Endolymphatic Radiotherapy in Malignant Lymphomas — Long Term Results*

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The lymphatic vessels of the dorsum of the foot have been used in the past seven years to inject with and without contrast material (Lipiodol, Ethiodol) different radioactive isotopes (^{131}I, ^{198}Au, ^{90}Y) in the attempt to treat metastatic retroperitoneal adenopathies of lymphomatous or carcinomatous type (1, 8, 12, 13, 15, 16, 17, 19, 26, 27, 28, 31). Due to the relatively simple technique (25, 35) the intralymphatic injection of radioactive isotopes has been tried first by *Chiappa* in Milan in 1961 (11) and pursued by numerous investigators throughout the world. In our Institutes since September 1961 a large program has been undertaken with the administration of Lipiodol fluid ^{131}I (endolymphatic radiotherapy) in malignant lymphomas, chronic lymphatic leukemia, carcinomas of testicle, cervix, prostate, urinary bladder, rectum and malignant melanoma (8, 11, 12, 13, 15, 16, 17, 27).

Special attention has been focused on malignant lymphomas and after two and a half years of experimental clinical trials, a therapeutic program including the systematic administration of Lipiodol ^{131}I to all cases with histologically proved malignant lymphomas was started in *May* 1964 (3, 4). Since very high tissue doses can be delivered with endolymphatic radiotherapy (1, 10, 19, 20), the rationale for its systematic use in all lymphoma patients regardless of the clinical stage, was to see whether the administration of Lipiodol ^{131}I could satisfactorily meet the requirements of radical, palliative and prophylactic radiotherapy. The principal aim of this report is to analize the experience achieved with 340 malignant lymphomas treated with different doses of Lipiodol ^{131}I and to discuss the advantages, limits and side effects of endolymphatic radiotherapy. Since a systematic treatment with high doses of Lipiodol ^{131}I has been started in *May* 1964, only the three year survival rate is presently available.

Material and Methods

This report includes only patients studied after admission to the National Cancer Institute of Milano, from September 1961 to December 1967.

Table 1 reports the number of patients treated per year with minimal and maximal doses of Lipiodol ^{131}I. The injection of radioactive contrast material has been performed according to the technique proposed by *Kinmonth* for diagnostic lymphography (21)

* Presented at the second international congress of lymphology (March 15–20, 1968, Miami, Fla. U.S.A.).

and described by *Chiappa* and co-workers for endolymphatic radiotherapy in several papers (11, 12, 13, 15, 16). The total amount of contrast material never exceeded the volume of 10 cc per each foot in adults and 5 cc in children. Every case was accurately evaluated 24 hours after the injection of contrast medium through postero-anterior, lateral and oblique films. Follow-up films were taken every 2 to 6 weeks according to the various clinical situations as long as the contrast material was visible on the radiographs (average 5–8 months, occasionally even after 2 years of cure).

Table I Number of patients treated per year with minimal and maximal doses of Lipiodol ^{131}I administered.

Year	Hodgkin's disease		Lymphoreticular sarcomas	
	No. cases	Doses (mC/cc)	No. cases	Doses (mC/cc)
1961	4	0.4 – 1.7	2	0.2 – 0.8
1962	25	0.5 – 2.0	24	0.6 – 1.8
1963	15	1.7 – 2.8	10	1.4 – 2.5
1964	20	2.0 – 2.5	27	1.9 – 2.5
1965–67	114	2.5	99	2.5
Total	178		162	

Re-injection of Lipiodol ^{131}I was carried out in 30 patients (20 with Hodgkin's disease and 10 with lymphoreticular sarcomas). The re-injection was performed because a retroperitoneal node recurrence was suspected or evident on the follow-up films, or when systemic signs and symptoms occurred without clinical and/or radiological evidence of lymphomatous lesions.

Results

Staging advanced due to abnormal lymphogram

All patients with the exception of those with primary involvement of stomach, bowel, bone, skin and other extranodal tissues, have been classified according to the new four-stage clinical classification proposed in 1965 for Hodgkin's disease (30); of 340 radioactive lymphograms 239 were carried out as part of the initial clinical evaluation (225 in patients with primary lymph node involvement and 14 with primary extranodal onset), while 101 were reassessment studies carried out during the experimental phase of endolymphatic radiotherapy. Although the distinction between initial and reassessment lymphograms has been made in a recent review (8) in this report for practical purposes we have pooled together all patients with primary lymph node involvement (table 2). The results of this study confirm that the number of silent retroperitoneal adenopathies is considerable in a malignant lymphoma classified on a clinical basis as stage I_1 and that the percent of staging advancement is progressive from stage I_1 to stage II in Hodgkin's disease, while lymphoreticular sarcomas behave more irregularly. This is due to their different mode of spread (6, 7, 29).

Table 2 Abnormal lymphograms performed from 1961 to 1967 with Lipiodol ^{131}I in 326 malignant lymphomas with primary lymph node involvement.

Clinical staging	Hodgkin's disease			Lymphoreticular sarcomas		
	No. cases	Abnormal lympho-grams	Staging advance-ment (%)	No. cases	Abnormal lympho-grams	Staging advance-ment (%)
I_1	36 (1)*	17	47	28 (1)	14	50
I_2	30 (1)	16	53	21 (1)	8	38
II	63 (2)	44	69	24 (1)	15	62
III	16	12		41	35	
IV	32	27		35	29	
Total	177	116		149	101	

* In brakets the number of patients with primary onset below the diaphragm.

Table 3 reports the abnormal initial radioactive lymphogram in 14 malignant lymphomas with primary extranodal involvement. Pathological nodes were detected in the para-aortic area in $^3/_5$ of the cases with gastric lymphoreticular sarcoma, in the iliac chains, in $^2/_3$ of the cases with lymphosarcoma of the buttock and in one primary lymphosarcoma of the parotid.

Table 3 Abnormal lymphograms performed from 1961 to 1967 with Lipiodol ^{131}I in 14 malignant lymphomas with primary extranodal involvement.

Primary site	Hodgkin's disease		Lymphoreticular sarcomas	
	No. cases	Abnormal lymphograms	No. cases	Abnormal lymphograms
Stomach			5	3
Small intestine			1	–
Skin			3	2
Bone	1	–	3	–
Parotid			1	1
Total	1	–	13	6

Effects of Lipiodol ^{131}I on the Lymphoid Tissue

The most important effect from the radiological point of view is a progressive and sometimes dramatic reduction in size of the opacified nodes. This node shrinkage occurred in various grades in practically all treated patients.

Obviously, it was more evident with high doses of radioactive material and more rapid when the adenopathies were adequately filled with the dye.

Our histopathologic experience is based on the evaluation of 10 autopsy cases and of 4 patients in whom one retroperitoneal node chain was removed during exploratory laparotomy about 3 weeks after the administration of Lipiodol ^{131}I (8). In none of these 14 cases there was a complete destruction of normal and pathologic lymphoid tissue throughout the retroperitoneal chains by endolymphatic radiotherapy. In all autopsied cases the disease was widespread. In 5 cases the predominant findings were of gross and microscopic node regression associated with active signs of disease. In the other 5 cases, a large number of lymph nodes showed no alterations secondary to Lipiodol ^{131}I because the lymphoma cells had completely replaced the normal lymphoid tissue.

Abnormal Distribution of Radioactive Contrast Material

In Table 4 the factors are listed which prevented in our 340 patients the performance of a radioactive lymphogram and the obstacles to obtain homogeneous and adequate distribution of Lipiodol ^{131}I throughout the inguinal and retroperitoneal nodes.

Table 4 Factors preventing a complete and homogeneous distribution of Lipiodol ^{131}I throughout the inguinal and the retroperitoneal node chains.

Factors	Lymphnode chains	Hodgkin's disease (178 patients)	Lymphoreticular sarcomas (162 patients)	Total patients
		No findings (R+L chains)	No. findings (R+L chains)	
Lymphography unfeasible in one foot		8	11	19
Extravasation in soft tissues		3	2	5
Lymphatic block	Iliac		2	6
	Para aortic	1	3	
By-pass	Iliac	3		3
	Inguinal		2	
Abnormal Lipiodol/lymphnode ratio	Iliac	3	4	
	Para aortic	28	34	79 (23%)
	All chains	5	9	
Total		51	67	112 (33%)

The lack of adequate filling of the para-aortic nodes seems to be far the most important obstacle to obtain a homogeneous distribution of the dye throughout the retroperitoneal node chains. This fact is particularly important in the treatment of Hodgkin's disease where the para-aortic lymph nodes are more often involved than the iliac, while the reverse occurs in lymphosarcoma and in reticulum cell sarcoma (6, 7). For this reason, in a large number of patients (about 50%) with abnormal inadequately opacified lymph nodes, the treatment was completed with external irradiation (^{60}Co).

Recurrence after ^{131}I

Table 5 reports the number of patients per stage with inguinal and retroperitoneal node recurrence or progression at different lengths of time after endolymphatic radiotherapy. A total of 40/295 patients followed for a minimum of 2 months (13%) had a relapse or new manifestations of disease in the nodal chains injected with ^{131}I. The majority of recurrences occurred within 3 years from the administration of radioactive contrast material. All patients received one or more courses of radical, palliative and prophylactic radiation therapy to the lymphoid areas above the diaphragm. Those in stages II, III and IV were also treated with different chemotherapeutic agents.

Table 5 Number of patients with recurrence or progression in the retroperitoneal chains treated with Lipiodol ^{131}I.

Type of lymphoma	Stage	Months after Lipiodol ^{131}I						
		0–6	7–13	14–20	21–27	28–34	35–41	60
	I_1					1		
	I_2				1			
Hodgkin's disease	II[2]							
	III[2]	2	3	3	3	4	1	
	IV[2]	1		1	1			
	I_1						1	
	I_2	1[1]						
Lymphoreticular sarcomas	II[2]		1	1[1]				
	III[2]	2	6	3		1		1
	IV[2]					1		
other primary sites			1					
Total: 40 patients		6	11	8	5	7	2	1

[1] Primary onset of disease below the diaphragm.

[2] Patients in these stages had one or more courses of chemotherapy and of external radiation therapy above the diaphragm.

In table 6 is listed the number of recurrences or progressions in the 40 patients. The relapses are reported in relation to the different lymph node chains, the initial lymphographic findings and the doses of Lipiodol ^{131}I administered. As it can be seen in 39 patients, a total of 44 recurrences were encountered (4 patients had a recurrence in the inguinal and iliac nodes at the same time). From this analysis it appears that the recurrence occurred mostly in the preferential sites of involvement for each type of lymphoma (in the para-aortic nodes for Hodgkin's disease and in the inguinal-iliac chains for lymphoreticular sarcomas), in adequately dye-filled adenopathies and in patients treated with high doses of Lipiodol ^{131}I.

Table 6 Number of recurrences or progression found in 40 patients and reported in relation to the different lymph-node chains, the initial lymphographic findings and the doses of Lipiodol ^{131}I.

Type of lymphoma	Lymphnode chains	No. recurrences	Lymphnodes at first lymphogram normal		abnormal		Doses of Lipiodol ^{131}I (mC/cc)		
			AF	IF	AF	IF	0.4–0.9	1.0–1.9	2.0–2.5
Hodgkin's disease	Inguinal	1			1				1
	Iliac	3	1		2			2	1
	Para aortic	15	3		10	2	1	2	12
	All chains	2			2		1		1
		21	4		15	2	2	4	15
Lymphoreticular sarcomas	Inguinal	10	1		8	1		2	8
	Iliac	8			6	2	2	1	5
	Para aortic	2	2						2
	All chains	3	1		2		2	1	
		23	4		16	3	4	4	15
Total		44	8		31	5	6	8	30

AF = Adequately filled with Lipiodol ^{131}I; IF = inadequately filled with Lipiodol ^{131}I.

Table 7 Side effects and complications secondary to endolymphatic radiotherapy in 340 malignant lymphomas.

Side effects and complications	Hodgkin's disease	Lymphoreticular sarcomas	Total
Extravasation necrosis	2	1	3
Lymphangitis	1	2	3
Hyperthyroidism	1		1
Hepatic insufficiency	2		2
Pulmonary insufficiency	2		2
Hemolytic anemia	1		1
Amenorrhea	12/69*	2/31*	14/100

* Menstruating females.

Side Effects and Complications

The side effects and complications observed in 340 cases after endolymphatic radiotherapy are listed in table 7. Permanent amenorrhea occurred almost always in females with very large iliac adenopathies (14/100 menstruating females).

In two patients with hepatomegaly, probably secondary to lymphomatous involvement of liver jaundice with high direct and indirect bilirubin, as well as high serum alkaline phosphatase, SGOT and SGPT occurred 10 and 13 days respectively after endolymphatic radiotherapy (2.5 mC/cc). They eventually died at home with the classical clinical picture of massive hepatic necrosis. In another group of patients without apparent signs of hepatic disease the liver function tests were studied during 3 weeks after the injection of Lipiodol ^{131}I. A temporary increase of direct bilirubin and alkaline phosphatase as well as a decrease of free colesterol and coline-esterase was observed (8).

Although pulmonary embolisation (9) was observed in several patients especially in presence of normal retroperitoneal nodes, no patients without pulmonary disease had signs or symptoms of respiratory insufficiency. On the other hand 2 patients with Hodgkin's disease involvement of both lungs complained of severe dyspnea, cyanosis and dry cough. One of these patients died within a week because of superimposed bronchopneumonia, while in the other patient, the symptoms of respiratory insufficiency gradually disappeared within ten days.

Scintigraphic studies have demonstrated that there is an accumulation of Lipiodol ^{131}I in the lungs and liver in the large majority of patients. This accumulation which is particularly considerable at the level of pulmonary tissue (table 8) decreases rapidly within 2 to 5 weeks and is unremarkable after the end of the second month (2).

Table 8 Maximal concentration, effective half-life of Lipiodol ^{131}I as well as the absorbed dose by different organs and tissues. (Data kindly provided by the Section of Physics, National Cancer Institute, Milano.)

Organs and tissues		CO (%)	Te (days)	Rads/mC
Lymphnodes		22.5	9.4	842
	Inguinal	5.3	10.1	
	Iliac	9.4	10.5	
	Para aortic	12.9	7.0	
Lungs		25.0	3.9	10.0*
Liver		2.1	8.2	2.0
Spleen		1.2	5.4	7.7
Thyroid		0.9	6.5	48.1

* For the lungs only β radiations have been calculated.

Histologic examinations of lungs and liver carried out after post mortem examination in 10 cases failed to demonstrate signs of postirradiation damages.

In one patient with Hodgkin's disease within 24 hours from the injection of Lipiodol ^{131}I (2.5 mC/cc) jaundice with elevated indirect bilirubin, severe anemia and reticulocytosis occurred. Coomb's test was negative. These findings compatible with the diagnosis of hemolytic anemia were associated with high blood levels of ^{131}I for about one week while the retroperitoneal nodes were poorly opacified.

Survival

The 3 year survival rate is now available for 53 patients (26 with Hodgkin's disease and 27 with lymphoreticular sarcomas) with stage III (fig. 1). These patients were obviously treated above the diaphragm with ^{60}Cobalt and received one or more courses of chemotherapy. None of the patients received external radiation therapy below the diaphragm.

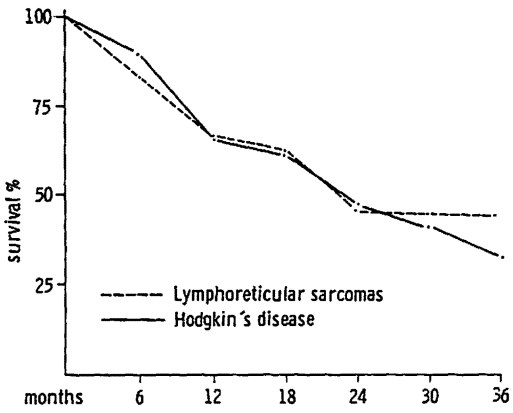

Fig. 1 Three year survival rate in stage III malignant lymphomas (Hodgkin's disease 26 patients, lymphoreticular sarcomas 27 patients) treated with external and endolymphatic radiotherapy and chemotherapy.

Discussion

The widespread use of lymphography in the different clinical stages of malignant lymphomas, as exhaustively reported in several papers (14, 18, 22, 24, 25, 33), led to fundamental reassessment in the therapeutic programs (32). Our lymphographic studies confirm that a considerable percentage of patients reveal abnormal lymphograms when the disease seems localized (stage I_1 and I_2) or moderately diffused (stage II). The presence of retroperitoneal adenopathies should be taken therefore into consideration at the moment of therapeutic decision (5).

The treatment for Hodgkin's disease localized above the diaphragm seems to be practically standardized in the mantle port. Radical doses of radiotherapy with curative intent, are delivered to all involved tissues while prophylactic or precautionary irradiation is given to adjacent clinically uninvolved lymphoid regions. Due to the fact that the large majority of lymphoreticular sarcomas do not spread like Hodgkin's disease through contiguous lymphatic areas prophylactic radiation therapy is usually withheld in these types of diseases.

The crucial point in the proper treatment of malignant lymphomas and particularly of Hodgkin's disease, remains stage III. At least, five more years will be required before it will be clear that extensive irradiation in continuity to all lymph node-bearing areas above and below the diaphragm increases appreciably the survival rate as in the earlier stages.

Seven years ago we began a clinical trial which included the systematic administration of endolymphatic radiotherapy to all patients with malignant lymphomas in the attempt to control the retroperitoneal extentions (3, 4). For radiologically negative retroperitoneal nodes, endolymphatic radiotherapy has been considered as a prophylactic treatment.

Although the patients presently available for longterm study are mainly those with far-advanced disease (stage IIIB and IV) requiring chemotherapy, our data must be

critically analyzed when endolymphatic radiotherapy is considered as a potential radical radiotherapeutic tool for the inguinal iliac and para-aortic nodes. In fact, one third (112/340) of the patients injected with radioactive contrast material could not obtain a uniform adequate filling of the lymph chains and consequently Cobalt teletherapy had to be given to about 50% of cases with inadequately opacified adenopathies. Therefore endolymphatic radiotherapy does not seem to meet the modern criteria of radical treatment particularly at the level of the para-aortic area where the abnormal lymph nodes above LII are often poorly opacified. This explains why the highest number of recurrences in Hodgkin's disease occurred at the level of the para-aortic nodes.

Furthermore, the fact that adequately (and even inadequately) dye filled lymph nodes show a rapid reduction in size in the large majority of patients does not mean that a radical treatment has been achieved. In fact our limited but convincing histopathologic material shows that, although Lipiodol ^{131}I at the dose of 2.5 mC/cc can produce a permanent destruction of lymphoid tissue, in presence of multiple large retroperitoneal adenopathies, a certain number of nodes, which varies from case to case, escapes entirely from the radiation effects, because they do not fill with the radioactive contrast material. Furthermore, within the same node, the irregular distribution of Lipiodol ^{131}I may produce a partial destruction of normal and/or pathologic lymphoid tissue leaving intact lymphoma cells from which a progression of disease will eventually ensue. These morphological findings explain the mechanism of recurrences.

The total number of recurrences is not high (13%). Nevertheless, it is significant that 15/21 developed only in the para-aortic area in Hodgkin's disease and respectively 18/23 in the inguinal-iliac nodes, i. e. where, being these regions among the preferential sites of involvement for each disease (6, 7), large adenopathies are usually present. On the contrary, only 8 patients with negative nodes at the moment of radioactive lymphography, developed a recurrence or progression. This indicates that endolymphatic radiotherapy could be of value as a prophylactic treatment, although at least five additional years will be needed before this statement will be supported by statistical evidence.

The principal side effect is represented by the Lipiodol ^{131}I into the lungs, thyroid and other tissues (2, 10, 20, 23); with the exception of two patients with lung-involvement, no signs of pulmonary insufficiency or mixedema, nor radiological or histological evidence of lung fibrosis were seen. The same applies to the liver.

In conclusion, the analysis of our large case material provides sufficient evidence to state that endolymphatic radiotherapy because of its frequent inadequate distribution should not be considered as a radical therapeutic tool for retroperitoneal adenopathies in stage III malignant lymphomas, although radical doses can be administrated to the level of single lymph nodes. Since side effects are minimal, endolymphatic radiotherapy can be employed as a prophylactic treatment in stage I and II, although further long-term studies are required; in our present program for the treatment of malignant lymphomas, the administration of Lipiodol ^{131}I is still carried out in all patients, but only with the purpose to irradiate prophylactically the retroperitoneal node chains, while if retroperitoneal adenopathies are present, external radiation therapy with radical doses is given in addition to endolymphatic radiotherapy (5).

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