Malignant Lymphomas: Further Studies on their Preferential Sites of Involvement and Possible Mode of Spread*

A. Banfi, G. Bonadonna, G. Carnevali, F. Fossati-Bellani

From the National Cancer Institute, Milan and the Institute of Radiology, University of Milan, Italy

In the past 10 years the therapeutic design for rational treatment of malignant lymphomas has been based primarily on the delivery of curative doses of radiation to all involved tissues if after accurate evaluation of its anatomical extent the disease appeared to be localized or moderately diffuse (11, 12). It is well known that routine lymphographic studies play a role of primary importance in the meticulous program of diagnostic evaluation (7). Lymphography in fact has been exhaustively proved to be mandatory for detecting clinically silent retroperitoneal extensions. This more precise definition of the actual lymph node involvement recently prompted a new four-stage clinical classification which was established for Hodgkin's disease on an international agreement (18).

On the basis of long-term therapeutic results the majority of clinicians believe that both Hodgkin's disease and lymphoreticular sarcomas (lymphosarcoma and reticulum cell sarcoma) are unicentric in origin but may have different patterns of spread. Previous studies performed by *Scheer* (21), *Rosenberg* and *Kaplan* (19), *Han* and *Stutzman* (10) and ourselves (2, 3, 4, 5) provided evidence that Hodgkin's disease spreads predominantly through adjacent and therefore predictable lymphatic areas while an irregular pattern of dissemination seems to occur in lymphoreticular sarcomas. Knowledge of the preferential sites of involvement as well as the patterns of initial spread in malignant lymphomas is obviously of primary importance to establish optimal treatment. In particular further evidence should be provided in favour or against prophylactic treatment to adjacent regions in apparently localized disease.

The present investigation has been undertaken in order to further contribute to the knowledge of these problems.

Material and Methods

The study was performed on three different groups of cases. The first group includes 500 consecutive untreated adults (200 with Hodgkin's disease and 300 with lymphoreticular sarcomas). The second group analyses 218 consecutive and untreated lymphoreticular sarcomas, whose primary disease occurred in the Waldeyer's ring. To the

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third group belong 71 consecutive untreated cases of malignant lymphomas occurring in children up to and including the age of 15 years (33 with Hodgkin's disease and 38 with lymphoreticular sarcomas).

All patients had a detailed clinical history and a complete physical as well as pharyngeal examination. One or two excisional biopsies were performed and the histologic diagnosis was confirmed by two pathologists in most cases. In the patients of the first group radiological examination including a postero-anterior and lateral chest film with mediastinal tomograms and skeletal survey (skull, spine, pelvis) were obtained in all cases. In some patients of the second and third group the skeletal survey was not always included in the initial evaluation. Among adult patients, including those with primary onset in the Waldeyer's ring, bilateral lower limb lymphography was carried out in 100 cases with Hodgkin's disease and in 128 with lymphoreticular sarcomas. In children lymphography was performed in 10 cases with Hodgkin's disease and in 7 cases with lymphoreticular sarcomas. Urography and pneumoretroperitoneum with tomography were performed mostly in those patients studied before the advent of lymphography. X-ray examination of the gastrointestinal tract was systematically performed in the large majority of the 74 patients with lymphoreticular sarcomas primary in the Waldeyer's ring studied with lymphography (3).

Laboratory studies have included in the large majority of cases a complete blood count, platelet count, erythrocyte sedimentation rate, bone marrow aspiration, alkaline phosphatase, bromsulfalein retention at 45', serum uric acid, calcium and protein electrophoresis.

In those patients studied within the past five years the hepatomegaly was also studied by liver scan with ^{198}Au and liver biopsy through peritoneoscopy.

After this diagnostic evaluation the patients were restaged according to what appears to be the new standardized clinical classification proposed at *Rye* for Hodgkin's disease (18). This classification has also been adopted for lymphosarcoma and reticulum cell sarcoma with primary involvement of lymph nodes and of Waldeyer's ring since an agreement on an international basis has not yet been achieved for these diseases. The anatomical regions for the above proposed clinical classification were also adopted (11).

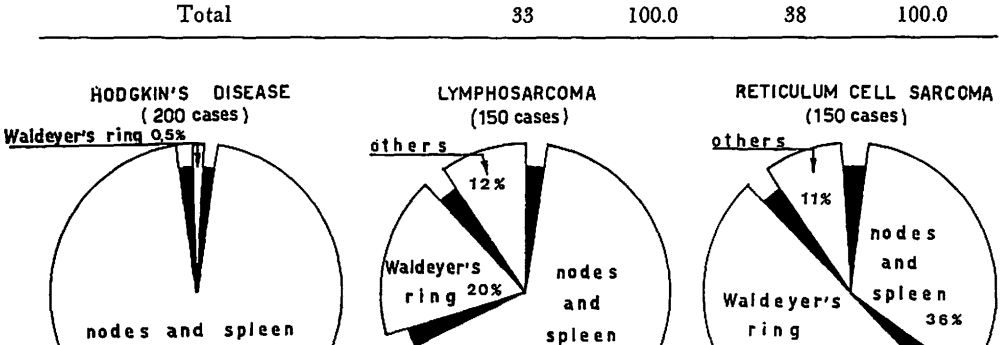
When treatment was completed patients were followed at frequent intervals (every 1–3 months according to the different clinical situations) in the out-patient department by at least one radiotherapist and one chemotherapist. Complete blood counts and chest x-rays were obtained almost routinely on each visit. Skeletal surveys as well as flat plates of the abdomen were repeated in cases with suspicious bone pain and to check on the previously opacified retroperitoneal nodes as long as the contrast material was present. Gastric series were repeated in case of epigastric distress.

Results

The analysis of the distribution of the various sites of involvement in the first group of patients (2, 4) shows that on admission in 200 cases of Hodgkin's disease the involvement was confined to lymph nodes and spleen in 199 patients (99.5%) and that in only one case (0.5%) the disease arose in Waldeyer's ring (table 1). On the contrary, the

Table 1 Percentage of involvement of lymph nodes and spleen, Waldeyer's ring and other sites on admission in untreated consecutive adults and children.

	Site of involvement	Hodgkin's disease		Lymphoreticular sarcomas	
		No. cases	%	No. cases	%
Adults	Nodes and spleen	199	99.5	155	52.0
	Waldeyer's ring	1	0.5	110	36.5
	Other sites	–	–	35	11.5
	Total	200	100.0	300	100.0
Children	Nodes and spleen	32	97.5	28	75.5
	Waldeyer's ring	–	–	2	6.5
	Other sites	1	2.5	8	18.0
	Total	33	100.0	38	100.0



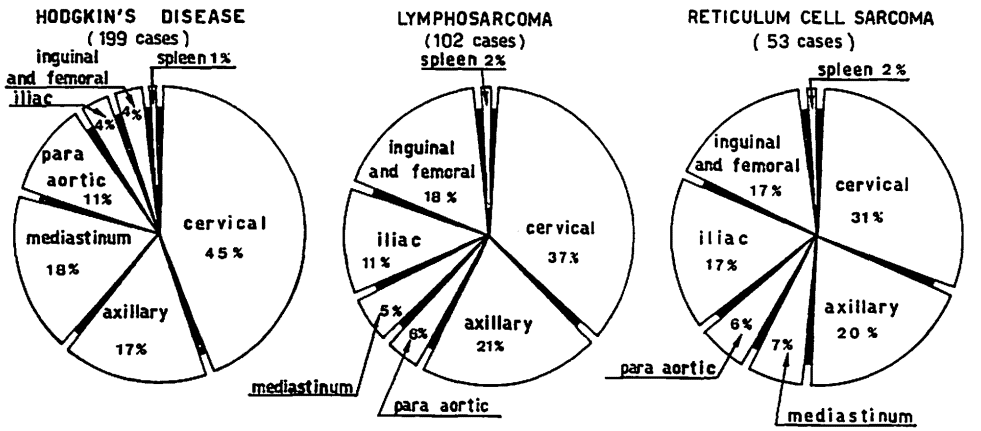
percent involvement of Waldeyer's ring is considerably higher in lymphoreticular sarcomas (36.5%) and increases from lymphosarcoma (20%) to reticulum cell sarcoma (53%) while the other sites (bone, liver, lung, lung parenchima, skin, gastro-intestinal tract, marrow) show no significant difference between these two diseases (12 and 11% respectively, average 11.5%).

A comparative study of the distribution among the different lymph node-bearing areas including spleen (patients evaluated with and without lymphography) reveals (2, 4) that the cervical area (cervical, supraclavicular, occipital and preauricolar nodes) shows by far the highest involvment in all three diseases but mostly in Hodgkin's disease (45%) and less so in reticulum cell sarcoma (31%). In lymphoreticular sarcomas the percentage of neck involvement is higher if one includes patients with primary disease in the Waldeyer's ring where extension to the cervical nodes is frequent. While the axilla appears to be equally involved, mediastinal (18%) and para-aortic (17%) adenopathies are more frequently found in Hodgkin's disease than in lymphosarcoma

and in reticulum cell sarcoma where there is a higher involvement of iliac (11–17%), inguinal and femoral (18–17%) nodes. The splenic involvement on admission seems to be rare in our material and practically identical in all three types of lymphomas (1–2%).

Table 2 Percentage of involvement of the different lymph node-bearing areas in patients with primary involvement of lymph nodes and spleen evaluated with lymphography.

Nodal areas	Hodgkin's disease (99 patients) %	Lympho-reticular sarcomas (67 patients) %	Nodal areas	Hodgkin's disease (99 patients) %	Lympho-reticular sarcomas (67 patients) %
Cervical	41	27	Iliac	6	23
Axillary	10	16	Femoral	1	17
Mediastinal	20	6	Splenic	2	2
Para-aortic	20	9			



The predominant "central" involvement in Hodgkin's disease rather than the "peripheral" pattern in lymphoreticular sarcomas is compiled in table 2 where the comparative study was carried out only in patients (always with nodal and/or splenic involvement) evaluated with lymphography. The more detailed investigation of the retroperitoneal space accounts here for the higher percentage of para-aortic adenopathies in Hodgkin's disease (20%) and respectively of iliac adenopathies in lymphoreticular sarcomas (23%).

The distribution of the various sites of involvement in untreated children (5) is reported in table 1. As previously seen in adults, Hodgkin's disease was confined to nodes and spleen in practically all patients (97.5%) while in comparison lymphoreticular sarcomas revealed appreciable involvement of the Waldeyer's ring (6.5%) and considerable extension to extranodal sites (18%). Since only in 17 of 71 children a lymphographic study was carried out, the comparative detailed analysis of the distri-

bution among the different lymph-node bearing areas is not reported with the exception of mediastinum. This area was definitely more involved in Hodgkin's disease (18.5%) than in lymphoreticular sarcomas (5.5%).

As far as the involvement of the different areas of the Waldeyer's ring on admission is concerned in 42.2% of patients the lesion was arising from the tonsil, in 34.4% from the nasopharynx, in 12.1% from the mesopharynx, in 8.1% from the base of tongue and in 2.8% from the soft palate (3).

The mode of spread has been studied by counting the number of untreated patients with contiguous and non contiguous adenopathies as well as the next sites of involvement after initial radiation therapy. Table 3 shows that in about 2/3 (66%) of adults with Hodgkin's disease the adenopathies were found to be distributed in adjacent lymphoid areas while this finding occurred only in 35% of lymphoreticular sarcomas.

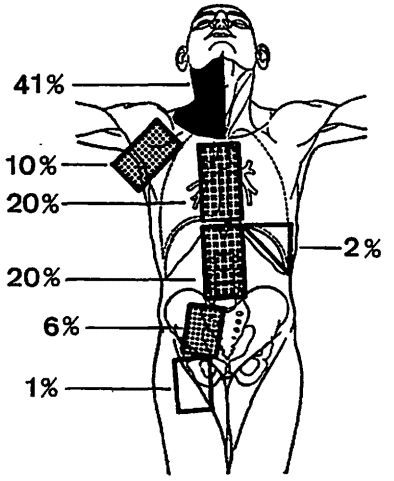
Table 3 Malignant lymphomas in adults with primary onset in lymph nodes. Number of patients classified at stage I_2, II and III with contiguous involvement as well as mode of spread in patients classified at stage I_1, I_2 and II with contiguous involvement (modified by *Banfi* et al., courtesy of Europ. J. Cancer, 1968).

Histologic type		Involvement		Spread	
		No. cases	contiguous	No. cases	contiguous
Hodgkin's disease	without lymphography	73	54 (74%)	79	57 (72%)
	with lymphography	80	47 (59%)		
	Total	153	101 (66%)		
Lymphoreticular sarcomas	without lymphography	53	19 (36%)	44	20 (45%)
	with lymphography	54	18 (33%)		
	Total	107	37 (35%)		

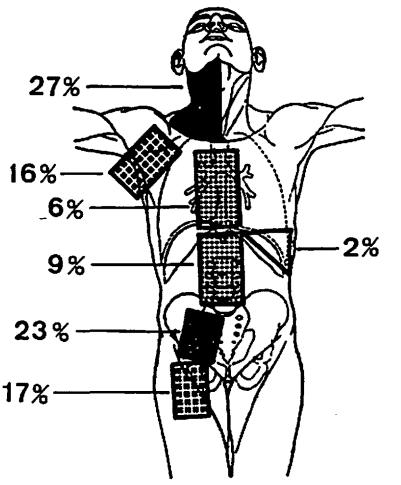
In the group of patients with Hodgkin's disease in whom the diagnostic evaluation included a foot lymphogram, the percentage of contiguous involvement is lower (59%) than in those without lymphographic study (74%). This is due to the fact that lymphography detected retroperitoneal extensions in a number of patients with neck or axillary nodes without concomitant involvement of the mediastinum. Hodgkin's disease may have arisen in the para-aortic area and spread via the thoracic duct to the cervical and/or axillary regions without involving the mediastinum.

Table 3 reports also the sites of extension in new areas after receiving localized radiation therapy. After lymphography only few patients classified as stage I_1 (cervical onset) had precautionary irradiation to the mediastinum. In 72% of cases with Hodgkin's disease the next site of involvement after initial treatment was found in adjacent lymph node bearing areas. This finding occurred only in 45% of lymphoreticular sarcomas. Furthermore, in Hodgkin's disease the first site of extension after localized radiation therapy occurred practically always in lymph node regions; however in lymphoreticular sarcomas this was found also in viscera or bones. In the limited case material examined children seem to behave as adults (5).

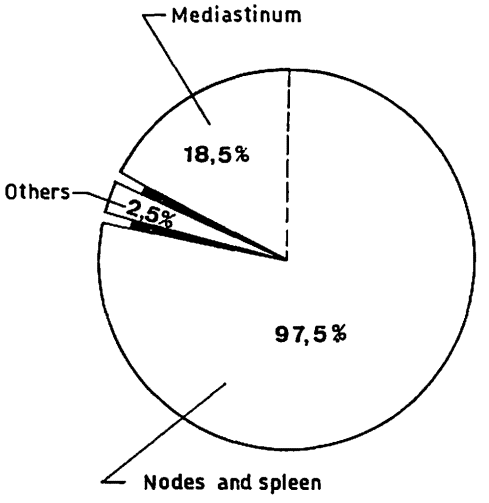
Hodgkin's Disease (99 cases)



Lymphoreticular Sarcomas (67 cases)



Hodgkin's Disease (33 cases)



Lymphoreticular Sarcomas (38 cases)

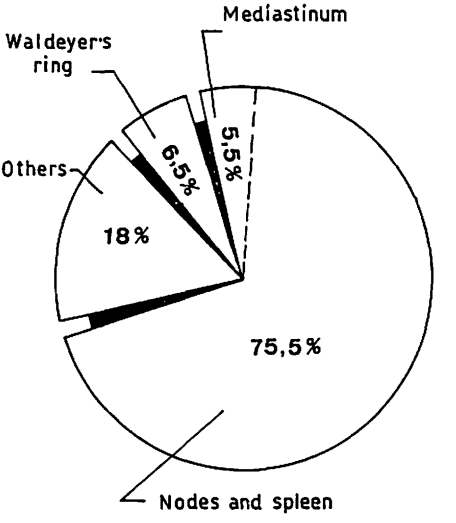


Table 4 outlines the sites of extension observed on admission in 218 cases with lymphoreticular sarcomas having primary involvement of the Waldeyer's ring. A striking difference can be seen between the two groups of patients studied with and without lymphography. Lymphography lowers considerably the number of patients with localized (Waldeyer's ring) and regional (Waldeyer's ring and cervical nodes) disease, while it increases the percentage of cases with extensions to sites below the diaphragm. The lymphographic studies furthermore revealed that the iliac chains were more frequently involved than the inguinal and para-aortic node groups. This some-

what elective spread to the iliac nodes accounts almost entirely for the high difference in the percentage of contiguous regional involvement between the groups of patients evaluated with and without lymphography (29.7% versus 63.3%). It is worthwhile to point out that involvement of the gastrointestinal tract (mainly stomach) either at the time of admission or early in the follow up occurred in 16.2% of the group of patients studied with lymphography (3). In most of these 74 cases x-ray of the gastrointestinal tract was systematically performed. In this particular group of lymphoreticular sarcomas the next site of recurrence after local radiation therapy was observed in lymphoid regions above the diaphragm (25%), below the diaphragm (16.2%) and in extranodal tissues (62.5%).

Table 4 Lymphoreticular sarcomas with primary onset in the Waldeyer's ring. Comparative study showing the anatomical spread in patients evaluated respectively without and with lymphography.

Anatomical extent	Without lymphography (144 patients) %		With lymphography (74 patients) %	
Waldeyer's ring only	20.1	83.4	9.5	39.2
Waldeyer's ring and cervical nodes	63.3		29.7	
Involvement of distant nodes	10.3		45.9	
Involvement of extra nodal sites	6.3		14.9	
Total	100%		100%	

Discussion

From our study performed on a relatively large number of patients some points deserve special consideration. They can be summarized as follows:

1. In Hodgkin's disease of adults and children primary extranodal involvement is at least rare. This is not true for lymphoreticular sarcomas where the Waldeyer's ring is frequently involved and in much higher percentage than usually reported in the literature (8, 17). Furthermore, in the sarcoma group primary involvement of other extranodal sites is not unusual.
2. The comparative study of lymph node involvement at first diagnostic evaluation has revealed that apart from the cervical regions the involvement in Hodgkin's disease is, predominantly "central" (mediastinal and para-aortic) while in lymphoreticular sarcomas it is mainly "peripheral" (axillary, iliac and inguinal).
3. In Hodgkin's disease the number of cases (adults and children) with contiguous involvement and contiguous spread after local radiotherapy is higher than in lymphoreticular sarcomas. The number of cases with contiguous spread becomes higher in Hodgkin's disease if one considers that the primary onset occurs in the para-aortic area and spreads via thoracic duct to the neck and the axillae.
4. In patients with primary sarcomas of the Waldeyer's ring the retroperitoneal nodes and the stomach are involved in a relatively high percentage of cases with disease otherwise localized to the pharynx or extended only to the contiguous cervical nodes.

Some of these observations could be in part explained on the basis of what has been stated before, i.e. that in Hodgkin's disease there is a proportionally higher involvement of the deep central lymphoid areas (mediastinum, and para-aortic nodes). Therefore the possibility that the next lymphatic site of involvement occurs in an adjacent area becomes very high. Nevertheless the tendency to spread through contiguous lymphoid regions is clearly supported by the numerous cases where the primary onset occurred in a non deep central lymphatic area (e.g. neck) and the next site or sites of involvement after radiotherapy were detected in contiguous regions. All these data as well as those of recent successes with radiation therapy provide a convincing evidence that Hodgkin's disease may in fact be unicentric in origin and spread initially through predictable contiguous lymphoid areas. The recent observation of Sternberg-Reed cells in the blood (6) could be explained by invasion of veins as observed by Rappaport in 10% of cases, especially with lymphocytic depletion (15). This, as well as the dissemination into the blood stream via the thoracic duct lymph (10), could account for visceral and bone marrow involvement.

The cure achieved with radiation therapy in a relatively high percentage of cases of localized lymphoreticular sarcomas primary in the lymph nodes (9, 13) or in the Waldeyer's ring (3) supports the concept that also these neoplastic disorders may be unicentric in origin. However, from our study it appears that more than 50% of cases spread early to non adjacent lymph node groups and to viscera or bones. This could be due to vascular invasion (13) although histopathologic studies are not yet available. Clinical and lymphographic studies (2, 3, 4, 5, 16) suggest that in a high percentage of cases these sarcomas may arise in lymphoid regions below the diaphragm (retroperitoneal nodes and gastrointestinal tract). Therefore they could spread early through the thoracic duct to distant non contiguous nodes and especially to the blood stream. This is especially true in children (5, 16). Furthermore in our material, with systematic gastric series involvement of the stomach (sometimes confirmed at surgery) was particularly frequent in patients with disease limited to the pharynx or spread only to the cervical nodes. This suggest that at least in some of these patients the disease may arise at the same time in the Waldeyer's ring and in the gastrointestinal tract (3).

The results of our investigation on the preferential sites of involvement and the possible mode of spread in malignant lymphomas lead to two practical conclusions. The first re-emphasizes that bilateral foot lymphography, although not exempt from occasional problems of interpretations, remains today the most appropriate diagnostic tool to explore the retroperitoneal nodes. Therefore it should be performed routinely in all patients with biopsy-proved diagnosis of malignant lymphoma, no matter what the apparent primary onset and the initial extent of involvement appears to be. In case of equivocal evidence the exploration of the retroperitoneal space should be completed with pneumoretroperitoneum or with urography and cavography, and even through an exploratory laparotomy. Furthermore, x-ray examination of the gastrointestinal tract and gastroscopy should be performed in all patients with lymphoreticular sarcomas.

The second conclusion is the fact that as already emphasized by other authors (11, 12, 13, 14, 20) precautionary radiation therapy is more indicated in Hodgkin's disease than in

lymphoreticular sarcomas with primary lymph node onset. Among those sarcomas arising in the Waldeyer's ring prophylactic irradiation to the cervical nodes is indicated only in those patients in whom the disease, after exhaustive diagnostic evaluation, is found to be limited to the pharynx (1).

Summary

The authors studied the preferential sites of involvement as well as the mode of spread in untreated patients with malignant lymphomas of adults and children with primary onset in lymph nodes and in the Waldeyer's ring. Primary involvement in Hodgkin's disease was confined to lymph nodes and spleen in 99.5%. In lymphoreticular sarcomas there was a high rate of primary involvement of the Waldeyer's ring and of other extranodal sites. Besides the cervical regions lymph node involvement in Hodgkin's disease occurred predominantly in the mediastinum and in the para-aortic area, while in the lymphoreticular sarcomas mainly the axillary, iliac and inguinal regions were affected. The study of the mode of spread showed that in untreated Hodgkin's disease the number of cases with contiguous involvement was 66%, while in lymphoreticular sarcomas it was only 35%. Furthermore, after localized radiation therapy Hodgkin's disease had a higher (72%) tendency to recur in adjacent lymphoid regions than lymphoreticular sarcomas (45%). The retroperitoneal nodes and the stomach were rather frequently involved in patients with primary onset in the Waldeyer's ring. The results of this study have obvious therapeutic implications.

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Dr. Gianni Bonadonna, Dr. A. Banfi, Dr. G. Carnevali, Dr. F. Fossati-Bellani, Istituto Nazionale Tumori, Via Venezian 1, Milano - Italy