called "clinical stage" which serves as a reliable alternative for the "pathological stage" with many patients. While in some respects the techniques are competitive by producing similar information, they can be complementary in other respects by producing unique information. Furthermore, it is not always necessary to produce the highest degree of accuracy attainable in clinical staging, as other factors -e.g. the histologic type of disease- influence the choice of therapy as well.

From a radiologic point of view the chest and abdomen are the main regions of interest in staging patients with malignant lymphoma. The soft tissues and skeletal parts of the extremities, the head and neck region, and the central nervous system are not routinely screened radiologically in asymptomatic subjects, because of the very low yield.

Although the same radiologic techniques are equally important in the follow-up of patients during and after treatment, this aspect is not part of the present study.
The main subject is the evaluation of radiologic techniques in staging patients with newly diagnosed and untreated malignant lymphoma, or restaging patients with recurrent disease after a period of complete remission.

1.5.1 The abdomen

1.5.1.1 The lymph nodes

Lymphography and -more recently- CT are available to examine the infradiaphragmatic nodes. CT also offers the possibility to examine other organ systems in the abdomen, and to visualize more lymph-node regions than lymphography.

In chapter 2 and 4 the diagnostic performance of CT and lymphography in HD and NHL respectively are discussed. Literature data are summarized, and own results are given. The main goal is to determine whether the two methods are overlapping, competitive or complementary, and to answer the question what would be required for optimal staging.

1.5.1.2 The spleen

Staging laparotomy showed the unreliability of non-invasive examination methods for determining the presence or absence of lymphoma in the spleen.
In chapter 3 and 5 the results of CT-based estimations of size of the spleen in relation to its histologic state, in patients with HD and NHL respectively are presented.
The critical comments by radiodiagnostic experts from Stanford Medical School following chapter 3 show that our concepts of splenic index calculation remain subject of discussion.

1.5.2 The chest

The chest can be examined for lymphoma by conventional radiography, conventional tomography or computed tomography (CT). These 3 techniques are increasingly accurate in the same order, but also more costly, and cumbersome to the patient.
In chapter 6 the literature is reviewed, and the results with our patients are presented. The diagnostic performance of each examination is evaluated, and the results are analysed to define the most desirable approach in the examination of the chest for staging purposes.

1.5.3 Uncommon manifestations

In chapter 7 the uncommon radiologic observation of calcification in lymph nodes, afflicted with HD and NHL is described. The literature is reviewed, and the clinical significance is indicated.

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Chapter 2

LYMPHOGRAPHY AND ABDOMINAL COMPUTED TOMOGRAPHY IN STAGING HODGKIN DISEASE.

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ABSTRACT

Lymphography and abdominal CT were performed in 78 patients staged for Hodgkin disease. In 82% of all patients, both examinations agreed on the presence or absence of lymph-node involvement. In the group of 39 patients undergoing lymphography prior to CT, the agreement was 90%. In the group of 39 patients with lymphography following CT, the agreement was 74%. In 50% of the patients with discrepant findings, lymphography revealed abnormal nodes compared with CT. Lymphography was abnormal in 26% of patients with a normal CT scan for the first examination, and in 9% of patients with a normal CT scan for the second examination.
It is concluded that lymphography is more reliable than CT with regard to the examination of the infradiaphragmatic lymph nodes.
CT performed after a normal or an abnormal lymphogram adds little additional information.
When CT is preferred as the initial examination in staging Hodgkin disease, lymphography only adds significant information when the CT scan is normal or equivocal.

INTRODUCTION

The development of effective treatment regimens in Hodgkin disease (HD) was partly based on the application of careful staging procedures to create patient groups with comparable states of disease. As final procedure, staging laparotomy with histologic examination of multiple tissue samples allowed a reliable determination of the so-called "pathological stage". As a result of this the diagnostic value of various non-invasive examination methods could not only be tested critically, but diagnostic criteria could also be formulated and adapted after comparison with histologic data.
In this way, lymphography has evolved into one of the most important radiologic staging examinations in HD, and this

is illustrated by numerous publications. Within a few years after its clinical application, Computed Tomography (CT) also managed to secure a place of its own in the staging process, although large series were not provided as liberally as with lymphography. Various authors have analysed the comparative value of CT and lymphography in staging HD, coming to different conclusions. Castellino et al. (1) conclude in a series of 107 patients that lymphography has a small but real advantage over CT. Crowther (2) draws the opposite conclusion in a series of 105 patients.

In the present report, the radiologic examination of abdominal lymph nodes by CT and lymphography in 78 patients with HD is analysed, with particular reference to the causes of discrepant and contradictory findings.

MATERIAL AND METHODS

During the years 1978 to 1985 lymphography and abdominal CT were performed in 78 patients with HD. Sixty-two patients had newly diagnosed, previously untreated disease, and 16 patients were staged for recurrent disease. The most common histologic subtype was nodular sclerosis (46), followed by mixed cellularity (14), lymphocyte predominance (10) and lymphocyte depletion (4). Four cases were unclassified.

Fifty-three patients were male, with an age range of 11 to 72 years (mean age 33 yrs.). The age of the 25 female patients ranged from 14 to 68 years (mean age 36 yrs.).

Bipedal lymphography was performed using standard techniques, with a total dose of 10 to 12 ml Lipiodol Ultrafluid in adult patients.

CT of the body was performed in 44 patients on an OHIO Nuclear 50 FS Delta Scanner with a scanning time of 18 seconds and a section thickness of 13.5 mm. Contiguous scanning of the whole abdomen was performed with the scans of the upper abdomen in suspended expiration. Twenty-nine

patients were examined on a Siemens Somatom DR 3 with a scanning time of 5 seconds and a section thickness of 8 mm at 16 mm intervals. Five patients were referred with a CT scan made elsewere. Intravenous contrast material was not administered routinely. Generally speaking lymph nodes larger than 1.5 cm were called pathologic, whereas nodes up to 1 cm were regarded to be normal. Nodes with an intermediate size were regarded as suspect or equivocal. For lymph nodes containing contrast medium after lymphography, limits were slightly higher, but not well defined.

The order in which CT and lymphography were carried out was determined rather arbitrarily, mainly depending on scheduling facilities.

The original interpretations of the lymphograms and the CT scans were maintained. In general, the report of the first examination was available to the radiologist performing the second examination. Although CT has the potential to visualize more lymph-node regions than lymphography, the overall conclusions of both examinations with regard to the lymph-node status (positive, negative, equivocal) were compared. Revision was only undertaken for better definition of the sites of lymph node involvement, and of the areas and causes of discrepancy.

Laparotomy with splenectomy was performed in 30 patients (1 patient with recurrent disease). Of the 16 patients with recurrent disease, 12 had previous laparotomy with splenectomy. In general, indications for staging laparotomy were clinical stages IIA or IIIA, that might be considered candidate for (loco)regional radiotherapy only, or patients with primary infradiaphragmatic disease presentation. In 3 patients removal of an enlarged spleen prior to the start of therapy was the main indication.

Evaluation of computed tomographic findings of the spleen has been the subject of a previous study (3), and will not be dealt with separately here.

RESULTS

The comparative results of CT and lymphography are summarized in tables I a-c. Both in the whole group and in the two subgroups, 50% of the discrepant findings consisted of a combination of a normal CT scan and an abnormal lymphogram, 7 patients in all. In all these patients the lymphogram was positive due to structural changes in nodes of normal size. Of these 7 patients, 5 have been included in the group with CT carried out before lymphography (figs. 1-2).

Table I a-c: Comparison of CT and lymphography report in 78 patients.

Table I a: Overall results. Concordance $^{64}/_{78}$ = 82%.

CT / lympho-graphy	-	+	±	total
-	32	3	1	36
+	7	32	1	40
±	2			2
total	41	35	2	78

Table I b: Comparison of CT and lymphography in 39 patients with lymphography performed before CT. Concordance $^{35}/_{39}$ = 90%.

CT / lympho-graphy	-	+	±	total
-	19	1		20
+	2	16		18
±	1			1
total	22	17		39

Table I c: Comparison of CT and lymphography in 39 patients with CT performed before lymphography. Concordance $^{29}/_{39}$ = 74%.

CT / lympho-graphy	-	+	±	total
-	13	2	1	16
+	5	16	1	22
±	1			1
total	19	18	2	39

Three patients showed the combination of a normal lymphogram and an abnormal CT scan: 1 patient with recurrent disease showed enlarged retrocrural nodes only, with normal retroperitoneal findings on CT and lymphography. One patient was thought to have enlarged iliac nodes with CT, but subsequent lymphography revealed no abnormalities. The third patient was presumed to have enlarged retropancreatic and retrocrural nodes, and normal lower retroperitoneal findings on CT and lymphography. Laparotomy in this patient revealed an involved spleen and involved celiac nodes only. The 4 remaining discrepancies were equally distributed over the other possible combinations, and in each case one of the examinations was reported as equivocal.

After comparing and weighing the CT and lymphography reports, the final (radiological) staging data showed that 34 patients were negative, 42 patients were positive, and 2 patients were equivocal with regard to the infradiaphragmatic lymph-node status.

Fourty-four patients were examined on the (slower) 2nd generation scanner, and discrepant findings in comparison with lymphography were recorded in 4 (= 9%). Thirthy-four patients were examined with the (faster) 3rd generation scanner, and discrepant findings were recorded in 10 cases (= 29%).

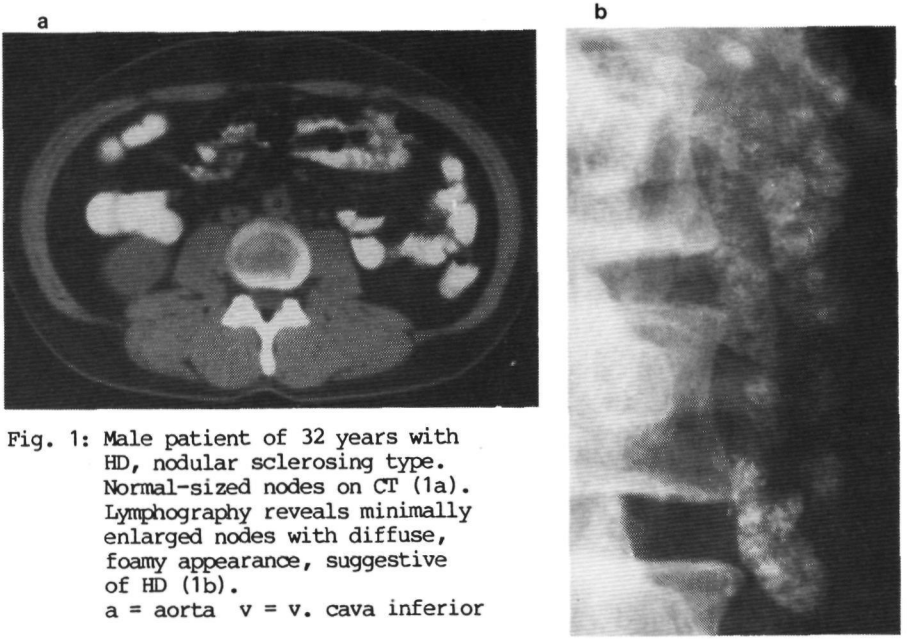

Fig. 1: Male patient of 32 years with HD, nodular sclerosing type. Normal-sized nodes on CT (1a). Lymphography reveals minimally enlarged nodes with diffuse, foamy appearance, suggestive of HD (1b).
a = aorta v = v. cava inferior

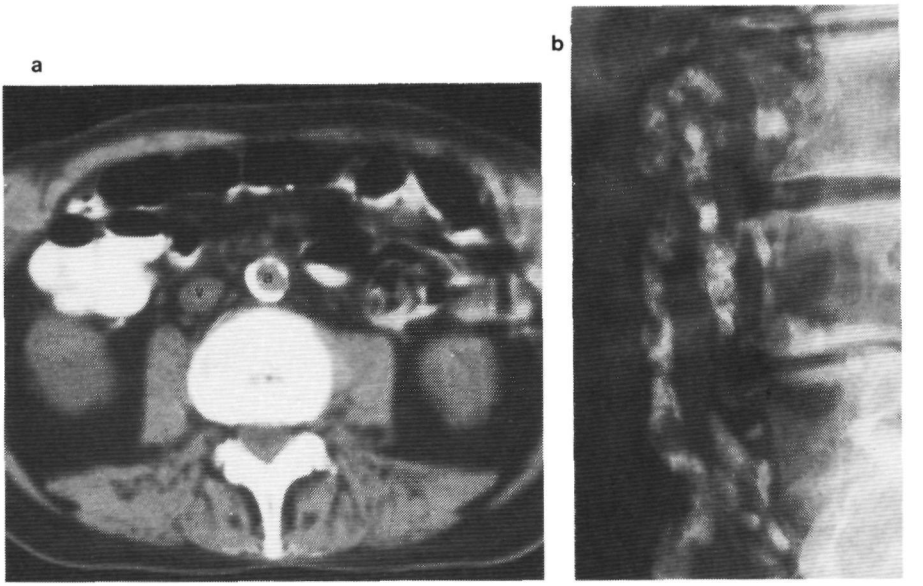

Fig. 2: Male patient of 64 years with HD, nodular sclerosing type. CT shows normal-sized retroperitoneal nodes (2a). Subsequent lymphography also reveals irregular structure and filling defects, suggestive of HD (2b).

Laparotomy was performed in 30 patients. With 3 patients only splenectomy was planned, and abdominal nodes were not biopsied. With 2 patients, the radiologically suspect nodes were not removed. This leaves 25 patients for radiologic-histologic correlation of lymph nodes (table II.)

Table II: Comparison of radiologic and histologic findings in 25 patients undergoing laparotomy with lymph-node sampling.

	accuracy	sensitivity	specificity
lymphography (contrast filled nodes)	23/25 (92%)	7/9 (78%)	16/16 (100%)
lymphography (all lymph nodes)	21/25 (84%)	7/11 (64%)	14/14 (100%)
CT (all lymph nodes)	20/25 (80%)	7/11 (64%)	13/14 (93%)
CT + lymphography	22/25 (88%)	9/12 (75%)	13/13 (100%)

Accuracy = Sum of correctly positive and negative diagnoses in the group.
Sensitivity = Correct diagnosis in patients having the disease.
Specificity = Correct diagnosis in patients not having the disease.

The diagnostic accuracy of lymphography in comparison with histology of the visualized lymph nodes amounted to 92%, with a sensitivity of 78% and a specificity of 100%. In 2 patients, affected nodes were found in the upper para-aortic (celiac) region only, outside the scope of the lymphogram. If the lymphogram was regarded to represent all abdominal lymph-node regions, the diagnostic accuracy would drop to 84% and the sensitivity to 64%. The specificity remains 100%, however.
The diagnostic accuracy of CT -potentially visualizing all abdominal lymph-node regions- amounted to 80% with a sensitivity of 64% and a specificity of 93%.

Retrocrural lymph nodes:
The CT scans of 76 patients were inspected for the presence of enlarged retrocrural lymph nodes (i.e. nodes larger than 6 mm (4)). Out of the 40 patients with pathologic abdominal nodes on CT or lymphography, 7 also revealed enlarged retrocrural nodes (18%). Only 1 patient showed enlarged retrocrural nodes in the absence of other abdominal lymph-node involvement. Six out of the total of 8 patients having retrocrural lymph-node enlargement also had enlarged mediastinal or hilar nodes on the chest X-ray, and in the remaining 2 patients findings in the chest were normal.

DISCUSSION

Hodgkin disease has to a large extent become a curable disease. Even advanced stages of primary or recurrent disease can nowadays be treated effectively.
On the other hand, there is a tendency to minimize treatment in the less advanced stages to avoid early and late side effects of chemotherapy and/or radiotherapy, such as pulmonary and cardiac damage, hypothyroidism, infertility, bone-marrow depression, and the development of secondary malignancies such as leukemia or non-Hodgkin lymphoma (5). Accurate staging is mandatory to tailor treatment to the stage, and to prevent over- or undertreatment.
Lymphography has become a major method for imaging the retroperitoneal lymph nodes. Numerous publications have appeared correlating radiologic and histologic findings (6-24; fig. 3). The total number of patients represented in figure 3 is 1903. Many series illustrate that an overall diagnostic accuracy of 90% or higher is obtainable. The mean accuracy rate is 87%. The associated sensitivity varies between 55% and 100%, with a mean value of 81%. The specificity varies between 72 and 100%, with a mean value of 89%.

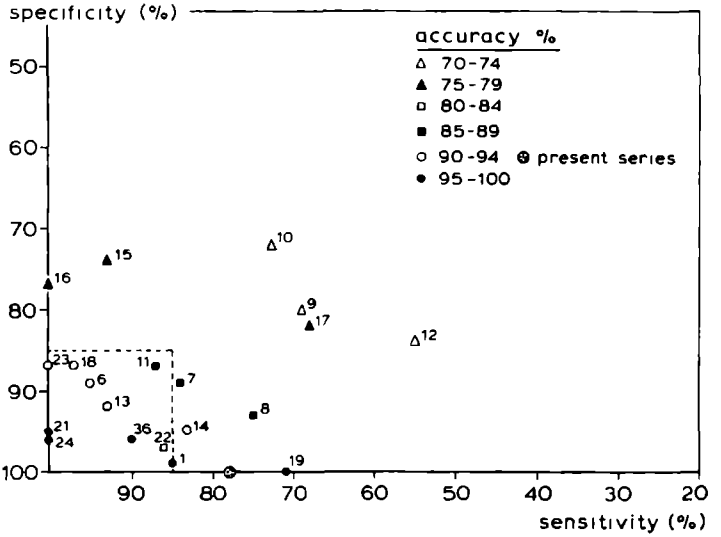

Fig. 3: Diagnostic performance of lymphography. Overall accuracy, sensitivity and specificity calculated from literature data on histologically verified lymphographies in patients with HD.
Numbers in accordance with references.

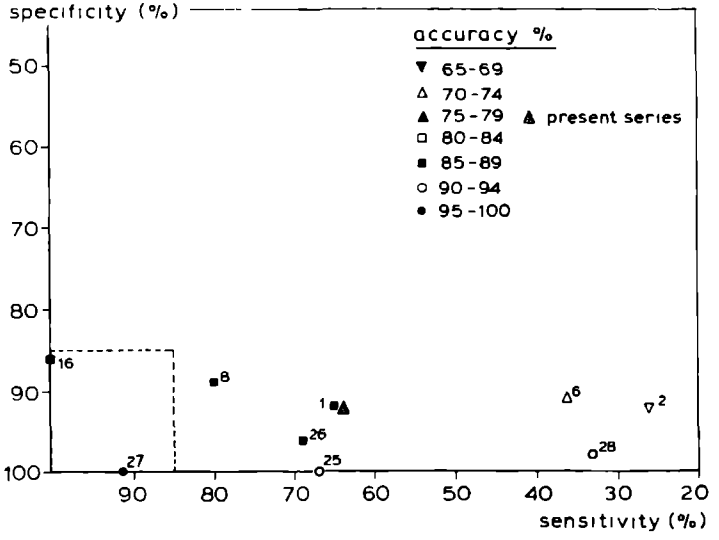

Fig. 4: Diagnostic performance of CT. Overall accuracy, sensitivity and specificity calculated from literature data on histologically verified CT-scans in patients with HD.
Numbers in accordance with references.
(Ref. 2 including lymph nodes and spleen.)

Comparable data on CT and histology of lymph nodes in HD are not as widely available.

Fig. 4 is a compilation of literature data presenting histologically controlled CT-studies in patients with HD. Series presenting mixed data on HD and NHL are not incorporated. From institutions publishing regularly, only the most recent data available from medical literature are included (1,2,6,8,25-28). The total number of patients represented in figure 4 is 441. The series of Castellino et al. (1) and Crowther (2) contain more than 100 patients each, the series of Clouse et al. (6) contains 54 patients, and the remaining series all consist of less than 40 patients. The relative scarcity of abdominal CT-evaluations is in contrast with the abundance of publications on lymphography in HD, but this is probably due to the fact that staging laparotomy is nowadays applied far less than before. The diagnostic accuracy of CT varies between 66% and 95%, with a mean value of 83%. The sensitivity in detecting lymph-node involvement varies from 26% to 100% (mean value 62%), and the specificity from 86% to 100% (mean value 92%).

These literature data indicate that the difference in diagnostic accuracy between CT and lymphography is due to the lower sensitivity of CT in detecting lymph-node involvement, or -in other words- CT leads to more false-negative diagnoses.

This general conclusion supports the conclusion of Castellino et al. (1). These authors established an overall accuracy for lymphography of 95%, and for CT of 87%. The figures for sensitivity were 85% and 65% respectively, and for specificity 98% and 92% respectively. Crowther (2) however, found a slightly greater sensitivity of CT in comparison with lymphography, even in the lymph-node areas covered by lymphography.

According to the literature data, the combined use of CT and lymphography in the same patients leads to discrepant findings in 4% to 33% of cases. (9,16,27-32). These

discrepancies consist mainly of normal CT-findings in combination with an abnormal lymphogram, and this is also illustrated by our personal series.

The overall discrepancy rate between CT and lymphography in our series of 78 patients was 18% (14 patients). When CT was the first examination performed, the discordance was greater than when lymphography was carried out first (26% and 10% respectively). This difference is probably due to the fact that in our clinical setting the diagnosis of the first examination is generally known to the radiologist performing the second examination. For the purpose of this study, we maintained the original reports, without retrospective modification. Apparently it happens that the primary lymphographic diagnosis is adopted when interpreting the subsequent CT scan, and only 2 false-negative CT scans occurred in this group (one case with histologic proof). The group of 39 patients undergoing CT prior to lymphography included the remaining 5 "false-negative" CT scans (one with histologic proof). There were also 2 equivocal CT-diagnoses in this group that were subsequently modified into normal and pathologic findings respectively by lymphography (one case with histologic proof). The fact that "false-negative" CT scans were surprisingly more frequent with the faster scanner, cannot be explained adequately. It seemed that an "equivocal" diagnosis was avoided in exchange for a "negative" diagnosis, in the knowledge that a lymphography would be carried out. It is suggested by our data, that the CT-diagnosis is more reliable when the examination is performed following lymphography, and its interpretation is known. This suggestion is corroborated by our study of patients with NHL undergoing both procedures. Comparable results were obtained with those patients (33).

A fair comparison of the diagnostic value of CT and lymphography can therefore only be made when the CT is performed first, and when the examinations are interpreted prospectively and independently.

Castellino et al. (1) conclude that in their hands lymphography has a real diagnostic advantage over CT in evaluating the retroperitoneal lymph nodes in 7 % of cases. Although our number of patients is considerably smaller especially when laparotomy is concerned, the comparison of CT and lymphography results in the total group of 78 patients makes clear that lymphography overruled the CT diagnosis in 9 patients (= 12%), whereas CT added information on the lymph-node status in only 1 patient (= 1%).

The answer to the question whether either one or both examinations should be performed in order to obtain the most accurate clinical staging data is determined by the influence these data will have on the final treatment strategy. Therefore a uniformly valuable answer can not be given. The following considerations may help in answering this question. A CT scan showing abdominal lymph-node enlargement generally does not have to be followed by a lymphogram, because false-positive CT-findings are uncommon. A normal abdominal CT scan excludes bulky disease in the lymph nodes, but minor abnormalities can still be found by lymphography in 10 to 20% of cases. When this uncertainty does not change treatment strategy, lymphography can be omitted.

Performing lymphography only, without subsequent CT scanning does not decrease the reliability of nonainvasive staging, because CT only rarely adds significant information on the lymph nodes. Although it is known that staging laparatomy can detect unexpected abdominal lymph node involvement after a normal lymphogram, these findings could only occasionally have been detected by CT.

The diagnostic errors in our series of 25 patients undergoing staging laparotomy with appropriate lymph-node sampling occurred in the upper abdominal lymph nodes in 3 of 4 cases. One patient showed a small focus of HD in a 8 mm large node, containing contrast medium after lymphography. This focus was clearly too small to be

visualized with CT or lymphography, even in retrospect. One patient showed involvement of a normal-sized spleen, splenic hilar, peripancreatic and celiac nodes. These nodes were situated outside the scope of the lymphogram, but on reviewing the CT scan, some of these nodes could be located (fig. 5).

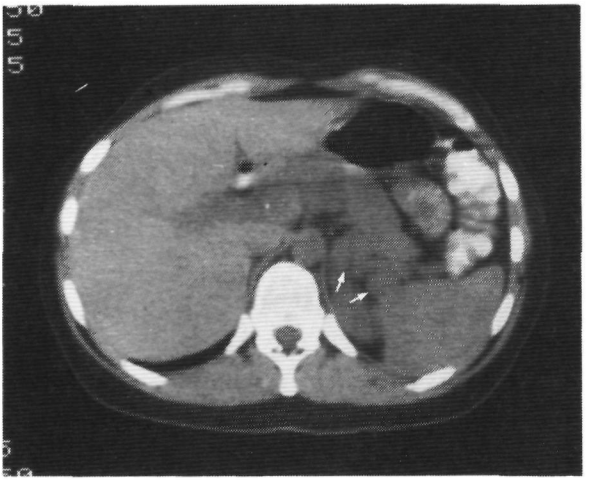

Fig. 5: Female patient of 34 years with HD, mixed cellular type. CT scan originally misinterpreted as showing no abnormalities. Staging laparotomy revealed an involved spleen and enlarged retropancreatic nodes, which were radiologically visible in retrospect (arrows).

In the third patient, CT was misinterpreted as showing enlarged retropancreatic and retrocrural nodes. Staging laparotomy revealed an involved normal-sized spleen and celiac nodes only.

In a fourth patient, staging laparotomy with histologic examination confirmed the negative CT and lymphography reports. However, a clinically suspect, superficial left inguinal lymph node was removed, and this node proved to be affected by HD. In retrospect, the node could be located, but definitive signs of malignancy could not be established radiologically. Finally, one patient was proven to have an involved spleen only after staging laparotomy, with negative findings at lymphography and CT

of lymph nodes being confirmed.
When CT and lymphography produce discrepant results in staging, the interpretation of the latter is generally preferred because lymph-node structure of apparently involved nodes usually presents characteristic images and therefore more specific information than assessment of size alone (34).
Revision of the negative CT scans in cases with positive findings with lymphography showed, that in most instances the size of individual lymph nodes was within the usual limits, but that a local concentration of such clearly visible, unenlarged nodes should have aroused suspicion.
Two out of the total of 27 patients (= 7%) undergoing staging laparotomy were excluded from evaluation because the radiologically suspect nodes were not biopsied. Although surgical staging is the final step to complete pathological staging, it should be realized that non-representative lymph-node sampling is a realistic problem occurring in about 10% of patients, even in very experienced hands (1,13,20,30). Intra-operative radiologic monitoring is apparently not able to reduce these sampling errors sufficiently.
The advantage of CT over lymphography by visualizing all abdominal lymph-node regions including the spleen is not to be translated in a more accurate staging potential (table II). Mesenteric lymph-node involvement is only occasionally the sole intra-abdominal finding (1). When present, the retroperitoneal nodes are mostly widely involved. The high para-aortic nodes are more often involved, but the size of these nodes is usually within normal limits when they are the only intra-abdominal finding.
Table II shows the radiologic findings related to laparotomy findings in various ways. Although the series is rather small, some speculative data can be distilled from it. Lymphography gives the best results when findings in the visualized lymph-node areas only are evaluated.

When non-visualized lymph-node areas are included, the accuracy rate drops due to a decreased sensitivity rate. The figures remain still slightly more favourable compared with the performance of CT with regard to the lymph nodes (all regions). The combined use of CT and lymphography in staging the abdominal lymph nodes improves minimally on the performance of lymphography only.

Anatomic substaging of stage III HD gives relevant clinical and prognostic information (35). Stage III_1 includes involvement of spleen, or splenic, celiac or portal nodes or a combination of these. Stage III_2 disease includes involvement of para-aortic, iliac or mesenteric nodes, with or without upper abdominal involvement. The former stage is associated with a better prognosis than the latter, and substaging results in different therapeutic regimens. Although CT and lymphography are relatively reliable in diagnosing stage III_2 disease, stage III_1 disease is subject to the insufficiencies of the methods as illustrated above. Three patients with stage III_1 disease in our series (2 patients with spleen and lymph-node involvement, 1 patient with spleen involvement only) were not correctly identified, but 1 patient with histologically proven spleen localization as the only pathological finding, was discovered by CT. Traditionally staging laparotomy has its greatest yield in revealing unexpected upper abdominal localization of disease, and will still be indicated when this information will modify the therapeutic strategy.

Retrocrural lymph nodes:
The retrocrural area is in fact the most inferior extension of the posterior mediastinum. When enlarged retrocrural lymph nodes are diagnosed with CT, there is a high probability of upper mediastinal involvement: 6 of our 8 patients with enlarged retrocrural nodes showed evidence of upper thoracic lymph-node enlargement.

Fourteen patients showed the combination of abnormal chest X-ray findings and enlarged infradiaphragmatic nodes: 6 of these (=43%) had enlarged retrocrural nodes. Fourteen patients had normal chest findings associated with infradiaphragmatic lymph-node involvement, and retrocrural nodes were found in 1 case (=7%). Only 1 case of enlarged retrocrural nodes in association with normal abdominal nodes was seen. This was a patient with recurrent disease, who had undergone abdominal lymph-node irradiation in the past. The detection of enlarged retrocrural nodes during abdominal CT scanning is therefore highly suggestive of upper mediastinal lymph-node involvement.

CONCLUSIONS

1. Literature data correlating radiologic and histologic findings in patients, examined for HD, uniformly show a lower diagnostic accuracy of CT in comparison with lymphography. This difference is caused by a lower sensitivity of CT and an equal specificity.
2. The above-mentioned conclusion also follows from the present study in 78 patients with HD. CT and lymphography disagreed in 18% of patients. When CT preceded lymphography the disagreement was 26%. When CT followed lymphography, the disagreement was 10%.
   Fifty percent of discordant findings consisted of a normal CT scan in combination with an abnormal lymphogram. In most of these cases, CT was carried out first.
3. When CT is performed as the first investigation, lymphography will only yield significant information when CT is normal or equivocal.
4. When lymphography is performed first, subsequent CT will only occasionally add significant information with regard to the lymph nodes.

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Chapter 3

THE SPLEEN IN HODGKIN DISEASE: DIAGNOSTIC VALUE OF CT.

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ABSTRACT

Findings of CT of the spleen were compared with those of histologic examination in 35 patients who had Hodgkin disease. CT provides a simple way to calculate splenic size. This index is also of value in the assessment of the histologic state of the spleen. An accuracy rate of 91%, specificity of 94%, and a sensitivity of 89% in diagnosing splenic localization of lymphoma was found in this study.

INTRODUCTION

In staging Hodgkin disease, the spleen has always been difficult to evaluate for the presence or absence of disease using non-invasive methods. Histologic examination following surgical removal of the spleen reveals a considerable number of pathologic findings in patients who have clinically occult disease.
With the introduction of body CT, it was hoped that a more accurate preoperative diagnosis would be possible. Whereas the value of CT in demonstrating abdominal lymph node involvement has been established, most published series until now show rather disappointing results in the assessment of the histologic state of the spleen.
Some pertinent radiologic, surgical, and pathologic-anatomic findings in the literature and in own patients were analyzed to determine the role of CT in investigating the spleen in patients who have Hodgkin disease.

MATERIAL AND METHODS

A comparison was made of CT and histologic findings in the spleens of 35 patients who had Hodgkin disease (HD). Findings for 27 patients were evaluated retrospectively and for eight patients prospectively. In 25 of the patients who had previously untreated HD, which was clinically staged IIA or IIIA, a staging laparotomy was

performed. Of these, three patients presenting with infra-diaphragmatic disease underwent laparotomy for both diagnostic and staging purposes.

In seven patients in whom recurrent disease was suspected, laparotomy with splenectomy and sampling of abdominal nodes was performed. Three patients died shortly after clinical evaluation for recurrent disease, and in these patients CT was correlated with autopsy findings.

In 26 patients, CT of the body was performed using an OHIO Nuclear 50 FS Delta Scanner with a scanning time of 18 seconds and a section thickness of 13.5 mm. Contiguous scanning of the whole abdomen was performed with the scans of the upper abdomen in suspended expiration. Five patients were examined using a Siemens Somatom DR 3 with a scanning time of 5 seconds, and a section thickness of 8 mm at 16 mm intervals. Four patients who had a CT examination elsewhere were referred.

Intravenous contrast material was not administered routinely. CT criteria for splenic involvement with lymphoma are splenomegaly and/or the presence of low-attenuation nodules. While there is general agreement that only nodules larger than 1 cm can be demonstrated with CT (1-6), the definition of splenomegaly is not uniform in the radiologic literature. Different criteria are applied by authors presenting CT-pathologic correlation in examination of the spleen (1-4,7,8). In the literature, the use of the splenic index as proposed by Lackner (3) offered the most practical definition of splenic size. We therefore calculated in review the splenic index in our patients, and applied the same calculation for the patients in the prospective study. The index is obtained by multiplying spleen thickness, width, and length as visualized on CT. The length is determined by adding all section-thicknesses (and intervals if used) on which the spleen is seen. The width is the longest (straight) organ diameter in the transverse (scanning) plane. The thickness is the distance between the center (inner) and peripheral (outer) surface, measured at the level of the splenic

hilum. When significant differences exist between anterior and posterior parts of the spleen, the mean value is taken (Fig. 1).

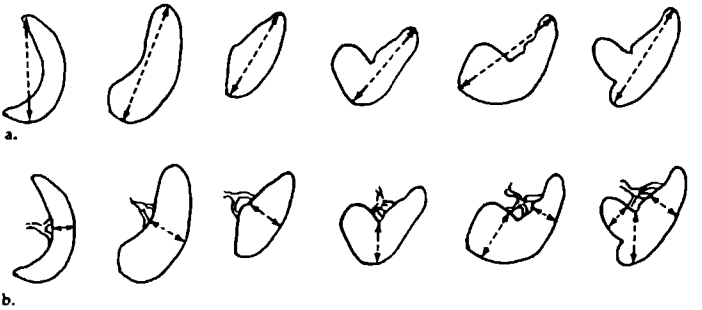

Figure 1:
Measurement of spleen dimensions in various spleen shapes (tracings from CT sections).
a. Width = longest transverse diameter, regardless of scan height through spleen or spleen orientation.
b. Thickness = distance from inner to outer surface, directly measured or mean value in cases with marked spleen asymmetry.

Lackner found values ranging from 120-480 for normal spleens. In our study we used these values to discriminate between normal and diseased spleens on CT. Furthermore, the spleens were evaluated for the presence of hypodense nodules. The weight of the spleen, as recorded immediately after removal at surgery, was noted.

To determine the histopathologic state of the spleen, the excised specimen was cut in slices of 0.5 cm thickness and inspected for macroscopic evidence of tumor localization. If present, tumor nodules were excised and 4 μ sections of the paraffin-embedded tissue blocks were studied microscopically. From macroscopically uninvolved spleens, at least five tissue blocks were taken from different areas. When no tumor could be demonstrated in sections of these blocks, the spleen was reported as pathologically negative. The histologic state of the liver was determined by examination of needle and wedge biopsy specimens obtained at laparotomy from both the left and right lobes, and from any grossly suspect area.

RESULTS

Twenty-three patients were male (aged 16-62 years) and 12 were female (aged 16-64 years). The most common histologic subtype was nodular sclerosis (n = 20), followed by lymphocyte depletion (n = 6), lymphocyte predominance (n = 4) and mixed cellularity (n = 3) HD. Two cases were unclassified. Laparotomy or autopsy was performed within a month after CT in 21 of 32 patients. The maximum interval was five months. The spleen was histologically positive for HD in 19 patients (54%) and negative in 16 (46%). The weight of 14 histologically negative spleens varied from 74-320 g (mean weight 190 g). The splenic index in this group varied from 153-690 (mean index 348). The weight of 17 histologically positive spleens varied from 103-1,687 g (mean weight 545 g). The splenic index in this group varied from 194-2,483 (mean index 1,010). When comparing the sum of indices with the sum of weights, it was calculated that the average spleen weight (in grams) was 0.55 x splenic index. In 20 of 31 patients (65%) the difference between calculated and actual weight was less than 25%, and in 27 of 31 patients (87%) the difference was less than 35%. However, these figures are biased by the fact that in this predominantly retrospective study the process of weight determination and the time interval between CT and laparotomy or autopsy were of course not strictly standardized.

Table I specifies the data concerning splenic index calculation in 27 patients studied retrospectively, in 8 patients studied prospectively, and the results in the total group of 35 patients.

Using the splenic index as an indicator of splenic involvement with lymphoma, it was found that 17 of 19 involved spleens had a splenic index over 480 (sensitivity 89%). Fifteen of 16 histologically uninvolved spleens had a splenic index lower than 480 (specificity 94%). The overall accuracy of the procedure therefore amounts to

32/35 (91%). These results are statistically significant ($P < .001$ using the χ^2-test with Yates correction). In only one of the spleens were low-attenuation areas visible on CT. Macroscopic findings of the operative specimens as registered in 14 histologically positive spleens revealed that nodules were visible in all these spleens, but only in five were nodules larger that 1 cm present. No nodules were visible in spleens that proved to be negative by histologic examination. The incidence of concurrent splenic and hepatic involvement with lymphoma is specified in table II. Hepatic involvement was not demonstrated in the absence of splenic involvement. The incidence of splenic and hepatic involvement in the various subtypes of HD is specified in table III.

Table I: Correlation of CT-splenic Index Calculation.

a)*		Histology	-	+	Total
	CT				
	-		11	1	12
	+		1	14	15
	Total		12	15	27
b)*		Histology	-	+	Total
	CT				
	-		4	1	5
	+		0	3	3
	Total		4	4	8
c)*		Histology	-	+	Total
	CT				
	-		15	2	17
	+		1	17	18
	Total		16	19	35

acc. = $^{32}/_{35}$ (91%)
sens. = $^{17}/_{19}$ (89%)
spec. = $^{15}/_{16}$ (94%)

*a) 27 patients studied retrospectively, and b) 8 patients studied prospectively; c) results of the combined groups.

Acc. = accuracy (percentage of correct diagnoses). Sens.= sensitivity (percentage of patients with histologically positive spleens in which CT findings were correctly interpreted as positive), Spec. = specificity (percentage of patients with histologically normal spleens in which CT findings were correctly interpreted as negative).

Table II: Comparison of Liver and Spleen Histology in 34 patients.*

Liver	Spleen +	Spleen -	Total
+	8	0	8
-	10	16	26
Total	18	16	34

* Hodgkin disease present (+) or absent (-) histologically.

Table III: Spleen and Liver involvement in 33 patients according to HD-subtype.

Subtype	No.	spleen -	spleen +	liver and spleen involvement
Nodular sclerosing	20	12	8	2
Lymphocyte depleted	6	0	6	3
Lymphocyte predominant	4	1	3	1
Mixed cellular	3	1	2	2
Total	33	14	19	8

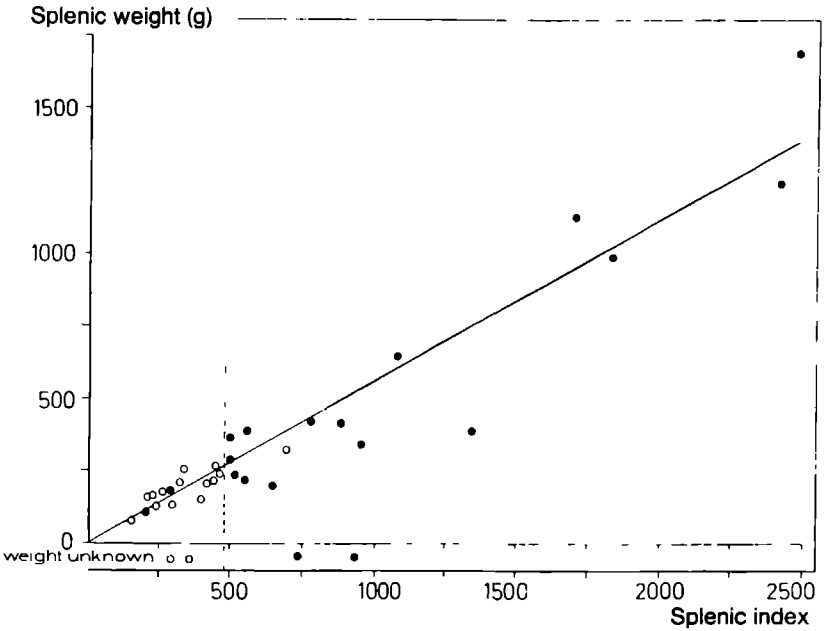

Figure 2: Correlation of splenic weight and splenic index of spleens positive (●) or negative (o) at histologic examination; splenic index of 480 as upper limit of normal range.

DISCUSSION

Laparotomy with splenectomy reveals clinically unsuspected areas of disease in 23-30% of patients who have Hodgkin disease (7,9-15). An advanced clinical stage, the presence of B-symptoms (9-11,13,16), and the mixed cellular histological subtype (9,10) are associated with an increased incidence of splenic involvement. However, conventional non-invasive diagnostic procedures are unreliable to assess eventual presence of disease in the spleen (9,12,13,16-18).

With the introduction of CT it became possible to visualize the size and internal structure of the spleen. However, reported series until now show rather disappointing results in demonstrating or excluding splenic involvement with lymphoma (1-8, 19-21).

Involvement of the spleen with lymphoma is nearly always visible macroscopically. The pathologist rarely finds lymphoma at histologic examination of a grossly normal looking spleen (2,6,9). This is confirmed by the present study. Usually, however, the size of most nodules is too small to be detectable by current CT techniques. Only nodules larger than 1 cm may become visible as low attenuation areas (1,2,4,5). Although intravenous contrast medium has not been used consistently in this or previous series, the beneficial effect of this procedure is doubtful (6). In fact, a recent report demonstrates that even in normal spleens an irregular contrast enhancement is not rarely observed after intravenous injection (22). This finding corroborates a previous report by Castellino et al. who employed splenic arteriography in patients who had HD (23). The efficacy of newly developed contrast media for specific enhancement of liver and splenic tissue is demonstrated (24) but their clinical use is not yet generally accepted.

The limited value of CT in detecting splenic tumor nodules is emphasized by this study, since only five of 14 histologically positive spleens contained nodules with a

diameter larger than 1 cm, and only one of these was detected with CT.

The most important parameter for clinical diagnosis of splenic involvement with lymphoma (HD or non-Hodgkin lymphoma) is enlargement of the spleen. However, evaluation of splenic size by palpation has proved to be rather unreliable, with 0-25% falsely positive diagnoses and 60-94% falsely negative diagnoses (9,12,13,16,18,25, 26). Moreover, an involved spleen is often found to be of normal size, whereas definite splenic enlargement occurs without histological evidence of disease (9,12,13,27,28). No strict correlation between the weight of an operative specimen and its histopathologic state has been established (9,12,13,17,25,26). As weight and size of an excised spleen are partially determined by the amount of entrapped blood, a variable bias is introduced by circulatory factors during operation, timing of vessel clamping, and uncontrolled loss of blood from the specimen before it is weighed.

Correlation between weight and histology therefore appeared to be less valid. Only a weight of over 400 g was found to be consistently associated with localization of lymphoma (9,16). In this series a marked discrepancy between weight and size as estimated by CT was sometimes recorded (fig. 2). The time lag between CT and laparotomy was not responsible for these differences.

A reliable determination of size and volume by means of CT is possible in vivo (29-31). However, most previous studies estimated splenic size in patients who had malignant lymphoma by employing crude criteria. Blackledge and Best et al. (4,7) diagnose splenomegaly when the organ extends below the ribs. Ellert and Kreel (8) diagnose enlargement when the spleen extends more than two thirds the distance between the posterior and anterior abdominal walls. The consequence of using incomplete or inexact criteria is a low accuracy rate associated with a high specificity (i.e., few false positives) and a low sensitivity (i.e., numerous false negatives) (fig. 3).

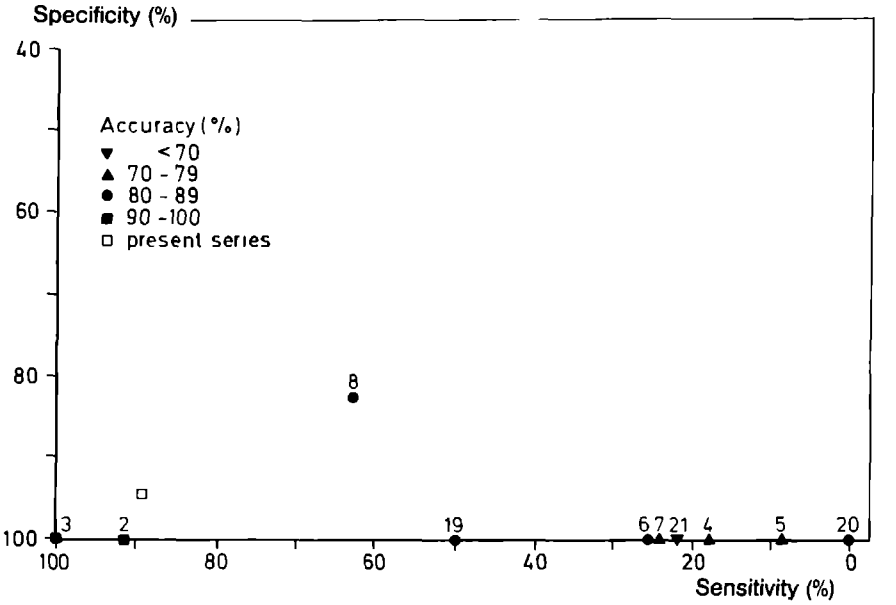

Fig. 3: Correlation of sensitivity and specificity as calculated from literature data on CT-pathologic correlation of the spleen. Numbers in accordance with bibliography.

When applying the receiver operating characteristic (ROC) concept (32) to these results, it is suggested that improvement in sensitivity without a marked loss in specificity should be possible by a more accurate definition of splenic size. Both series in which all three dimensions (length, width, and thickness) were measured on CT scans, have high accuracy rates with few falsely positive or falsely negative diagnoses (2,3).

Lackner et al. (3) introduced the term "splenic index" for the product of spleen thickness x width x length. This parameter appeared to be a reliable indicator of splenic size and involvement in his series. In 100 patients who did not have disease related to the spleen he found a maximum value of 480. In 11 patients who had malignant lymphoma, four spleens had an index well above 500, and all these spleens were histologically positive for lymphoma. The other seven spleens had an index below 500 and proved to be negative. In our patients, the original

CT reports were 71% accurate with regard to determination of splenic involvement. In review, using a splenic index of 480 as threshold value, the accuracy increased to 91%. As shown in figure 2, there appears to be a linear relationship between splenic weight and index. It is suggested that the splenic index can serve as an indicator for splenic weight in vivo. Splenic weight in grams amounts to approximately 0.55 x splenic index. The proposed range for normal spleens of 120 to 480 according to Lackner, would correspond to a weight range of 65 to 265 g. One falsely negative spleen in our series had an index of 194 and a weight of 103 g (case 6). Macroscopic examination revealed two tumor nodules smaller than 1cm. At microscopic examination, a multifocal spread of Hodgkin disease was present. Another falsely negative spleen weighed 195 g with a splenic index of 286. Histologically, several nodules smaller than 6 mm were visible. The only falsely positive spleen on CT in our series had an index of 690 and weighed 320 g (case 9). Histologic examination revealed signs of chronic congestion but no evidence of lymphoma.

An obvious advantage of using the splenic index rather than splenic weight as indicator of disease is that calculation of splenic index is an in vivo measurement, leaving the patient untouched and intact. It is conceivable that the diagnostic significance of the splenic index will be less reliable when this index approaches the threshold value of 480. When confirming data from the older literature that states that only spleens heavier that 400 g are consistently involved with lymphoma (9,16), one can increase the threshold value to 725. This implies a decreased sensitivity for the method, but fewer false positive CT diagnoses. For the present study this altered criterion would lead to an overall accuracy of 27/35 (77%), a sensitivity of 11/19 (57%), and a specificity of 16/16 (100%) (table IV).

The histologic findings in the liver in our patients confirm the earlier observations that liver involvement in

Table IV: Influence of increasing the threshold value from 480 to 725 with regard to diagnostic accuracy.*

CT \ Histology	-	+	Total
-	16	8	24
+	0	11	11
Total	16	19	35

accuracy = $^{27}/_{35}$ (77%)
sensitivity = $^{11}/_{19}$ (57%)
specificity = $^{16}/_{16}$ (100%)

* See text; compare with table Ic.

Hodgkin disease does not occur in the absence of splenic involvement (9,12,17,18). Conversely, in one patient (not included in this study) in whom positive findings of liver biopsy were obtained, an elevated splenic index of 732 was measured.

Although the number of patients in our series compares favorably with other series in the literature (1-3,6,8, 19-21), the validity of the splenic index as indicator of size and disease in the spleen in patients with HD will have to be tested in larger, prospective studies. Calculation of total splenic volume, as is possible with CT (29-31) will probably give an even more exact approach to the determination of splenic size.

CONCLUSION

CT is a reliable technique for visualizing size, shape, and structure of organs in vivo. In reviewing the literature and after evaluation of our patient material, it is suggested that the accuracy of diagnosing involvement of the spleen with HD can be improved by a more exact definition of splenic size using the splenic index. In 35 patients who had HD, a diagnostic accuracy of 91% was obtained with a falsely positive rate of 6% and a falsely negative rate of 11%. Application of this criterion, or the calculation of total splenic volume with CT, could increase the sensitivity of this technique that already has demonstrated a high specificity in the visualization of splenic and abdominal lymphoma.

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CRITICAL REVIEW

Investigative Radiology 1986; 21: 437-439

Albert A. Moss, MD, editor

This section of the journal is designed to present constructive comments on investigations which are reported in the world literature and which are within the scope of Investigative Radiology. In each case the authors of the original articles are given the opportunity to respond to the comments of the reviewers. The readers of the Investigative Radiology are invited to take part in the open exchange of opinions through Letters to the Editor.

The Spleen in Hodgkin Disease : Diagnostic Value of CT
Authors: S.P. Strijk, D.J. Wagener, M.J.J.T. Bogman, B.E. de Pauw, and T. Wobbes.
Publication: Radiology 1985; 154: 753-757.

SUMMARY OF THE ARTICLE

The authors correlate their estimates of splenic volumes, based on CT measurements, with the results of histologic examination of the spleen (staging laparotomy in 25 cases, laparotomy to establish recurrent disease in seven cases, and autopsy in three cases) from patients with Hodgkin's disease. They conclude that the CT-derived splenic volume (the "splenic index") is useful in assessing the histologic status of the spleen.

REVIEWERS' COMMENTS

This conclusion is made despite well-documented studies on Hodgkin's disease from numerous investigators indicating that the splenic weight (as determined at staging laparotomy) is a poor predictor of splenic histopathology. The authors contend that correlations of histology and the actual weight of the resected spleen are less valid than correlation of histology and the CT-derived volume ("splenic index"). They argue that variables are introduced by circulatory factors during surgery, timing of vessel clamping, and uncontrolled loss of blood from the spleen before weighing. This is an interesting concept, although the study does not address this specific point.

Given the current understanding of the histopathology of Hodgkin's disease involvement of the spleen, one would not expect a significant correlation between the splenic size (volume) or weight and the histopathologic examination, unless the organ is extensively involved with tumor (in which case such splenomegaly is readily detected by palpation, abdominal films, etc.). In patients with previously untreated disease, splenic lesions are often focal, nodular, and less than 1 cm in size. There is little to no surrounding edema or cellular infiltrate to add bulk to the spleen to produce significant changes in either weight or size (volume). Conversely, in patients with Hodgkin's disease, large spleens may not contain histopathologic evidence of tumor.

To test the authors' conclusions, we retrospectively reviewed the CT scans of 24 randomly chosen patients with previously untreated Hodgkin's disease who had CT scans followed by staging laparotomy and splenectomy. The CT scans were reviewed in a blind fashion (T.G.) and the "splenic index" was calculated according to the method described by Strijk et al.

Of the 24 cases we reviewed, 20 patients had nodular sclerosing Hodgkin's disease, 3 mixed cellularity Hodgkin's disease, and 1 lymphocyte depletion Hodgkin's disease. Ten of 24 (42%) patients had histologically positive spleens. The CT-derived "splenic index" (more than 480 being abnormal) showed an accuracy of 54% (13 of 24), a sensitivity of 30% (three of ten), and a specificity of 71% (ten of 14) in assessing the spleen. The weight of the resected spleen (more than 250 gm being abnormal) showed an accuracy of 58% (14 of 24), a sensitivity of 20% (two of ten), and a specificity of 86% (12 of 14). Neither a positive CT "splenic index" nor the weight of the resected spleen showed a strong correlation with a positive histopathologic examination ($P>.05$ using the χ^2 test with Yates correction). In our patients, the splenic weights averaged 36% of the "splenic indices," whereas Strijk et al. noted a ratio of 55%. It is

provocative to note that our largest measured spleen, with a "splenic index" of 1260 and a weight of 410 gm, on careful sectioning showed only two nodules of tumor, each measuring less than 1 cm, contributing approximately only 2 gm to the weight of the spleen.

Some aspects of the authors' study design could provide misleading information.

* Their calculations of splenic volumes and subsequent comparison with the histologic results were made retrospectively in 27 cases and prospectively in only eight cases. No reference is made to whether there was preliminary knowledge of the histologic results prior to review of the CT scans from those 27 patients examined retrospectively.
* The time between CT and histologic examination of the spleen was less than one month in 21 patients, and ranged up to five months in the rest. This long time interval precludes careful correlation of the CT data with the splenectomy specimen in a substantial number of cases.
* The presented data are incomplete, presumably due to the retrospective nature of the study. Thus, in four cases no splenic weight was recorded and in five of 19 histologically positive cases, the size of splenic lesions was not noted.
* The authors studied a nonhomogeneous patient population. Previously untreated Hodgkin's disease was newly diagnosed in 25 patients; 10 patients were evaluated for recurrent disease. This inclusion of patients with recurrent disease presumably accounts for the extremely large weights of several spleens, four of which measured over 1,000 gms, which is unusual in patients with untreated disease. The very high incidence of positive livers (eight of 34, or 24%) probably is explained by the inclusion of patients suffering relapse.
* The authors do not specify whether they used a consecutive patient population or if patients were

selected for this study. The percentage of their patients with histologic proof of splenic involvement (54%) is higher than the 38% noted by Kaplan (1) for 814 consecutive, unselected, previously untreated patients with Hodgkin's disease undergoing laparotomy and splenectomy at Stanford. Their higher incidence of splenic disease may be related to the inclusion of patients with recurrent disease in their series or may reflect a bias in patient selection.

Thus, the data that the authors present, showing a high degree of accuracy, sensitivity, and specificity (91%, 89%, and 94%, respectively) in correlating the CT "splenic index" with involvement of the spleen with Hodgkin's disease, bear uncertain significance with respect to the preoperative evaluation and staging of untreated patients. Perhaps the greatest error was not presenting the data derived from the 25 patients undergoing initial staging CT studies separately from those of the ten who had relapsing disease. The excessively long time intervals between the CT scan and histologic evaluation of the spleen in many cases is also disquieting.

In summary, there is little evidence to support the contention that spleen volume increases with early involvement by Hodgkin's disease. The authors' results of very high accuracy rates may be related to the design of the clinical experiment, as noted above. Using their criteria, we were unable to reproduce their high accuracy data in a group of 24 newly diagnosed patients.

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AUTHORS' RESPONSE

The fact that although CT has the potential for exact volume determinations in vivo, most series evaluating the spleen in patients with malignant lymphoma use criteria that yield diagnostic results of low accuracy and sensitivity, but of very high specificity, stimulated us to test the efficacy of better defined criteria. We are aware of the numerous publications in which splenic weight correlated poorly with spleen histology. There are some indications that the weight of an operatively obtained specimen may not reflect actual spleen size in vivo. Spleen size varies with respiration; Jahnke found differences of up to 9% between inspiratory and expiratory values in the same patient during the same investigation (1). Spleen size diminishes in reaction to intravenously administered epinephrine - Rosen found that size decreased up to 35% in normal controls, and up to 10% in a patient with Hodgkin's disease (2). Intraoperative spleen handling resulting in occlusion of arterial and venous flow also may induce uncontrollable deviations from the baseline flow (and blood content) of the untouched organ. Labrie determined the weight of the spleen, both in the operating room and in the pathology laboratory in 17 patients with Hodgkin's disease undergoing splenectomy. He established a mean difference of 40 gm (range, 10 to 110 gm), caused by the loss of blood from the specimen (3).

These observations led us to the hypothesis that the size of the organ in the intact patient might correlate better with the histopathologic state than the weight of the specimen after removal.

In response to the remarks of the reviewers, we have rearranged our original data, and we summarize the results here.

In ten patients, staged for recurrent disease, the spleen was involved in eight cases (five patients also had histologically demonstrated localization in the liver). Splenic index calculation in this group proved to have an

accuracy rate of 100%. In 25 patients with previously untreated disease, the spleen was histologically involved in 11 cases (44%, similar to the reviewers' series). Splenic index calculation showed an accuracy of 88% with a sensitivity of 82% and a specificity of 93%. These figures are slightly less favorable than the overall results in the 35 patients (91%, 89%, and 94% respectively).

Laparotomy was performed within one month in 16 of 21 patients (76%). The liver was involved in three of 25 patients (12%). Five patients were studied prospectively, and in many of the remaining patients the spleen histology was known at the time of review.

Patients were included in this study based on a CT scan prior to laparotomy, and did not receive systemic therapy in the meantime. Several other patients underwent laparotomy without having a CT scan, apparently to avoid undue time delay caused by a limited scanning capacity. We conclude from their previous article (4) that differences between our diagnostic results and those of reviewers are probably not sufficiently explained by a difference in patient selection. The composition of the two groups differs. Our 25 patients with Hodgkin's disease include five patients with the lymphocyte depleted variety, all of whom had an involved spleen at histologic examination.

All three diagnostic errors occurred in the group of patients with the nodular sclerosing variety that constituted 52% of the patients.

In comparison, the reviewers' group contained 20 patients with this histologic type (83%). These factors also may contribute to the difference in diagnostic accuracy.

In general, the validity of diagnostic tests is influenced by the way the data are obtained: we presented our study as a predominantly retrospective one with all known inherent deficiencies.

Even prospective studies in a larger, apparently homogeneous group may seem to lack consistency.

This can be illustrated by comparing the Stanford University data presented in 1983 and 1984 (4,5). Whereas

in 1983 (5) CT of the spleen in 87 patients still had a diagnostic accuracy of 68%, a specificity of 73%, and sensitivity of 61% (23 of 38 patients had a correctly positive CT diagnosis), the results in 1984 (4) on 121 patients showed a diagnostic accuracy of 58% with a specificity of 76%, and a dramatically decreased sensitivity of 33% (17 of 51 patients with a correctly positive CT diagnosis). Because diagnostic criteria were apparently unchanged, this difference must have been the results of a significant change in composition of the patient groups.

Our empirically derived formula for spleen weight estimation (weight = 0.55 x splenic index = 0.55 x length x width x thickness) closely resembles the formula used for spleen volume estimation by scintigraphic and ultrasonographic methods (6-8) that are based on the assumption of an ellipsoid model for the spleen (volume = 0.52 x length x short diameter x long diameter). We cannot explain the fact that the reviewers found a correlation factor of 0.39.

We are generating normal values for spleen size by splenic index calculation and volume calculating methods with CT (9,10).

Preliminary data suggest that a splenic index value of 480 is valuable in most patient groups, but that a higher upper limit threshold will have to be adopted for young men. Until these values become established, we continue to use our "old" values.

Our article does not contend that spleen volume increases with early involvement in Hodgkin's disease. We present the results of a (predominantly) retrospective study, which suggest that a better definition of spleen size in vivo improves the diagnostic value of CT. We noted the need for a prospective study to evaluate our observations further. We do not propose an additional investigation in patients with Hodgkin's disease, but hope to derive more information from a radiologic examination that most patients already undergo. We present an easily applicable

criterion for estimation of spleen size that can be adapted at will to find an acceptable balance between sensitivity and specificity.

We are grateful to the reviewers for testing our method in a sample of their material. The fact that they could not reproduce our favorable results is neither unexpected nor discouraging. As more data become available, we may find that the criterion of CT-splenomegaly is only valuable under certain conditions, eg, in recurrent disease or with unfavorable histologies.

Until then, we hope to extend our experience.

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REVIEWERS' REPLY

We thank the authors for responding to our review by reanalyzing their orginal data per our suggestion. This reanalysis confirms our impression that (1) when the spleen is involved with recurrent disease, the degree of involvement is more extensive than at initial presentation, (2) increased splenic size might show a significant correlation with histologically-proven disease in the setting of disease relapse, (3) their study was biased by mixing these two patient populations, ie, those with newly diagnosed disease and those with relapsing disease. Few data are available, however, to assess the ability of a normal splenic size to rule out splenic disease in these patients.

Our concerns remain - that the data, in the manner in which it was originally presented, might mislead the casual reader to believe the CT scan-derived estimates of splenic volume would be useful predictors of splenic disease in patients who present with Hodgkin's disease for initial staging. Given the far-reaching implications of these potential conclusions, we feel that additional attention should have been given to the study design, and even more importantly to the format in which the data was originally presented in the published article.

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Chapter 4

LYMPHOGRAPHY AND ABDOMINAL COMPUTED TOMOGRAPHY IN STAGING NON-HODGKIN LYMPHOMA.
With an analysis of discrepancies.

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ABSTRACT

Ninety-one patients with non-Hodgkin lymphoma (NHL) were subjected to CT and lymphography. Both examinations agreed on 74 patients (81%) with regard to the infradiaphragmatic lymph nodes. In patients undergoing CT prior to lymphography, the concordance amounted to 75%. When lymphography was the initial examination, the concordance amounted to 86%.

Lymphography was abnormal in 30% of patients with a normal CT scan and in 93% of patients with an abnormal CT scan as the first examination. CT was abnormal in 4% of patients with a normal lymphogram and in 84% of patients with an abnormal lymphogram as the first examination.

CT did not detect mesenteric or retrocrural lymph-node enlargement in the absence of retroperitoneal lymph-node involvement. Eleven patients had extranodal manifestations of disease (excluding liver and spleen), and 3 were detected primarily with CT. Lymphography is the most complete examination for the infradiaphragmatic lymph nodes for staging purposes. Although CT outlined the disease better, it changed the lymphographic diagnosis in only 2 % of patients. Lymphography modified the CT-stage in 15% of patients. When abdominal CT is performed first in staging patients with NHL, lymphography will only yield additional information when CT is normal or equivocal.

INTRODUCTION

The diagnostic value of lymphography in patients with Hodgkin disease (HD) and non-Hodgkin lymphoma (NHL) has been established in numerous series. Ample correlation between radiologic and histologic findings in pelvic and retroperitoneal lymph nodes has been procured. Computed tomography (CT) is another imaging modality, which can not only visualize the same region of interest, but also offers the opportunity to evaluate other body regions. While in HD staging laparotomy is still regularly performed and provides histologic control of the

diagnostic methods, treatment strategies in patients with NHL are nowadays largely dictated by the histologic grade of malignancy of the specific type of lymphoma. By many institutions staging laparotomy is only indicated in selected cases, and this is the main reason why comparison of CT-findings with histologic data is not available now on such a large scale as in the earlier days of lymphography. As a result of this, the diagnostic value of CT in patients with NHL can mostly be related to the findings of lymphography and to the clinical course only. When both imaging methods are used in the same patient it may happen that the results of these examinations appear to be contradictory. In the present report lymphography and CT findings with a group of 91 patients having NHL are discussed, with an analysis of discrepancies.

MATERIAL AND METHODS

During the years 1978 to 1984, 91 patients with NHL underwent lymphography and abdominal CT as part of a staging procedure. Eighty-five patients were examined for primary, untreated disease and 6 patients were staged for recurrent disease. Sixty-two patients were male and 29 were female. Ages ranged from 15 to 75 years in male patients (mean age 50 years) and from 16 to 74 years in female patients (mean age 51 years).

Lymphography was performed using standard techniques, and was interpreted using generally accepted diagnostic criteria based on structure rather than size of the visualized nodes (5).

CT was performed in 58 patients with an OHIO Nuclear 50 FS Delta Scan with a scanning time of 18 seconds and a slice thickness of 13.5 mm, and with contiguous scanning of the whole abdomen. In 29 patients scanning was performed with a Siemens Somatom DR 3 with a scanning time of 5 seconds and a slice thickness of 8 mm at 16 mm intervals. Four patients were referred with a CT scan made elsewhere. Diluted water-soluble contrast medium was administered

orally in all patients, but intravenous contrast medium injection was not routinely performed. The main CT criterion for diagnosing lymph-node abnormality was its size. Nodes with a diameter exceeding 1.5 cm were considered pathologic, and when smaller than 1 cm they were considered normal. Nodes with an intermediate size were regarded as equivocal, but when a group of nodes of this size was seen, this was considered to be suspect (7,13,15, 18,20). For retrocrural nodes, normal size was limited up to 6 mm (3, 13). The order of both investigations was arbitrarily in the early years, while in later years CT was carried out first when time schedule allowed. The original interpretations of the CT and the lymphogram were maintained in this study. Generally, interpretation of one examination was performed with knowledge of the result of the previous examination.

Although CT visualizes more lymph-node regions than lymphography, the final overall conclusions of either report (positive, negative, equivocal) were compared, including the lymph-node regions that cannot be reached with lymphography. Cases with divergent conclusions were reviewed to define the area of discrepancy. The CT scans were reviewed for specification of the various lymph-node regions involved (retroperitoneal, mesenteric, retrocrural). Organ involvement was noted and spleen size was calculated in retrospect using the splenic index.

The splenic index (14,24) is calculated by multiplying spleen length, width, and thickness. Spleen length is the sum of all slice thicknesses (and intervals if used) on which the spleen can be seen. Spleen width and thickness are the largest (straight) organ diameters from anterior to posterior border, and from internal to external surface respectively. According to previous studies (14), an index of 480 is used as upper limit of what is considered normal. By definition, a higher index indicates splenomegaly, and is suspect for histologic involvement with lymphoma (23,24). Spleen histology was available with 10 patients (5 laparotomy, and 5 autopsy cases).

RESULTS

1. Retroperitoneal lymph nodes

CT and lymphography were performed in 91 patients with a histologically confirmed diagnosis of NHL (table 1). The results of both examinations were in agreement in 74 patients (= 81%). There was disagreement in 17 patients (= 19%). The region and cause of discrepancy are specified in table 2.

Table 1 : Comparison of CT and lymphography diagnosis in 91 patients. Overall concordance $^{74}/_{91}$ = 81%. ( ) = %.

CT / lymphography	+	-	±	total
+	35 (39)	8 (9)	3 (3)	46 (51)
-	2 (2)	39 (43)	3 (3)	44 (48)
±		1 (1)		1 (1)
total	37 (41)	48 (53)	6 (6)	91 (100)

Table 2 : Summary of discrepancies in 17 patients with divergent CT and lymphographic diagnosis.

CT / lymphogr	+	-	±
+		2 cases: insufficient CT scan 6 cases: normal sized nodes	3 cases: borderline sized nodes
-	1 case: unfilled inguinal node 1 case: enlarged celiac nodes		1 case: insufficient CT scan 2 cases: borderline sized nodes
±		1 case: inguinal node not included in CT scan	

The largest group of discrepancies consisted of 8 patients (= 9%) in whom the CT scan was normal, but in whom the lymphogram was abnormal. In all these cases, lymphography revealed textural abnormalities in nodes of normal size (fig. 1,2). In 2 out of these 8 patients, histologic examination of lymph nodes from the involved region confirmed the lymphographic findings. In another patient, the marked decrease in size of the pathologic nodes during chemotherapy supported the lymphographic diagnosis. In 1 patient progressive lymph-node enlargement occurred in the lymphographically involved area during radiotherapy of a nasopharynx mass, and this was regarded as a support for the lymphographic diagnosis. In 2 patients, the CT scan was insufficient due to motion-artifacts.

The comparative findings of CT and lymphography were also correlated to the order in which the investigations were performed (table 3 a,b).

When lymphography was performed as the initial examination there was a concordance of 86% with subsequent CT-findings. When CT was the first examination performed the concordance with the subsequent lymphography amounted to 75%. CT was performed as the first examination in 7 out of 8 patients having a normal CT scan and an abnormal lymphogram.

Table 3a : Comparison of CT and lymphography in 51 patients. Lymphography performed before CT. Concordance $^{44}/_{51}$ = 86%. ( ) = %.

CT / lympho-graphy	+	-	±	total
+	21 (41)	1 (2)	3 (6)	25 (49)
-	1 (2)	23 (45)	1 (2)	25 (49)
±		1 (2)		1 (2)
total	22 (43)	25 (49)	4 (8)	51 (100)

Table 3b : Comparison of CT and lymphography in 40 patients. CT performed before lymphography. Concordance $^{30}/_{40}$ = 75%. ( ) = %.

CT / lymphography	+	-	±	total
+	14 (35)	7 (17)		21(52)
-	1 (3)	16 (40)	2 (3)	19(48)
±				
total	15 (38)	23 (57)	2 (5)	40(100)

2. Mesenteric and retrocrural lymph nodes

Nine out of 91 patients (= 10%) were found to have mesenteric lymph-node enlargement with CT, and in all these patients either CT or lymphography was positive for retroperitoneal node involvement.
Three out of 27 patients with a normal chest X-ray and abdominal node involvement had retrocrural lymph-node enlargement (= 11%). Eight out of 14 patients with an abnormal chest X-ray and abdominal node involvement had enlarged retrocrural nodes (= 57%). No instance of retrocrural lymph-node enlargement was detected in the presence of normal abdominal findings.

3. Liver and spleen

Splenic index calculation was used to estimate splenic size and served as an indicator for splenic involvement with lymphoma. The results are summarized in table 4. An enlarged spleen was more frequently seen in the presence of abnormal infradiaphragmatic nodes.

Table 4 : Correlation between splenic index (s.i.) and infra-diaphragmatic lymph node status in 84 patients.

s.i.	n (%)	Lymph nodes normal	Lymph nodes abnormal
≤ 480	54 (64)	31 (37)	23 (27)
> 480	30 (36)	8 (10)	22 (26)
total	84 (100)	39 (47)	45 (53)

Spleen histology was available with 10 patients. The spleen was histologically normal in 5 patients, and involved with lymphoma in the remaining 5 cases. The diagnostic accuracy of splenic index calculation was 100%. Percutaneous liver biopsy was performed in 57 patients. In 11 of them, localization of lymphoma was proven histologically. However, CT was suggestive in only 1 patient (marked hepatomegaly), and inconspicuous in all other patients.

4. Involvement of other organs

Seven patients had gastro-intestinal localization of NHL. However, this diagnosis was made or suggested by physical examination, endoscopy, or Barium-examination prior to CT in all cases, and was in fact the first clinical manifestation of disease in 5 patients. In 2 of them, CT and lymphography were otherwise normal.
Involvement of both kidneys, homolateral kidney and adrenal gland, lumbar spine and (female) genital system was discovered in 1 patient each. These patients also showed retroperitoneal lymph-node involvement with CT or lymphography. In addition, there were 2 patients with extra-abdominal skeletal involvement, and 1 patient with lymphoma of the cerebellum as the primary localization and manifestation of disease.

DISCUSSION

The diagnostic accuracy of lymphography in malignant lymphoma (HD and NHL) varies between 69% and 95%, with a sensitivity of 85% to 100% and a specificity of 74% to 98% (2,4,6,7,14,16,17,25). The accuracy of CT is lower (62% to 82%), with a specificity of 75% to 93% (equal to lymphography), but with a lower sensitivity of 65% to 86% (2,4,6,7,14,16,17,25). However, histologically verified CT studies in patients with NHL exclusively are scarce, due to the decreased number of staging laparotomies (21).
The present study in 91 patients with NHL is also predominantly based on probability diagnoses with lymphography as the gold standard. Only 5 patients underwent laparotomy after initial staging.
The concordance between lymphography and CT reports in the literature in patients with malignant lymphoma varies between 76% and 100%, with an average of 87% (1,9,12,14, 15,20,22). Usually the discrepancies are explained by the fact that lymphography reveals textural abnormalities in nodes of normal or minimally increased size. In the present study a concordance between the CT and lymphography report was found in 81% of cases. As expected most discrepancies consisted of a normal or equivocal CT scan in combination with an abnormal lymphogram (table 1,2 - fig. 1,2).
In retrospect most of the abnormal lymph nodes seen by lymphography were identifiable on the CT scan, but they were usually not or only minimally enlarged.
There was a striking difference when the discrepancies were related to the order of the examinations. When lymphography had been performed first, the subsequent CT scan was false-negative in only 1 out of 25 patients (4%). Conversely the subsequent lymphogram was abnormal in 7 out of 23 patients (30%) with a normal CT scan as the first investigation. These discrepancies were proportionally divided between the slower and the faster scanner, and were therefore not exclusively related to

technical factors: motion-artifacts due to the longer exposure time with the slower scanner was the incriminating factor in 2 patients.

The difference in concordance between CT and lymphography in relation to the sequence of investigations is probably related to the fact that in our clinical setting the result of the first examination is generally known to the radiologist performing the second examination. It apparently occurs that during the interpretation of an abdominal CT, the final conclusion of the preceding lymphography is adopted. Another factor contributing to the high yield of lymphographic abnormalities in patients with a normal CT scan might be that only patients with a high index of suspicion and with an as yet unconfirmed generalized disease were selected for lymphography. However, due to the retrospective character of this study, this hypothesis could not be verified. The assumption that the lymphographic diagnosis was correct in these 7 patients, was proven histologically in 2 patients. In the remaining 5 patients the characteristic lymphographic appearance of the nodes in conjunction with clinical data and follow-up made the lymphographic diagnosis probable.

Our data imply, that - when both imaging techniques are compared for their diagnostic value - it is not only necessary to interpret the examinations independently, but also to specify the order of the examinations, and the awareness of the results of the first examination.

CT discovered abnormalities in infradiaphragmatic nodes in 2 out of 44 patients (5%) with a normal lymphogram. In one of these patients, the discrepancy was caused by the presence of an enlarged inguinal node, which had not stored contrast medium after lymphography. This node was palpable on physical examination. In the second patient, who had NHL of the stomach, CT visualized enlarged nodes around the celiac axis, outside the scope of the lymphogram. The other nodes were normal with both methods. CT and lymphography in these 2 patients were therefore not contradictory, but complementary. CT reports

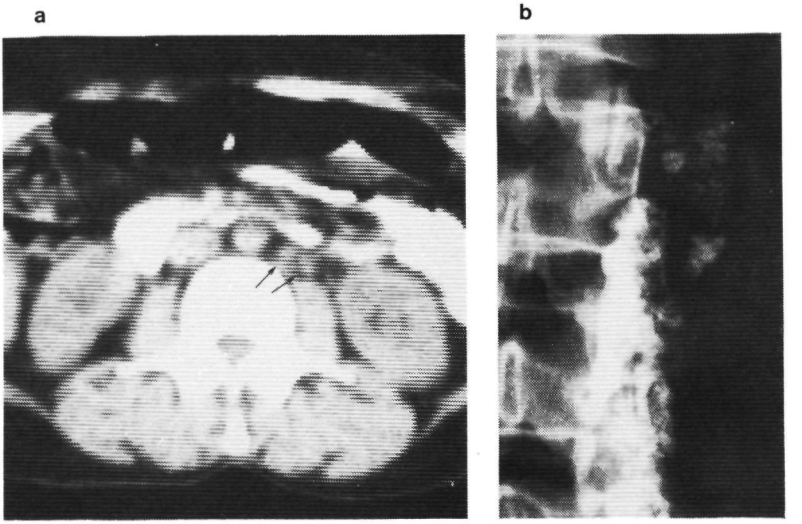


Fig. 1: Left-sided para-aortic nodes (arrows) of 1 cm diameter, interpreted with CT as normal (1a).
Lymphography demonstrates lymphomatous appearance (1b).

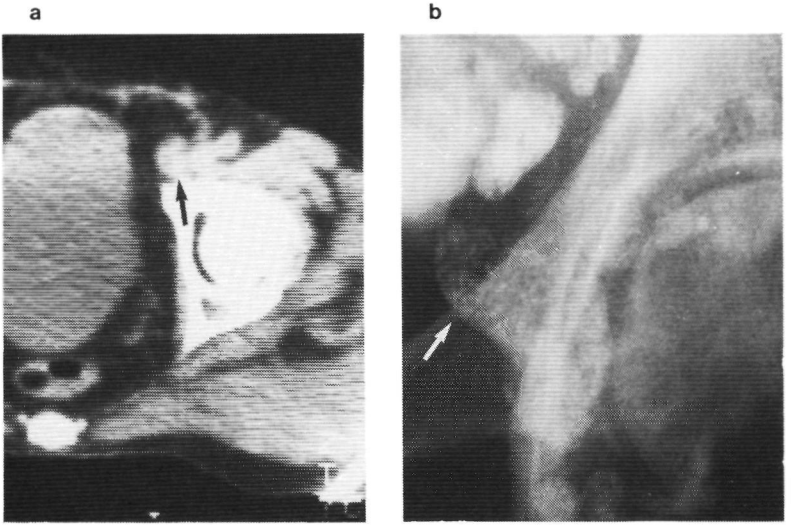
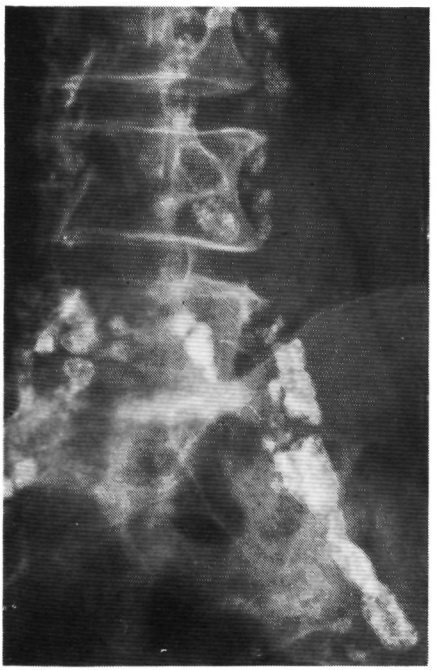


Fig. 2: Left-sided inguinal nodes (arrows) of 13 mm diameter, with CT interpreted as normal (2a).
Lymphomatous appearance at lymphography (2b).

that appeared to be false-positive when compared with lymphography reports were not met. Two patients in whom CT was performed first had equivocal reports: one due to inadequate scanning technique, and one due to the presence of borderline-sized nodes. Subsequent lymphography was normal in both cases.

Contrast medium in lymph nodes causes an increase in size of the nodes. When CT is performed after lymphography, lymph-node size should therefore be interpreted carefully because the actual size of nodes can be overestimated. This may lead to equivocal or false-positive interpretations. This phenomenon may explain that CT was interpreted to be equivocal due to borderline lymph-node enlargement in a patient with lympographically normal nodes. In 3 other patients CT was equivocal after a positive lymphogram, and in all these cases the nodes were likewise not or minimally enlarged with lymphography (fig. 3).

a



b

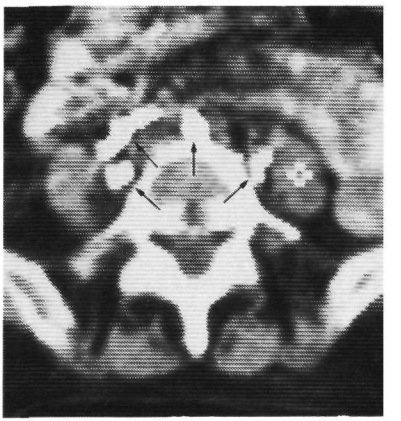


Fig. 3:
Normal-sized lymph nodes with lymphomatous appearance (3a).
With CT, these nodes are of equivocal size(3b).

The relatively large number of equivocal CT-diagnoses was acceptable in our clinical setting, because most patients had or would have a lymphogram, after which a definitive (clinical) staging diagnosis was made. With increasing experience, and improvement of scanning technique, the confidence in the CT-diagnosis also increased, and lymphography was gradually less frequently performed. It is realized that CT cannot visualize minimal disease in lymph nodes, but many patients with NHL are scheduled for systemic treatment anyway. At present, lymphography in patients with NHL is only performed in our hospital when CT is normal or equivocal, and when the information obtained could lead to a change in treatment strategy.
Staging laparotomy in patients with NHL reveals involved mesenteric nodes in up to 51% of cases, more commonly in association with involved retroperitoneal nodes than with normal retroperitoneal findings (4,6,11,17).
Mesenteric lymph-node enlargement was detected with CT in 9 out of our 91 patients (10%), but exclusively in conjunction with abnormal retroperitoneal nodes on CT or lymphography. Involved mesenteric and celiac nodes may be present when the lymphogram is negative, but are then usually not markedly enlarged, making discovery by CT more difficult (11). The actual incidence of mesenteric lymph-node involvement in our patients could not be determined because staging laparotomy was not routinely performed. The relatively low yield of CT in our series suggests that involved mesenteric nodes in our patients were probably overlooked, and supports the contention that CT contributes little in correcting the deficiencies of other non-invasive staging methods in this regard.

Abdominal CT can detect subtle enlargement of the so-called retrocrural lymph nodes, which are in fact nodes in the postero-inferior portion of the mediastinum (8). Ellert (9) diagnosed retrocrural lymph-node enlargement in 23% of patients. In the present series, CT visualized enlarged retrocrural nodes in 57% of patients with

combined retroperitoneal and upper mediastinal node involvement. In patients with abdominal node involvement and normal chest findings, CT detected retrocrural node enlargement in 11%, and thus proved supradiaphragmatic spread of disease. Enlarged retrocrural nodes were not detected in patients with normal abdominal CT or lymphography findings.

Staging laparotomy reveals splenic involvement with lymphoma in 30% to 50% of cases (4,17). In previous studies we analysed the efficacy of splenic index calculation with CT in patients with HD (24) and with NHL (23).
An accuracy rate of over 90% with an equally high sensitivity and specificity rate in diagnosing splenic involvement with lymphoma could be obtained in these studies. In the present study, the splenic index was calculated retrospectively in 84 out of 91 patients (table 4).
The spleen was enlarged (i.e. an index over 480) in 30 patients (36%) and of normal size in the remaining 54 patients (64%). In 10 cases the spleen was available for histologic examination, and the diagnostic accuracy of splenic index calculation was 100%.
According to Castellino et al. (6) 89% of patients with a normal lymphogram proved to have a histologically normal spleen, whereas in 52% of patients with a positive lymphogram the spleen was involved.
In the present study, the spleen was of normal size by splenic index calculation in 80% of patients with a normal lymphogram, whereas the spleen was enlarged in 49% of patients with a positive lymphogram. These results are not markedly different from the results of Castellino et al., and suggest that splenic index calculation as a parameter for splenic involvement with lymphoma might be helpful. For a definitive answer, a larger, prospective study is necessary.
Liver involvement is difficult to diagnose with CT,

resulting in a very low sensitivity (26). Fifty-seven patients in the present study were subjected to a blind percutaneous liver biopsy, and lymphoma was demonstrated in 11 cases (19%). CT of the liver was normal in all cases except 1 with positive histologic findings. False-positive CT-scans were not encountered.

Organ involvement (other than liver and spleen) is not uncommon in patients with NHL (9,10,17,19). Seven out of 91 patients in the present series had gastro-intestinal localization of lymphoma, but in all patients this was known or suspected by physical examination, Barium examination or endoscopy prior to staging. Furthermore, it was the first clinical manifestation of disease in 5 patients. Except for 2 patients all had concomitant retroperitoneal lymph-node involvement.

In one patient bone abnormalities adjacent to a region of massive lymph-node enlargement were noticed with lymphography. One patient each showed involvement of both kidneys, homolateral kidney and adrenal, and the female genital system. Abdominal organ involvement in the absence of lymph-node involvement was not detected with CT in our series, although this may occur (10).

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Chapter 5

THE SPLEEN IN NON-HODGKIN'S LYMPHOMA: DIAGNOSTIC VALUE OF COMPUTED TOMOGRAPHY.

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ABSTRACT

CT of the spleen was correlated with histologic examination or clinical data in 53 selected patients with non-Hodgkin's lymphoma.
Calculation of the splenic index with CT by multiplying spleen length, width and thickness is a simple and quick procedure to define splenic size in vivo.
A good correlation was found between size of the spleen, as estimated by splenic index calculation, and the proven or probable histologic state of the spleen.

INTRODUCTION

The size of the spleen in patients with Hodgkin's disease (HD) or non-Hodgkin's lymphoma (NHL) is generally regarded as an unreliable indicator of splenic involvement. Apparently normal-sized spleens often reveal localization of lymphoma, whereas spleens thought to be involved on the basis of non-invasive examination methods are not uncommonly histologically normal. Computed tomography (CT) has made it possible to outline the size of the spleen more exactly, but most published series showed a poor correlation between CT of the spleen and histology. Overall accuracy rates varying from 60 to 100%, with a sensitivity ranging from 0 to 100% and a specificity ranging from 80 to 100% have been reported (1,2,4,6,7,15, 16,18,19). These results may be explained partially by the use of different and obviously insensitive criteria.
In a previous report (16) we analysed the value of the "splenic index" as an in vivo indicator of splenic size and involvement in patients with HD. An overall accuracy of 91% with a sensitivity of 89% and a specificity of 94% could be obtained in evaluation of splenic involvement in a series of 35 patients.
The objective of the present study is to evaluate the results of splenic index calculation in patients with NHL.

MATERIAL AND METHODS

CT findings of the spleen were evaluated retrospectively in 53 patients with NHL, examined during the years 1978 to 1985. These patients were selected from the population of patients with NHL attending the Department of Hematology of our Hospital, after either direct or indirect evidence of the histologic state of the spleen had been available (group A and group B respectively). Because staging laparotomy was not performed routinely, we gathered data from various sources.

Group A consisted of 33 patients of whom histology of the spleen was obtained by means of autopsy (23 patients) or laparotomy (10 patients). Staging laparotomy was performed in 3 patients, and laparotomy with splenectomy for other than staging purposes in the remaining 7 patients.

Group B consisted of 20 patients of whom splenic tissue for a direct histologic diagnosis was not available. The probable presence or absence of disease in the spleen in these cases was deduced from data on clinical and pathological stage, such as histologically proven liver involvement (11 patients) or from follow-up during at least 4 years with patients with limited disease who were treated locally (9 patients). A positive liver biopsy was considered to be an indirect sign of splenic involvement. A recurrence-free survival after local (involved-field) radiotherapy was regarded as a confirmation of initially negative CT findings. These patients are referred to in figure 2 as "indirect histology" cases.

CT was performed in 45 patients on an Ohio Nuclear 50 FS Delta Scanner with a scanning time of 18 seconds. Contiguous scanning with a slice thickness of 13.5 mm of the upper abdomen was performed during suspended expiration.

Intravenous contrast material was not administered routinely. Seven patients were examined on a Siemens Somatom DR 3 with a scanning time of 5 seconds and a slice

thickness of 8 mm at 16 mm intervals. One patient was referred with a CT scan made elsewhere.
The splenic index according to Lackner et coll. (13) was calculated by multiplying spleen length, width and thickness as measured with CT. Spleen length is considered to be equivalent to the sum of all slice thicknesses (and intervals if used) on which the spleen is to be seen. Spleen width and thickness are the (straight) antero-posterior and transverse organ diameter respectively, usually at the level of the splenic hilum (fig. 1).
Lackner found an index of 480 as upper limit in a series of 100 normal spleens. We adopted this value to define normal spleen size on CT. By definition, an index higher than 480 indicated splenic enlargement, and this was regarded as a radiological sign of splenic involvement.

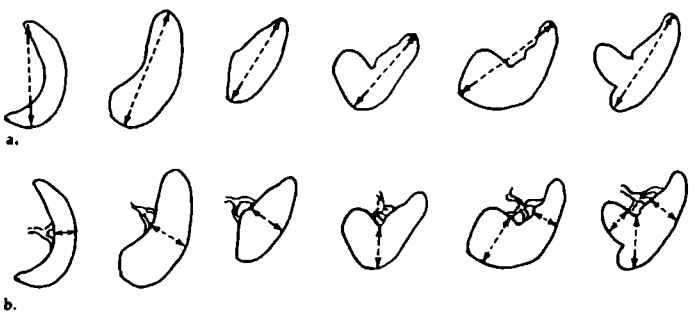

Fig. 1: Measurement of spleen dimensions in various spleen shapes (tracings from CT sections).
a. Width = longest transverse diameter, regardless of scan height through spleen or spleen orientation.
b. Thickness = distance from inner to outer surface, directly measured or mean value in cases with marked spleen asymmetry.

(Reprinted from S.P. Strijk et coll.: The spleen in Hodgkin disease: diagnostic value of CT. Radiology 154 (1985), 753. With permission.)

RESULTS

Group A, patients of whom spleen histology was available.

This group consisted of 33 patients, of whom 10 were female and 23 were male. The ages ranged from 20 to 81 years, with a mean age of 57 years.
Three patients underwent primary diagnostic and staging laparotomy with splenectomy because of infradiaphragmatic disease presentation. None of them had liver or spleen involvement. The splenic index ranged from 342 to 454 (mean value 449), and splenic weight ranged from 156 g to 320 g (mean value 255 g).
Seven patients underwent laparotomy for therapeutic splenectomy. The spleen was histologically involved in all cases. The splenic index ranged from 621 to 3278 (mean value 1923). In 4 patients splenectomy was performed after completion of clinical staging, prior to therapy. The 3 other patients had received therapy, or showed clinical progression of disease between the moment of CT and splenectomy, and this made comparison of splenic index and weight less valid. Hepatic involvement with lymphoma was demonstrated in 2 of 4 patients with liver histology available.
In 23 patients radiologic findings were correlated with autopsy data. Three patients had a splenic index lower than 480, and the spleen proved to be histologically uninvolved. The remaining 20 patients had splenic involvement at the time of death. The splenic index in the latter group ranged from 509 to 3888 (mean value 1240). Splenic weight at autopsy ranged from 290 g to 1910 g. The interval between radiologic examination and autopsy varied from 10 to 210 days (average: 85 days).
Moreover, most patients in the autopsy-group were characterized by generalized disease. Causes of death were mainly intractable progress of disease, complicating diseases or a combination of both. Hepatic involvement by lymphoma was demonstrated in 16 out of 18 patients of whom

liver histology was available.
In the total group of 33 patients, splenic index calculation showed an accuracy rate of 100% in predicting the histologic state of the spleen (table 1a).

Table 1a: Group A, 33 patients of whom spleen histology was available.

CT \ Hist.	-	+	total
-	6	0	6
+	0	27	27
Total	6	27	33

Group B, patients of whom spleen histology was not available.

Eleven patients had hepatic involvement demonstrated by percutaneous liver biopsy. Six patients were female, 5 were male. Ages ranged from 30 to 67 years (mean age 42 years). The biopsy was taken between 13 days before and 9 days after CT. The splenic index ranged from 416 to 1985 (mean value 804). Two patients had an index below the threshold value of 480. One of these patients had just finished 6 courses of chemotherapy. The remaining 9 patients had an index above 480.
A control group consisted of 9 patients with NHL and localized disease (stage IA or IE clinically). Five were female, 4 were male. Ages ranged from 43 to 82 years (mean age 62 years). They all received local radiotherapy and were followed 4 to 7 years without signs of recurrence or progression of disease. The splenic index in this group ranged from 146 to 399 (mean value 285).
Due to the lack of definitive histologic data on the spleen in this group of patients, only extrapolated accuracy, sensitivity and specificity rates were calculated. They amounted to 90%, 82% and 100% respectively (table 1b).

Table 1b: Group B, 20 patients of whom spleen histology was not available.

Hist.* / CT	-	+	total
		**	
-	9	2	11
+	0	9	9
Total	9	11	20

* no direct histologic proof available (see text).
** one patient examined after treatment.

Table 2 compares the histology of liver and spleen in 26 patients with material available. All 17 patients with histologically proven hepatic involvement had splenic involvement as well.

Table 2 : Comparison of spleen and liver histology. Localization of lymphoma present (+) or absent (-).

liver / spleen	-	+	total
-	5	0	5
+	4	17	21
Total	9	17	26

Figure 2 presents a diagram comparing splenic index and splenic weight. In a previous study on patients with HD (16), the mean weight proved to be equivalent to 0.55 x splenic index. This conversion factor is transferred to figure 2, which shows the results of the present study.

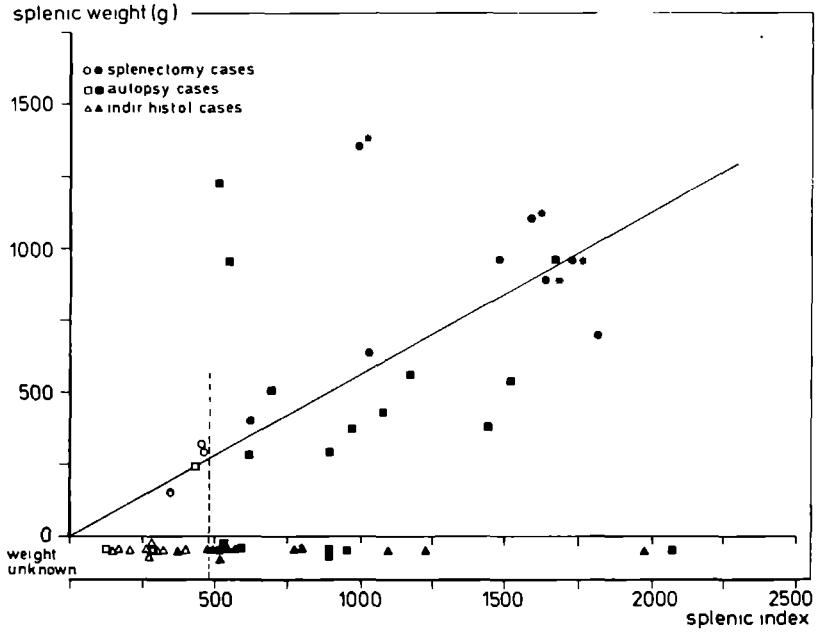

Fig. 2: Correlation between splenic weight and splenic index of involved (● ■ ▲) or uninvolved (o □ △) spleens (see text). Splenic index of 480 as upper limit of normal range.
(* The actual weight and index of these spleens were both divided by factor 2 in order to simplify inclusion in the diagram).
INDIR. HISTOL. CASES: indirect evidence of spleen histology only (see text).

DISCUSSION

With patients suffering from malignant lymphoma (HD and NHL), subjected to staging laparotomy, the spleen is found to be histologically involved in 23% to 50% of cases (3, 5,6,9,10,12,14,17). Although there is an increasing incidence of splenic involvement with increasing weight of the specimen, there is no absolute correlation between weight as measured after splenectomy and histologic state. Only spleens weighing more than 500 g were consistently involved with lymphoma, whereas lymphoma was not infrequently absent in smaller spleens (8,10,17). Determination of the weight of the spleen after operative

removal is liable to inaccuracies, because it is influenced by the operative technique and the variable amount of blood contained in or lost from the specimen. We evaluated the correlation of splenic index calculation by CT with regard to splenic involvement. In this way an in vivo measurement of splenic volume is made. In a previous report we discussed the value of CT in examination of the spleen in patients with HD (16). Calculation of the splenic index - a parameter for splenic volume and weight in vivo - appeared to be of value in determining the presence or absence of disease in the spleen in these patients with a sensitivity of 89%, a specificity of 94%, and an overall accuracy of 91%. Herter et coll. (11) applied a similar measurement in 34 patients with malignant lymphoma (27 HD, 7 NHL) and established a diagnostic accuracy of 83% with a specificity of 86% and a sensitivity of 77%.

In the present study we assessed whether splenic size determination with CT could be of value in the examination of patients with NHL. In HD, the presence and extent of intra-abdominal disease are important factors, directly influencing the choice of therapy in many cases.In NHL, not only the stage of disease, but also the histologic classification is important, because both factors influence the prognosis to a varying extent. Staging laparotomy has now largely been abandoned as a routine procedure in most patients with NHL. Routine clinical staging including bone-marrow biopsy, liver biopsy, lymphangiography and/or CT is usually found to give sufficient information.

The composition of the present patient group is basically different from our previous study, because data were not mainly obtained from patients subjected to staging laparotomy. The present evaluation of splenic index calculation in patients with NHL has therefore the nature of a feasibility study, due to the unhomogeneous and selected composition of the patient group. The final conclusions should be considered against this background.

The main indication for staging laparotomy in our Hospital is a clinical stage IA or IIA in patients with NHL of intermediate or high-grade malignancy.
Because this condition occurs in only a minority of patients, a relatively small number of histologically verified normal spleens in patients with NHL are included in the present series. The splenic index in these 3 laparotomy patients was within normal limits. Likewise, in 3 patients having a histologically normal spleen at autopsy, the splenic index was not increased. We also found a normal splenic index (ranging from 146 to 399) in a group of 9 patients with NHL and limited disease extent who had received local radiotherapy only, resulting in complete remission. In these 9 cases the spleen was not histologically examined but the clinical course made the assumption very likely, that the spleen was not involved as none of the patients showed signs of recurrence of disease during a follow-up period of 4 to 7 years.
Indications for therapeutic splenectomy are signs of hypersplenism (anemia, leukopenia, thrombocytopenia), local discomfort due to massive enlargement and infarctions, or the need for reduction of tumor volume. In these patients the spleen will usually be markedly enlarged, and virtually always involved with lymphoma. Seven patients were included in this group. The splenic index ranged from 621 to 3278 (mean value 1923). The spleen proved to be involved with lymphoma in all cases.
Finally, patients dying from lymphoma usually have poorly responsive or recurrent disease associated with a large tumor volume and sometimes complicating diseases. The splenic index in the 20 patients with an involved spleen at autopsy ranged from 509 to 3888, with a weight of the autopsy specimen of 290 g to 1910 g. In 3 other patients, the splenic index was not increased and at autopsy the organ was found to be not involved.
Literature data indicate that the presence of lymphoma in the liver practically always implies that the spleen is involved as well (9,17). We confirmed this finding: all

patients with proven hepatic involvement, of whom splenic tissue was available, also showed splenic involvement (table 2).

Consequently, a positive liver biopsy can be regarded as reflecting splenic involvement. In this study we have included 11 patients with a positive liver biopsy of whom spleen histology was not available. Two patients had an index within the normal range i.e. lower than 480. In 1 of them, the liver biopsy was taken after completion of 6 courses of chemotherapy. Pretreatment CT was not available, and it might be speculated that this false-negative reading was in fact due to a decrease in splenic volume after therapy.The other (untreated) patient with biopsy-proven hepatic involvement and a normal-sized spleen on CT has to be regarded by our criteria as a false-negative CT-reading.

Summarizing the data presented above, we may conclude that the calculation of the splenic index with CT in the group of 33 patients of whom spleen histology was available resulted in a diagnostic accuracy of 100% in discriminating normal from involved spleens. It should be stressed again that patient selection was not at random, but biased in favour of patients having splenomegaly and advanced disease.

In the second group of 20 patients with only indirect proof of spleen histology, the extrapolated figures for accuracy, sensitivity and specificity are 90%, 82% and 100% respectively.

Similar results will probably not be attainable with patients with NHL presenting for initial staging. A prospective study on this subject with use of splenic index calculation or employing CT-facilities for more exact volume calculations, and an evaluation in a group of patients undergoing staging laparotomy would provide a conclusive answer on the validity of our results.

According to our previous study in patients with HD, the average spleen weight is approximately equal to 0.55 x splenic index (16). Thus, an index of 480 as upper limit

for normal size (13) corresponds to a weight of 265 g.
Several other studies revealed that a splenic weight of more than 500 g consistently implicated splenic involvement (8,10,17). It was calculated that weight determination when using a weight of 500 g as threshold value would for the present series result in an accuracy of 77%, a specificity of 100% and a sensitivity of 72%.
A weight of 500 g would be equivalent to an index of 910. Application of this modified index threshold to the same group of patients in our series would result in a diagnostic accuracy of 73%, a specificity of 100% and a sensitivity of 67%.
Both results are not substantially different and support the value of splenic index calculation as an easy in vivo measurement, at least as reliable as weight determination.
The splenic index calculation offers an alternative to define splenic size in vivo, and obviates the crude criteria used by most authors. It can also be used to document splenic size in follow-up studies.
In the clinical staging of patients with malignant lymphoma it may be of value to derive more information from the abdominal CT that has already been performed in most patients. It is our experience (16) that a threshold value of 480 is highly reliable in separating normal-sized from enlarged spleens, or histologically normally from histologically involved spleens.
The threshold value can be chosen arbitrarily, in which case a higher value decreases the sensitivity but also decreases the number of false-positive diagnoses.

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Chapter 6

RADIOLOGIC EXAMINATION OF THE CHEST IN STAGING HODGKIN DISEASE AND NON-HODGKIN LYMPHOMA.

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Submitted for publication

ABSTRACT

Radiologic examinations of the chest in 331 patients with malignant lymphoma (204 patients with non-Hodgkin lymphoma (NHL), 127 patients with Hodgkin disease (HD)) were evaluated retrospectively. Tomography of the mediastinum was performed in 52 cases. No additional information was obtained in patients with a clearly normal or abnormal chest radiograph. Only with patients with equivocal chest radiographs tomography was helpful.
Computed tomography (CT) of the chest was performed in 76 cases (49 NHL, 27 HD). This revealed abnormalities in 7% of patients with a normal chest radiograph (14% in HD, 4% in NHL). CT revealed additional lesions in 23% of patients with an abnormal chest radiograph (20% in HD, 25% in NHL). Overall, CT changed the clinical stage of disease in only 2 out of 76 cases (3%). Both patients had HD, and thus CT was responsible for a change of the clinical stage in 2 out of 27 patients with HD (7%), and in none of the patients with NHL.

INTRODUCTION

Hodgkin disease (HD) and non-Hodgkin lymphoma (NHL) frequently show intrathoracic spread at the time of initial diagnosis, and chest radiography is therefore one of the most rewarding examinations in the staging of these patients.
Conventional tomography and computed tomography (CT) are more time-and-money-consuming examinations, but may provide additional information in a number of cases. However, the final impact on initial diagnosis and staging seems to be very limited (1).
In the present study we discuss the radiologic examinations of the chest (conventional radiography, mediastinal tomography, computed tomography) in a group of 331 patients staged for primary or recurrent malignant lymphoma.

MATERIAL AND METHODS

During the years 1978 to 1985, radiologic examination of the chest was performed in 331 patients with malignant lymphoma undergoing staging for either newly diagnosed and untreated, or recurrent disease.

All patients had frontal and lateral chest radiographs. Fifty-two patients also underwent frontal tomography of the mediastinum, incidentally supplemented by lateral tomography of the hila and/or retrosternal space.

Seventy-six patients underwent CT of the chest. Of these, 15 patients were examined with the use of an Ohio Nuclear 50 FS Delta Scan, with a scanning time of 18 seconds, and a slice thickness of 13.5 mm. Contiguous scanning of the whole chest was performed during suspended inspiration. Fifty-eight patients were examined with the use of a Siemens Somatom DR 3 with a scanning time of 5 seconds, and a slice thickness of 8 mm at 8 or 16 mm intervals. Three patients were referred with a CT scan made elsewhere. Intravenous contrast medium was not routinely administered.

Practically all patients with equivocal findings at chest radiography underwent mediastinal tomography or computed tomography. However, most patients had definitely normal or abnormal chest radiographs, and during the years of the study, there were no strict indications for carrying out additional examinations in these patients. The relative distribution of supplementary examination in the various patient groups divided by type of disease and findings at chest radiography is given in table 1.

The specific examinations were evaluated for the presence of enlarged lymph nodes (suggesting involvement with lymphoma) and for the presence of extranodal localization of lymphoma. The lymph-node regions (mediastinal, hilar, retro- and parasternal) were not evaluated separately, but any local, regional or generalized involvement was coded as "positive" for chest involvement.

Extranodal manifestations of disease (pulmonary

parenchyma, pleura, chest wall, bone) were recorded separately.

The initial reports of the various examinations were maintained. Revision of the radiologic examinations was undertaken in cases with divergent results in order to determine the cause of the discrepancy.

Table 1: Relative frequency of radiologic examinations in 331 patients with malignant lymphoma (NHL : n = 204 and HD : n = 127).

			% supplementary examination	
chest radiograph		n	tomography	CT
normal	NHL	143	6	20
	HD	66	12	21
	total	209	8	20
abnormal	NHL	50	18	32
	HD	53	32	19
	total	103	25	25
equivocal	NHL	11	55	45
	HD	8	38	38
	total	19	47	42

RESULTS

Radiologic examination of the chest was performed in 331 patients with malignant lymphoma. Two hundred and four patients had NHL and 127 patients had HD. A survey of the radiologic examinations is given in table 1.
Of the 204 chest radiographs in patients with NHL, 143 (= 70%) were normal, 50 (= 25%) were abnormal, and 11 (= 5%) were equivocal.
Of the 127 chest radiographs in patients with HD, 66 (= 52%) were normal, 53 (= 42%) were abnormal, and 8 (= 6%) were equivocal.
In patients with NHL having normal chest radiographs (n = 143), an additional examination was performed by tomography in 9 (= 6%) and CT in 28 (= 20%). In patients with HD having normal chest radiographs (n = 66), additional examination was performed by tomography in 8 (= 12%) and CT in 14 (= 21%).
In the NHL-patients having an abnormal chest radiograph (n = 50), additional examination was performed by tomography in 9 (= 18%) and CT in 16 (= 32%)of them. In the HD-patients with an abnormal chest radiograph (n = 53), additional examination was performed by tomography in 17 (= 32%) and CT in 10 (= 19%).
Overall 36% of patients with NHL and 43% of patients with HD underwent additional examination.
Of the 127 patients with HD, 96 (= 76%) had newly diagnosed and untreated disease, and 31 (= 24%) were staged for recurrent disease. The number of CT scans carried out was distributed proportionally between the groups. Of the 204 patients with NHL, 173 (= 85%) had newly diagnosed and untreated disease, and 31 (= 15%) were staged for recurrent disease. In these patients the CT scans were distributed proportionally too.
Because discrepant findings in chest radiology of patients with HD and NHL having either primary or recurrent disease were relatively few, the results of the various examinations are evaluated together.

Chest radiograph versus CT

Table 2: Comparison of chest radiograph (Xth) and CT in 76 patients (NHL : n = 49 and HD : n = 27). Lymphoma localization radiologically present (+), absent(-) or equivocal (±).

Xth	CT	-	+	total
-	NHL	27	1	28
	HD	12	2	14
	total	39	3	42
+	NHL		16	16
	HD		10	10
	total		26	26
±	NHL	3	2	5
	HD	2	1	3
	total	5	3	8
total	NHL	30	19	49
total	HD	14	13	27
grand	total	44	32	76

The discrepancies between the chest radiographs and CT scans are summarized in table 3.

CT revealed enlarged intrathoracic lymph nodes in 3 out of 42 patients with a normal chest radiograph (= 7%). This occurred in 1 out of 28 patients with NHL (= 4%) and in 2 out of 14 patients with HD (= 14%) (fig. 1). All CT scans were abnormal with regard to the lymph nodes in patients with an abnormal chest radiograph. However, in 3 of the patients (1 out of 10 with HD (= 10%), and 2 out of 16 with NHL (= 13%)) CT also detected intrapulmonary lesions not visible on the chest radiograph (fig. 2). In 2 other patients (with NHL and HD) with pleural and pulmonary localization respectively which were visible on the chest radiograph, CT detected additional mediastinal lymphadenopathy (fig. 3).

In 8 patients with an equivocal chest radiograph, CT was normal in 5 and abnormal in 3 cases.

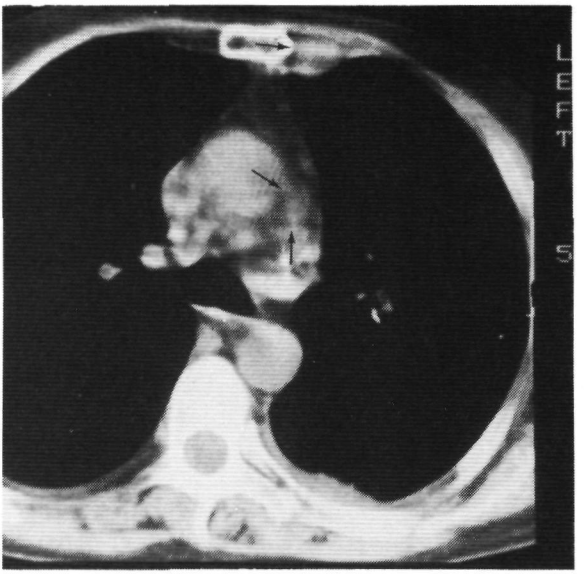
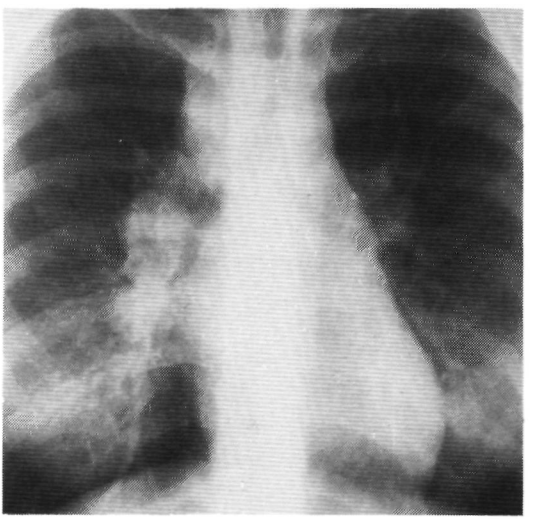


Fig.1: Case 3. Female patient of 63 years with HD. Chest radiograph normal. CT reveals enlarged left internal mammary nodes, and enlarged nodes in the aortic-pulmonary window.
Also minimal amount of pleural fluid.

a



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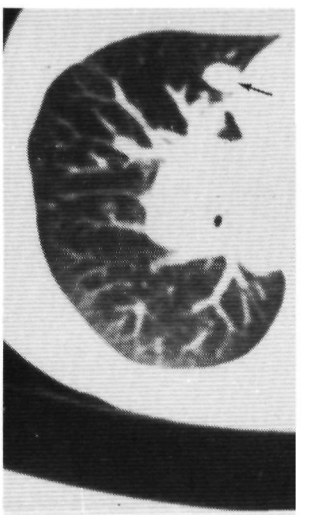

Fig. 2 : Case 4. Female patient of 15 years with HD.
2a: Enlarged mediastinal and hilar lymph nodes.
2b: CT demonstrates intrapulmonary lesion (arrow) anterior to the right hilum, not visible on AP and lateral chest radiograph.

Table 3: Specification of discrepancies between chest radiograph and CT. Localization of lymphoma radiologically present (+) or absent (-).

Pat. nr.	Hist.	chest radiogr.		CT		change of clin. stage	notes
		nodes	extra-nodal	nodes	extra-nodal		
1	NHL	-	-	+	-	-	
2	HD	-	-	+	-	-	chest wall lesion externally visible; fig. 4
3	HD	-	-	+	-	+	primary infradiaphragmatic presentation; fig. 1
4	HD	+	-	+	+	+	fig. 2
5	HD	-	+ (pleura)	+	+	-	
6	NHL	+	+ (pleura)	+	++	-	additional pleural lesions
7	NHL	-	+ (lung)	+	+	-	pulmonary parenchyma recurrence; fig.3
8	NHL	+	+ (lung)	+	++	-	additional pulmonary nodules; abdominal organ localization
9	NHL	+	-	+	+	-	also gastro-intestinal localization

Chest radiograph versus tomography

Table 4: Comparison of chest radiograph (Xth) and tomography (tom.) in 52 patients (NHL : n = 24 and HD : n = 28). Lymphoma localization radiologically present (+), absent (-) or equivocal (±).

Xth	tom.	-	+	±	total
-	NHL	9			9
	HD	8			8
	total	17			17
+	NHL		8	1	9
	HD		17		17
	total		25	1	26
±	NHL	3	3		6
	HD	1	2		3
	total	4	5		9
total	NHL	12	11	1	24
total	HD	9	19		28
grand	total	21	30	1	52

Conventional antero-posterior tomography of the mediastinum confirmed definitely normal and abnormal chest radiographs in all but one case.

In 9 patients with equivocal findings, tomography was normal in 4, and abnormal in 5 cases. No additional extra-nodal localizations were diagnosed.

DISCUSSION

Intrathoracic spread of lymphoma is a freguent occurrence in patients with HD or NHL. The incidence in patients with newly diagnosed HD is reported to be as high as 67%, whereas the incidence in patients with NHL is generally lower - up to 43% (2-5). A comparable difference is evident in the present series: 42% and 25% respectively. Intrathoracic manifestations of lymphoma usually consist of enlarged lymph-node masses in the mediastinal, hilar, retrosternal (thymic) and parasternal (internal mammary) regions. Involvement of lung parenchyma is much more uncommon: 11.6% in HD and 3.7% in NHL according to Filly et al. (3). Usually, there is accompanying mediastinal or hilar lymph-node involvement in these cases, at least in newly diagnosed patients with HD. In patients with NHL, and in patients with recurrent disease, isolated pulmonary lesions occur more frequently (3,6).

Conventional tomography:

Standard frontal and lateral chest radiography is a highly informative examination in patients with malignant lymphoma. Multiple lymph-node regions can be evaluated at one glance. Full-lung tomography can give a significant amount of additional information, but Castellino et al. (1) found that the clinical stage of disease changed in only 1.2% of patients. North et al. (7) found an equally low yield.

The superiority of full-lung tomography over conventional chest radiography in detecting intrathoracic abnormalities when staging is concerned is not the fact that tomography visualizes more involved lymph-node regions.

A change of stage is effectuated by detecting enlarged nodes in a patient with a normal chest radiograph, by visualizing extranodal spread of disease, or visualizing parenchymal, pleural or chest wall localizations. The latter findings upstage the patient to stage IV disease, and influence the choice of therapy directly in many

cases. In our retrospective study frontal mediastinal tomography proved to be ineffective, probably because only parts of the lungs were visualized. None of the examinations yielded additional information, whereas Castellino et al. found unexpected abnormalities with full-lung tomography in 21.4% of patients (1). It is our experience that mediastinal tomography proved to be useful in patients with equivocal chest radiographs only, and it was not rewarding when the chest radiograph was either clearly normal or abnormal.

Computed tomography:

The superiority of CT compared with chest radiography and tomography suggests that this technique will have a higher yield (8-12). Comparable data, as produced by Castellino on lung tomography (1) are still not available in medical literature. Rostock (12,13) diagnosed unexpected intrathoracic disease in 5 out of 10 patients suffering from HD having a normal chest radiograph. Shiels et al. (14) found evidence of lymphoma in 2 out of 24 patients (= 8%) having HD and a normal chest radiograph. Cohen et al. (15) found that chest CT changed the stage of disease in 6 out of 22 children (27%) investigated for malignant lymphoma. Khoury et al. (16) detected pathologic findings in 5 of 18 patients with NHL having a normal chest radiograph (= 28%).

CT was indeed more productive than conventional radiology in our patients.

In 3 out of 42 patients with a normal chest radiograph (= 7%), CT revealed intrathoracic lymph-node involvement (cases 1-3) (fig. 1). The 3 patients had newly diagnosed, untreated disease. In 1 of these patients, HD was found in a biopsy of a retro- and parasternal mass that protruded on the outside of the chest wall, and that was palpable at physical examination (fig. 4). CT therefore did not modify the clinical stage for this patient. In the 2 remaining patients, the clinical stage was changed in only 1 case.

A normal chest radiograph in combination with lymph-node

enlargement discovered by CT occurred in 4% of patients with NHL, and in 14% of patients with HD. This is compatible with the fact that chest involvement occurs more frequently in HD (as already demonstrated) and that lymph nodes involved with HD tend to be smaller than in NHL, and easier escape detection with conventional techniques.

Although our group is small, it conforms to the conclusion of Castellino et al., that supplementary investigation of the chest in NHL is the least rewarding. In their experience, it gives significant additional findings in only 1.1% of patients (1). These authors found in HD in 6.7% of cases significant information leading to change of stage and/or therapy.

Two other patients in the present series had only pulmonary and pleural lesions respectively shown by the chest radiographs. CT subsequently visualized enlarged mediastinal nodes (fig. 3). However, these findings did not change the stage of disease in these patients.

We did not compare the potential difference in the number of involved lymph-node regions diagnosed with either CT or chest radiography. It has been proven that treatment plans are influenced significantly by this aspect of superiority of CT (12,17,18), but clinical staging will not be markedly affected.

The greatest profit of performing full-lung tomography, -and a fortiori CT-, lies in the detection of occult mediastinal disease and unexpected pulmonary abnormalities. The latter finding will usually upstage the patient to stage IV disease and modify the treatment plan accordingly. Castellino et al. (1) found with full lung tomography such lesions in 4.5% of patients. Shiels found in 2 out of 11 patients with HD and an abnormal chest radiograph additional abnormalities with CT (14).

In the present study, CT detected additional lesions in 6 out of 26 patients with unequivocally abnormal chest radiographs (cases 4-9). Three out of these were intrapulmonary lesions, not visible on the chest

radiographs (fig. 2), 1 was a pleural lesion, and in 2 cases mediastinal lymph nodes were seen in patients with lung lesions. Two out of these 6 patients had HD, and thus additional findings were made in 20% of patients with HD and an abnormal chest radiograph.
The remaining 4 patients had NHL, and thus CT was responsible for additional findings in 25% of NHL-patients with an abnormal chest radiograph.
In 4 of the 6 patients, these additional lesions implied a clinical stage IV, but 3 patients were already known to have stage IV on the basis of other clinical data. The 2 remaining patients already had stage IV disease by radiology, and the additional CT-findings were thus not influential. As in most series, histological examination of the pulmonary lesions was not performed.

Summarizing the results, we can draw the following conclusions from the present material:

1. CT revealed abnormalities in 7% of lymphoma patients with a normal chest radiograph (14% in HD, 4% in NHL).
2. CT revealed additional lesions in 23% of lymphoma patients with an abnormal chest radiograph (20% in HD, 25% in NHL).
3. CT changed the clinical stage of disease in only 2 out of 76 patients with malignant lymphoma (3%). Both patients had HD, and thus CT was responsible for a change in the clinical stage in 2 of 27 patients with HD (=7%), and in none of the patients with NHL.

Thus, the net result of using CT as an additional examination in the staging procedure was of only minor importance, again confirming the conclusions of Castellino et al. (1) relating to the performance of full-lung tomography.
Routine CT of the chest seems not to be justified in each patient, presenting with malignant lymphoma. It should only be performed when potential additional information might influence therapy strategies.

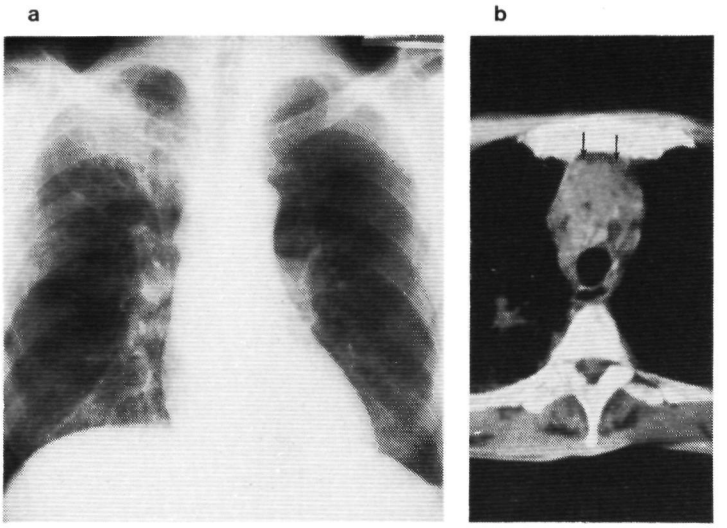

Fig. 3: Case 7. Female patient of 57 years with (histologically proven) recurrence of NHL in the right lung.
Enlarged retrosternal nodes (fig. 3b) not seen on chest radiograph (fig. 3a). Also enlarged left axillary nodes.

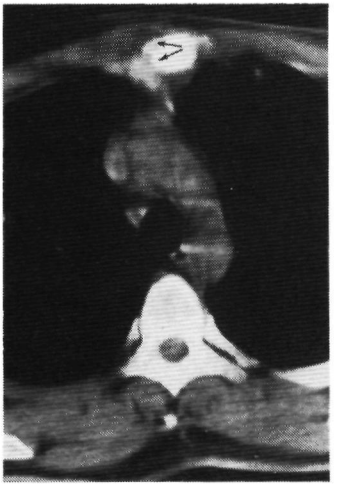

Fig. 4: Case 2. Male patient of 33 years with HD.
Retro- and parasternal lesion on the right side, infiltrating the pectoral muscle. Lesion was not visible on chest radiograph, but was palpable.
Biopsy of this lesion revealed HD.

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Chapter 7

LYMPH NODE CALCIFICATION IN MALIGNANT LYMPHOMA PRESENTATION OF NINE CASES AND A REVIEW OF THE LITERATURE.

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ABSTRACT

Lymph node calcification in malignant lymphoma is an uncommon radiologic finding. Eight cases are added to the 61 cases of lymph node calcification following radiation therapy for Hodgkin's disease, assembled from the literature. The typical radiographic appearance of punctate calcifications, usually found in the upper mediastinum, at times together with egg-shell type calcification, is confirmed. The mean time before appearance of calcification was 3 years after initial treatment. The calcification seems to be associated with a good prognosis and longterm survival. In addition, the radiologic and clinical findings in a patient with non-Hodgkin's lymphoma who developed calcifications in the involved area after treatment are presented.

INTRODUCTION

Calcification of lymph nodes in patients with malignant lymphoma is an uncommon finding. Most reports concern patients with Hodgkin's disease (HD) undergoing radiation therapy (3,4,6,7,9-17,19-26,28). Few reports describe the appearance of calcification after chemotherapy alone (1,2, 6). Lymph node calcification (LNC) following therapy for non-Hodgkin's lymphoma (NHL) is only infrequently mentioned in the literature (2,6). Even more unusual is the occurrence of LNC in patients with untreated malignant lymphoma; only three reports could be traced in the literature (5,8,27).

The present account gives a short review of the literature on this subject, and findings in 9 patients are presented, 8 with LNC after radiation therapy for Hodgkin's disease, and one with LNC after therapy for non-Hodgkin's lymphoma. A summary of the findings in the 8 patients with HD and LNC after therapy is given in the Table, and the remaining patient is reported in more detail.

table

Summary of patient data (Hodgkin s disease)

Case No	Sex	Initial diagnosis					Initial therapy		Calcification		Clinical course		
		Year	Age	Localization	Histol	Stage	RT	ChT	Localization	Time to appearance (yrs)*	Follow up (yrs)	Recurrence	Present state
1	F	1956	41	Mediastinum, supraclav	*	II	+	–	Paratracheal	3	28	–	N E D
2	F	1964	19	*	*	*	+	–	Ant mediastinum	(15)	20	–	N E D
3	F	1967	23	Mediastinum, cervical	N S	II	+	–	Ant mediastinum, paratracheal, right paracaval (abd)	(9) (14)	17	1974 abd 1981 abd 1984 abd	Alive with active disease
4	F	1968	29	Mediastinum, supraclav , cervical	N S	II	40 Gy, mantle field	–	Ant mediastinum	3	16	–	N E D
5	M	1970	20	Mediastinum, supraclav , cervical	N S	II	40 Gy, mantle field	–	Ant media stinum	4	14	1971 axilla abd	N E D
6	F	1973	21	Mediastinum, supraclav abd	M C	III	40 Gy mantle field 35 Gy, paralumb	+	Ant mediastinum	(8)	11	1979 cervic mediast 1980 axilla 1981 submand	N E D
7	M	1974	32	Mediastinum, cervical	N S	II	+	–	Ant mediastinum	(5)	10	–	N E D
8	F	1980	30	Mediastinum, abd	N S	III E	49 5 Gy, media- 40 Gy, paralumb	+	Ant mediastinum	2	4	1984 sternum	Still under treatment

* = data not available N S = nodular sclerosing M C = mixed cellularity ( )= earlier post-treatment radiography not available
RT = radiation therapy ChT = chemotherapy N E D = no evidence of disease

CASE REPORT

A 37-year-old male was referred in March 1982 with a lymph node mass in the left inguinal region, associated with marked edema of the leg and the scrotum. Abdominal CT showed the lesion to be continuous with a left-sided psoas mass (Fig. 1a). A biopsy yielded the diagnosis of NHL (immunoblastic type). Treatment consisted of combination chemotherapy, irradiation (32 Gy) and again chemotherapy. The lesion diminished in size but did not disappear completely.

In August 1983, the disease reappeared in the left inguinal and right cervical nodes. Soft tissue calcifications in the left para-iliac lymph node region were then noted at CT (Fig. 1b) and at radiography of the pelvis. Despite combined treatment modalities, the patient died in December 1983 with widespread disease, confirmed at autopsy.

DISCUSSION

The first description of spontaneous lymph node calcification in HD dates back to 1956, a case record of the Massachusetts General Hospital (5) presenting a patient with HD in calcified pelvic lymph nodes. In the discussion of this case an allusion is made to 2 cases of LNC occurring after radiation therapy. Those cases are probably part of the series of 9 patients described by Wyman & Weber in 1969 (28). This latter report describes the occurrence of LNC in HD after radiation therapy in more detail. The publication of Reboul & Delorme in 1956 (21) on 4 cases with -what they assumed to be- 'mediastinal pleural calcifications' after irradiation for HD is probably the first on this subject.

Incidence and occurrence. Twenty-two reports on LNC after radiation therapy for HD, comprising altogether 61 patients were assembled from the literature (3,4,6,7,9-17, 19-26,28) However, this phenomenon should not be so infrequent, as various authors found an incidence of LNC after irradiation in up to 6.5 per cent and 8 per cent of their patients (3,22). The age of the patients at the onset of disease varied from 11 to 68 years, with a mean age of 30 years (males 32 years, females 28 years). The interval between treatment and registration of calcification varied from 5 months to 19 years (mean interval 5 years). Sex distribution in a group of 47 patients showed a 5:3 ratio with female preponderance. Of 18 cases with the current histologic subclassification for HD specified, 10 were in patients with the nodular sclerosing type. This is compatible with the predominance of this type in an average population of patients with HD. The data on the 8 patients in the present table all fit well into this incidence profile. It should be noted that a closely spaced follow-up was not available in all cases. In the cases with an adequate radiologic follow-up (cases 1,4,5,8) the mean time before appearance was 3 years.

The occurrence of LNC in NHL seems to be more uncommon, as only 4 cases could be traced in the literature (2,6). Calcification was noted between 4 and 7 months after treatment. In the case described in this report calcification was noted on a CT scan 17 months after the initial treatment. A radiograph of the involved area revealed subtle punctate and streaky calcium deposits. In 4 cases of LNC after chemotherapy mentioned in the literature, calcification was noted between 4 months and 5 years after treatment (1,2,6). Finally, as far as is known, only 3 cases of LNC in untreated HD have been described (5,8,27). In all cases, histologic confirmation of nodal involvement was available.

Radiographic appearance. Post-therapy lymph node calcification occurs only in abnormal nodes. It usually starts as fine, punctate calcific densities, gradually assuming a coarse, nodular or confluent appearance (3,6,9, 10,28) (Fig. 2). With time, the area of calcification may shrink, leading to a denser and more nodular structure. The area of calcification gradually increases in size (Fig. 3a-d) without concomitant lymph node enlargement. In about 20 per cent of cases a more or less continuous peripheral, rim-like calcification appears, the so-called egg-shell type (6,10,13,28). The radiographic appearance is similar in HD and in NHL, after irradiation and chemotherapy, and in spontaneous or post-therapy calcification. In fact, the radiographic image is non-specific and can be seen in a variety of other diseases such as tuberculosis, sarcoidosis, histoplasmosis, silicosis, and other disorders as well (14, 25, 28). In all the present cases with LNC in the mediastinum or the pulmonary hilar region, there was also paramediastinal fibrosis due to mantle-field irradiation (Fig. 2b, 3a). Calcified lymph nodes mostly appear in the upper mediastinum, although in many patients other involved lymph node regions have been treated in the same way. However, LNC outside the thorax does occur (6,19,20)

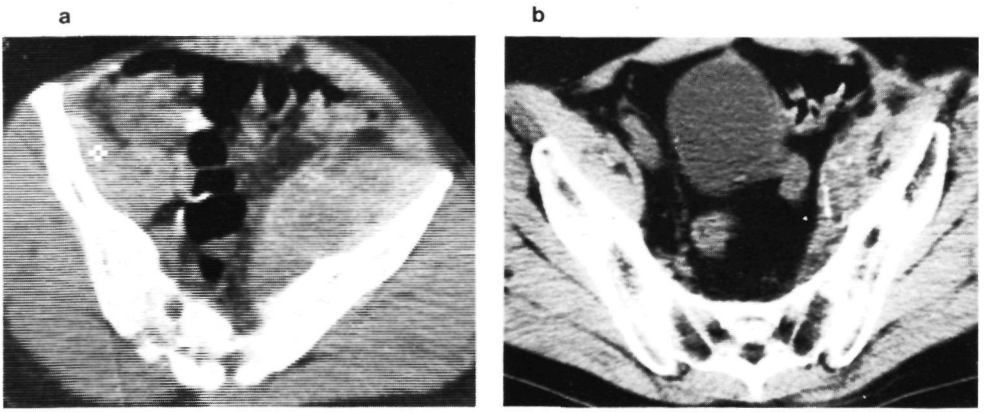

Fig. 1: Case 9, non-Hodgkin's lymphoma. a) CT scan shows increased volume of iliopsoas compartment, thickening of gluteal muscles and subcutaneous edema on the left side. b) CT scan after treatment. Decrease of tumor volume. Soft tissue calcification in left parailiac region.

(Fig. 3e). The cases of spontaneous LNC reported in the literature showed a predominant punctate calcification.

Clinical significance. Post-irradiation lymph node calcification is said to occur mainly in young females with massive mediastinal lymph node involvement and with preference for the nodular sclerosing form of HD (10,14). However, in the review of the literature, and including the present observations, both sexes, all ages, stages and histologic types of HD have been described in conjunction with LNC.

The occurrence of calcification is usually associated with a good prognosis with regard to survival. Relapse of the disease in these patients does occur, but only rarely in the area of calcification (10,14,22,28). The 8 patients with LNC after irradiation in the present report have survived for 4 to 28 years after the initial diagnosis and treatment. Four patients suffered from a relapse, but could be treated successfully. In the ninth case, a patient with non-Hodgkin's lymphoma, the course of the

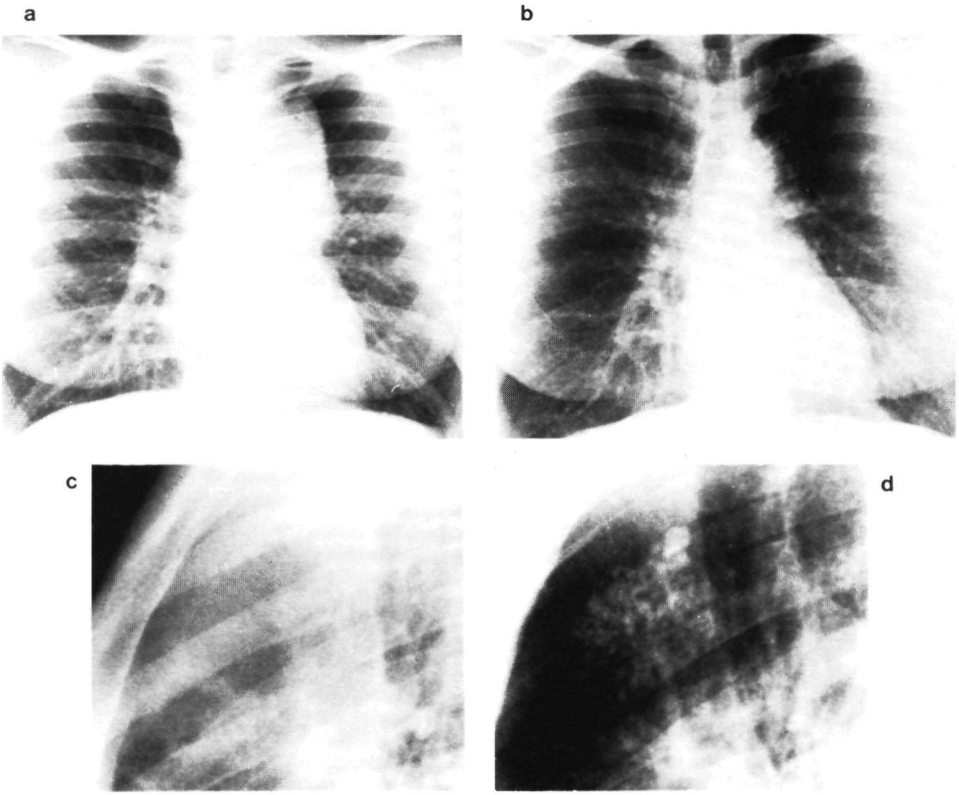

Fig. 2: Case 4, Hodgkin's disease. a, c) At initial presentation a large anterior mediastinal lymph node mass is present. b, d) Thirteen years after radiation therapy coarse nodular calcifications in the left anterior mediastinum. Also moderate paramediastinal fibrosis.

disease was more dramatic. Despite combined treatment modalities, recurrence and progression of the disease led to death 21 months after the initial diagnosis.

Calcification in lymph nodes after therapy probably occurs in areas with hemorrhage and necrosis, where fibrous healing subsequently follows ('dystrophic calcification') (1,19). Though there appears to exist an increased chance of calcification after higher doses of radiation, LNC is also noted after relatively low doses (3,6,16,22,28).

Some authors hold that calcification reflects healing and can therefore be regarded as a more or less successful

host reaction to the tumor (3,11). This concept should tally well with the occurrence of long-term survival in many of these patients. Foci of necrosis can at times be observed histologically in untreated Hodgkin tissue (18), although calcification in these areas is apparently very rare. This fact might nevertheless explain the potential for spontaneous calcification in punctate form, as reported in the literature.

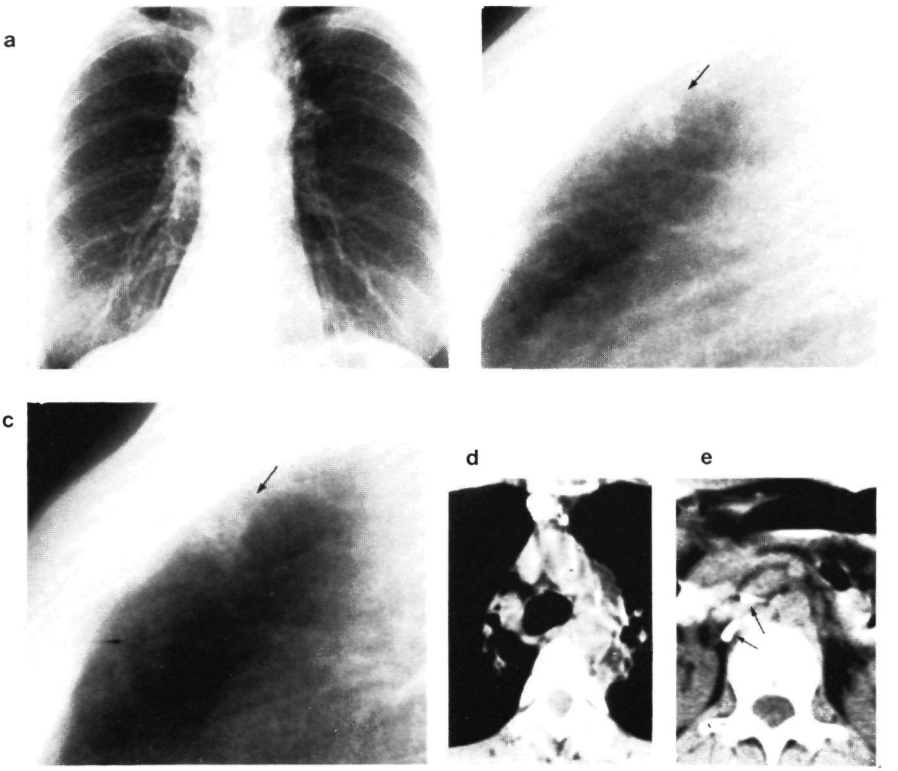

Fig. 3:
Case 3. Hodgkin's disease. a) chest film, 16 years after diagnosis and treatment. Marked (para) mediastinal fibrosis. b,c) lateral view (detail) shows this anterior mediastinal calcification in 1976 (b) and 1983 (c). Slight increase in volume of calcification is apparent (arrow) d) CT scan shows retrosternal calcifications e) CT scan of abdomen shows calcification in paracaval nodes (arrows).

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Chapter 8

Summary and conclusions

8.1 The abdomen
8.1.1 The lymph nodes
8.1.2 The spleen

8.2 The chest

8.3 Uncommon manifestations

Samenvatting en conclusies

8.4 Inleiding

8.5 De buik
8.5.1 De lymfklieren
8.5.2 De milt

8.6 De thorax

8.7 Ongewone beelden

8.1 THE ABDOMEN

8.1.1 The lymph nodes

Literature data correlating radiologic and histologic findings in infradiaphragmatic lymph nodes in patients with Hodgkin disease (HD) and/or patients with non-Hodgkin lymphoma (NHL) invariably show a lower diagnostic accuracy of CT in comparison with lymphography.This difference is due to the lower sensitivity of CT. This is the direct result of the fact that lymphography visualizes both lymph-node size and structure, whereas CT judges lymph-node size only. Architectural changes in normal sized nodes escape detection with CT.

In the present study the comparative diagnostic performance of CT and lymphography have been evaluated in patients with HD (chapter 2) and in patients with NHL (chapter 4). The final conclusions of both studies concurred.

Lymphography was abnormal in 17% of patients with HD having a normal CT scan, and in 17% of the patients with NHL having a normal CT scan. This discrepancy occurred mainly when CT was performed first. Conversely, when lymphography appeared to be normal, CT only occasionally detected abnormalities in infradiaphragmatic nodes, even though CT is able to visualize more lymph-node regions.

The following conclusions with regard to staging can be drawn:

* Lymphography remains the single, most accurate radiologic examination of abdominal nodes. When lymphography is either normal or abnormal, additional CT only rarely influences the final staging data.
* The advantages of CT in comparison with lymphography are that CT is easier and faster to perform, is less invasive than lymphography and imposes less discomfort on the patient. Repeat studies with good reproducibility are possible during surveillance of the patient. Follow-up studies with lymphography are also easy to perform with visualization of minimal changes in size

and structure, but only in a period of about 1 year after the initial examination. For further follow-up, repeat injections of contrast are then required.
For these practical purposes, CT is usually preferred as the first examination in the staging of patients with malignant lymphoma, despite its lower diagnostic yield. In this set-up, lymphography only adds information in a minority of patients, i.e. when CT is normal or equivocal. If an abnormal lymphogram would not influence subsequent management after a normal CT scan, it can be omitted.

* CT gives a more complete survey of the infradiaphragmatic lymph-node state than bipedal lymphography. However, it cannot compensate for the shortcomings of lymphography that became evident by carrying out staging laparotomy. In fact, the lower sensitivity of CT in comparison with lymphography indicates that staging laparotomy will continue to play a part when exact information on disease extent is mandatory.

8.1.2 The spleen

Non-invasive examinations of the spleen are historically unreliable in evaluating the presence or absence of lymphoma. As argued in chapters 3 and 5, it appeared from literature data, that a more exact determination of spleen size with CT might increase the diagnostic accuracy.
The "splenic index" (= width x length x thickness) appeared to be useful for better definition of spleen size, and for discrimination of uninvolved from involved spleens.
In a series of 35 patients with HD undergoing laparotomy with splenectomy, a diagnostic accuracy of 91% was obtained with a specificity of 94% and a sensitivity of 89%.
With patients having NHL, splenic index calculation and histologic verification were only possible in a heavily selected group of patients, and the diagnostic accuracy amounted to 100%. The (extrapolated) accuracy, specificity and sensitivity in a group of 20 patients without spleen

histology available, amounted to 90%, 100% and 82% respectively. These biased results indicate that splenic index calculation can be of value. It is questionable whether the hypothesis can be substantiated further, because of the lack of laparotomy data.

8.2 THE CHEST

The role of radiologic examinations of the chest in staging patients with malignant lymphoma is discussed in chapter 6.
Chest radiography was supplemented by tomography of the mediastinum in 52 patients with malignant lymphoma. No additional information was obtained in patients with a clearly normal or abnormal chest radiograph. Only in the event of an equivocal chest radiograph a tomogram was helpful.
CT on the contrary, revealed abnormalities in 7% of patients with a normal chest radiograph. CT detected minimal to moderately enlarged mediastinal or parasternal lymph nodes that were not visible with chest radiography. In 23% of the patients with an abnormal chest radiograph, additional lesions were found with CT, mostly in the form of pulmonary nodules. On the whole, CT changed the clinical stage of disease in only 3% of patients in whom it was performed, and this only occurred in patients with HD.
It is advised to perform CT not routinely in patients with malignant lymphoma, but to reserve it for those cases in which treatment strategy will be modified due to the additional positive findings.

8.3 UNCOMMON MANIFESTATIONS

The radiologic observation of calcification in lymph nodes afflicted with HD is an uncommon occurrence (chapter 7). This phenomenon is associated with a good prognosis. The incidence of lymph node calcification in NHL is too rare to draw conclusions with regard to clinical significance.

8.4 INLEIDING

"Maligne lymfomen" is de verzamelnaam voor kwaadaardige aandoeningen die uitgaan van het lymfatische systeem. Er worden 2 hoofdgroepen onderscheiden: de ziekte van Hodgkin (afgekort: MH) en de zogenaamde non-Hodgkin lymfomen (afgekort: NHL). Deze ziekten tasten meestal de lymfklieren aan, maar kunnen ook voorkomen in alle andere organen (milt, lever, beenmerg, maagdarmstelsel, longen etc.).
De maligne lymfomen waren in 1983 verantwoordelijk voor 2.7% van de totale kankersterfte in Nederland (863 personen). Daar staat tegenover dat veel patiënten -vooral met MH- door de moderne behandelingsmogelijkheden worden genezen, of langdurig in een goede toestand kunnen worden gehouden bij niet volledige genezing.
De vorm van behandeling hangt mede af van de uitgebreidheid (stadium) van de ziekte. Röntgenonderzoek zoals lymfografie, computertomografie (CT) van borst- en buikholte, longfoto's en gewone planigrafie kan tal van lymfkierstations en organen zichtbaar maken, en vormt een belangrijk onderdeel van het zogenaamde stadiëringsonderzoek.
In dit proefschrift wordt nagegaan wat de mogelijkheden en beperkingen zijn van verschillende radiologische onderzoektechnieken. Getracht wordt de vraag te beantwoorden in hoeverre diverse onderzoeken elkaar aanvullen dan wel overlappen, hoe betrouwbaar zij zijn in het aantonen van de ziekte-uitbreiding, en op welke manier zij ingepast kunnen worden in het stadiëringsonderzoek.
MH en NHL worden apart besproken -niet alleen vanwege de histopathologische verschillen- maar ook vanwege verschillen in klinische presentatie, gedrag en prognose.
In hoofdstuk 2 en 4 wordt CT van de buik met lymfografie vergeleken. Waar mogelijk, wordt tevens gecorreleerd met histologische bevindingen bij laparotomie. In hoofdstuk 3 en 5 wordt de waarde van CT met betrekking tot het onderzoek van de milt geëvalueerd. In hoofdstuk 6 wordt het onderzoek van de thorax besproken. Hoofdstuk 7 staat los van het stadiëringsonderzoek, en demonstreert enkele onge-

wone radiologische verschijningsvormen.

8.5 DE BUIK

8.5.1 De lymfklieren (hfdst. 2 en 4)

Literatuur gegevens met betrekking tot het radiologisch en histologisch onderzoek van de lymfklieren onder het diafragma bij patiënten met MH of met een NHL wijzen op een lagere betrouwbaarheid van CT vergeleken met lymfografie, als gevolg van een lagere sensitiviteit. Dit is het gevolg van het feit dat met CT alleen de grootte van de lymfklieren wordt beoordeeld, terwijl lymfografie behalve de grootte ook de inwendige structuur zichtbaar maakt. De conclusies uit eigen onderzoek komen overeen met de literatuur en stemmen overeen bij patiënten met MH en NHL. Lymfografie liet afwijkingen zien in de lymfklieren bij 17% van de patiënten met MH, en bij 17% van de patiënten met NHL, bij wie de CT-scan normaal was. De discrepanties traden voornamelijk op wanneer CT vóór de lymfografie was verricht. Met CT werden zelden afwijkingen aangetoond wanneer de lymfografie normaal was.

De volgende conclusies worden getrokken met betrekking tot het stadiëringsonderzoek:

* lymfografie is het meest nauwkeurige onderzoek van de abdominale lymfklieren. Na een normaal of abnormaal lymfogram levert een CT scan zelden, voor de stadiëring relevante, extra gegevens op.
* CT is gemakkelijker en sneller uit te voeren dan lymfografie, en is minder belastend voor de patiënt. Herhalingsonderzoeken, met goede reproduceerbaarheid zijn eveneens gemakkelijk uitvoerbaar.

  Lymfografie is een enigzins invasief onderzoek, en duurt in vergelijking met CT betrekkelijk lang. Contrôleonderzoeken zijn daarentegen sneller en gemakkelijker uitvoerbaar, en maken minimale veranderingen in de klieren reeds zichtbaar. Gemiddeld is na ± 1 jaar het contrastmiddel zover verdwenen dat contrôle niet meer mogelijk is, en zou opnieuw contrastmiddel moeten worden

ingebracht.
Om praktische redenen wordt CT meestal als eerste onderzoek verkozen, ondanks de iets lagere betrouwbaarheid. Een lymfografie is alleen dan zinvol wanneer de CT géén, of onduidelijke afwijkingen laat zien. Als een afwijkend lymfogram na een normale CT scan het beleid evenwel niet beïnvloedt, kan het achterwege worden gelaten.

* CT geeft een volledige beeld van de lymfklieren onder het diafragma dan lymfografie. Echter, de tekortkomingen van lymfografie die bij stadiëringslaparotomie aan de dag traden worden met CT niet opgevangen. Stadiëringslaparotomie zal in voorkomende gevallen niet vermeden kunnen worden.

8.5.2 De milt (hfdst. 3 en 5)

Het niet-invasieve onderzoek van de milt (palpatie, röntgenfoto, nucleaire scan) is in het verleden niet erg betrouwbaar gebleken met betrekking tot het aantonen of uitsluiten van lymfoom localisaties. Uit literatuurgegevens kregen wij de indruk dat door een meer exacte bepaling van de miltgrootte met CT de betrouwbaarheid verhoogd zou kunnen worden. Hiertoe werd aan de hand van de CT-scans de zogenaamde miltindex berekend (= lengte x breedte x dikte). Een waarde van 480 werd gehanteerd als grens tussen normale en vergrote milten, resp. histologische normale en aangetaste milten.
Bij 35 patiënten met MH bij wie de milt verwijderd werd, bleek het mogelijk op deze manier een diagnostische nauwkeurigheid van 91% te behalen (6% fout-positieve en 11% fout-negatieve diagnoses).
Bij 33 patiënten met NHL was de milt beschikbaar voor histologisch onderzoek, en de diagnostische betrouwbaarheid van de miltindex berekening bedroeg 100%. Bij 20 andere patiënten met NHL werd de milt "indirect" geëvalueerd, waarbij een betrouwbaarheid van 90% werd verkregen met 0% fout-positieve en 18% fout-negatieve diagnoses.
Echter, deze beide NHL-groepen bestonden uit zeer geselecteerde patiënten, zodat de resultaten geen absolute waarde

hebben, maar gezien moeten worden als aansporing tot verder onderzoek. Dit zal echter waarschijnlijk niet mogelijk zijn omdat stadiëringslaparotomieën, die het materiaal moeten leveren, nog slechts sporadisch worden verricht bij patiënten met NHL.
Het "addendum" na hoofdstuk 3 plaatst enkele kanttekeningen bij onze waarnemingen.

8.6 DE THORAX (hfdst. 6)

Bij 52 patiënten werd behalve een thoraxfoto in achtervoorwaartse en zijdelingse richting ook een planigrafie (= tomografie) van het mediastinum verricht. In geen van de gevallen waarin de thoraxfoto duidelijk normaal of abnormaal was, werd de conclusie gewijzigd. Alleen wanneer de thoraxfoto twijfelachtige bevindingen liet zien, droeg de planigrafie bij aan de vorming van een zekere uitspraak.
Bij 76 patiënten werd een CT-scan van de thorax verricht. Bij 7% van de patiënten met een normale thoraxfoto werden toch afwijkingen gevonden, in de vorm van licht tot matige vergrote klieren. Bij 23% van de patiënten met een afwijkende thoraxfoto werden met CT extra afwijkingen gevonden. Evenwel, over de gehele groep gezien, veranderde de CT het klinisch stadium in slechts 3% van de patiënten, en dan nog uitsluitend bij patiënten met MH. Het routinematig verrichten van CT van de thorax bij iedere patiënt die gestadieerd wordt vanwege maligne lymfoom lijkt derhalve niet zinvol. Alleen in die gevallen waarin de extra bevindingen het beleid beïnvloeden, is CT aangewezen.

8.7 ONGEWONE BEELDEN (hfdst. 7)

Verkalkingen in lymfklieren bij MH worden zelden radiologisch aangetoond, en dan vrijwel uitsluitend na bestraling. Dit fenomeen gaat gepaard met een goede prognose. Dit blijkt uit de literatuur, en uit een groep eigen patiënten. Verkalkingen in klieren na behandeling wegens NHL zijn zeer zeldzaam, en de klinisch betekenis ervan is niet duidelijk.

WOORDEN VAN DANK

Velen hebben bijgedragen aan de totstandkoming van dit proefschrift. Aan de praktische uitvoering van de honderden röntgenonderzoeken hebben tientallen radiodiagnostisch laboranten (m/v) meegewerkt, terwijl vele assistenten zich met meer of minder enthousiasme over de uitvoering van de lymfografieën hebben gebogen.
Belangrijke patiëntengegevens werden verkregen dank zij de medewerking van de afdelingen Hematologie (hoofd: Prof.Dr. C. Haanen), Radiotherapie (hoofd: Prof.Dr. W.A.J. van Daal), en Medische Oncologie (hoofd: Prof.Dr. D.J.Th. Wagener).
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Voor de foto's in de oorspronkelijke artikelen, en in dit proefschrift dank ik de heren W. Witte en Th. Janssen.
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Het proefschrift zelf werd met veel geduld, toewijding en vaardigheid door Sjana Serhalawan verzorgd.
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CURRICULUM VITAE

De schrijver van dit proefschrift werd geboren op 22 maart 1947 te Leiden. Aan het St. Bonaventura Lyceum aldaar werd in 1965 het einddiploma gymnasium-ß behaald. Hij studeerde geneeskunde aan de Rijksuniversiteit te Leiden, en behaalde in november 1972 het artsexamen.
De militaire dienstplicht werd tot maart 1974 vervuld op de afdeling Radiologie van het Militair Hospitaal 'Dr. A. Matthijsen' te Utrecht, onder leiding van de radiologen A. v.d. Beek en J.M.H. Blom.
Op 1 april 1974 begon hij zijn opleiding radiodiagnostiek in het St. Radboudziekenhuis te Nijmegen (Hoofd: Prof.Dr. Wm. Penn).
Na zijn inschrijving in het specialistenregister per 1 april 1978, is hij als staflid verbonden aan het Instituut voor Radiodiagnostiek van het St. Radboud-ziekenhuis (hoofd tot 1982: Prof.Dr. Wm. Penn; thans Prof.Dr. J.H.J. Ruijs). Tot zijn deel-vakgebied behoren alle (diagnostische, interventionele en oncologische) aspecten van de abdominale radiologie.

STELLINGEN

1. Het verschil in diagnostische nauwkeurigheid tussen CT en lymfografie bij patiënten met maligne lymfoom berust voornamelijk op een verschil in sensitiviteit ten nadele van CT.

2. CT is geen alternatief voor stadiëringslaparotomie.

3. De informatie verkregen met behulp van CT en lymfografie is voor 85% overlappend en voor 15% aanvullend. Tegenstrijdige informatie kan meestal afdoende verklaard worden.

4. Het routinematig verrichten van een CT van de thorax als onderdeel van het stadiëringsonderzoek bij patiënten met de ziekte van Hodgkin of non-Hodgkin lymfoom is niet zinvol.

5. De in-vivo bepaling van de miltgrootte met behulp van de CT-miltindexberekening kan aanwijzingen geven over eventuele lymfoomlocalisatie in de milt bij patiënten met de ziekte van Hodgkin of non-Hodgkin lymfoom.

6. Het optreden van lymfklierverkalkingen bij de ziekte van Hodgkin is een prognostisch gunstig teken.

7. Het verrichten van een lymfografie na een abdominale CT-scan levert alleen additionele informatie op wanneer de CT géén of twijfelachtige afwijkingen laat zien.

8. Magnetic Resonance Imaging (MRI) is een gevoelige methode voor het opsporen van afwijkingen in het beenmerg bij patiënten met leukemie, maligne lymfoom of metastasen.
   (DO Olson et al., Invest. Radiol. 1986; 21: 540-546).

9. Wanneer bij patiënten met een niet-seminomateuze testistumor wordt gekozen voor een zogenaamd "wait and see" beleid, dan dient bij screening op retroperitoneale lymfkliermetastasen zowel een abdominale CT-scan als een lymfografie te worden verricht.

10. Bij de bepaling van de resectabiliteit van een pancreastumor kan een percutane transhepatische portografie (PTP) bij een groot deel van de patiënten worden vermeden door het uitvoeren van een intra-arteriële digitale subtractie angiografie (i.a. DSA) van de a. mesenterica superior en de truncus coeliacus.

11. Bij vergelijking van de mortaliteit van palliatieve behandeling voor maligne galgangobstructie door percutane, endoscopische of chirurgische drainage, dient met name gelet te worden op het aanwezig zijn van een verlaagd serum-albuminegehalte en een verhoogd bloedureumgehalte als prognostisch ongunstige variabelen.
(D Bonnel et al., Radiology 1984; 152: 347-351.)

12. Bij patiënten met manifestaties van het solitair rectum ulcus syndroom is een defecografie geïndiceerd om een functionele defecatiestoornis op te sporen.
(JHC Kuijpers et al., wordt gepubliceerd in Ned. Tijdschr. Geneeskd.)

13. Echografisch zichtbare, zwevende stenen in de (niet-geopacificeerde) galblaas bevatten zeer waarschijnlijk gas (Mercedes Benz fenomeen).
(SP Strijk et al., Gastrointest. Radiol. 1981; 6: 261-263.)

14. De radiodiagnost kan bijdragen aan vermindering van het aantal diagnostische verrichtingen door de aanvraag net zo kritisch te beoordelen als de foto's.

Nijmegen, 16 januari 1987 S.P. Strijk