特別掲載

Clinical Study on Radiotherapy for Malignant Lymphoma Originating in the Head and Neck

By

Taiichi Miyazaki

Department of Radiology Hiroshima University Medical School
(Department Chief: Professor Tsuyoshi Koyama)

頭頸部原発の悪性リンパ腫に対する放射線治療に関する臨床的研究

広島大学医学部放射線医学教室（主任　小山豪教授）
宮　崎　泰　一

（昭和43年9月6日受付）

頭頸部に原発した悪性リンパ腫は放射線感受性が高く，腫瘍縮少に要する線量は，他の悪性腫瘍に比較すると少線量で充分可能である．しかしその予後は楽観すべきものではなく，原発巣のみの照射では早晩遠隔転移を来し，死の転帰を来す症例が大部分である．

著者は，頭頸部に原発した悪性リンパ腫をPetersの分類に従い3期に分類し，この症例に対し手，足にリンパ管造影を施行し，各時期における症例に対する鎖骨上下窩，腋窩，後腹膜，骨盤内リンパ節に対する転移率をX線学的に求めた．頸部までに限局した1期，2期，症例に対して頸部リンパ節群を含んだ原発巣照射及び鎖骨上下窩，縦隔洞に対し系統的予防照射を行い，原発巣のみに対して行つた照射群との間の予後を比較した．更に系統的予防照射が全身的に及ぼす影響を容積線量と各種化学検査との関係で検討し，1，2期症例の様に全身状態の良好な症例では，安全に且つ充分行い得る事を確信し，更に第3期症例に対しては，上記照射以外に傍腹部大動脈領域，骨盤内，鼠径部に対し系統照射を行い得るかにつき，若干の経験を述べ，頭頸部原発の悪性リンパ腫に対する放射線治療の可能性につき検討した．

Introduction

Malignant lymphoma is essentially highly radiosensitive, and a small dose is sufficient for tumor regression as compared with other malignant tumors.

Its prognosis, however, is not necessarily optimistic, and even in very early cases originating in the head and neck, it usually takes a fatal course with the development of distant metastases within six months to one year from treatment.

Historically, during the first part of the 20th century when radiation equipment had not yet been sufficiently developed, a small dose of 1000 R or less was delivered to only the primary lesion.

Subsequently, with the development of various types of radiation equipment, different methods of exposure have been devised, and Peters and Middlemiss (1) reported in 1958 that ideally the adjacent lymphatics should also be irradiated in addition to the primary lesion.

Henry S. Kaplan (2) confirmed this view, and further contributed to the improvement of the 5-year survival rate by the use of super-voltage equipment.

There still, however, is no agreement on the pathogenesis of malignant lymphoma, and it has been postulated to be of unicentric or multicentric origin.

If, inspite of this lack of agreement, it is assumed to be of unicentric origin, this would mean in combination with its high radiosensitivity that local radiation therapy is not only meaningful but truly appropriate.

If, on the other hand, it were of multicentric origin, local radiation therapy for malignant lymphoma would be less significant, and systemic treatment by chemotherapy, etc. must be relied upon.

Radiotherapy may perhaps be entirely meaningless.

However, at the present time, local radiation therapy for malignant lymphoma is widely recognized as being more effective than any other method with a higher survival rate.

In view of this, I believe that malignant lymphoma is of unicentric origin and that it presents a multicentric appearance due to the development of metastatic lesions to other regions. Accordingly, I have used radiation therapy and also have made some improvements in the method of irradiation for this condition.

The histological picture of malignant lymphoma is variable, and Kuramitsu et al. (3) have made a classification into four types: reticulum-cell sarcoma, lymphosarcoma, Hodgkin's disease and giant follicular lymphoma.

Custer and Bernhard (4) and others maintain that since all lymphomas develop from usual mesenchymal stem cells, these types tend to occur in combination with transition from one type to another.

In actual practice, it frequently is difficult to distinguish these four types on biopsy and therefore, I treat all four types collectively as malignant lymphoma.

For the treatment of malignant lymphoma originating in the head and neck, I have replaced previous methods of irradiating only the primary lesion by a method in which extensive exposure to the primary lesion is delivered by a large field including the contiguous lymphatics for systematic prophylactic irradiation to areas where metastases are likely to occur.

This method was previously described in a preliminary report by the author (5), and has been found to be effective for cases in stages 1 and 2. Further considerations have been given to the method, results and side effects, and will be reported here.

Subjects

The subjects included in this paper are patients with malignant lymphoma originating in the head and neck who had been treated since 1963 by radiation from a Toshiba cobalt 60, 2000 Cui teletherapy unit at the Radiology Department of Hiroshima University Medical School Hospital, and in whom six or more months had elapsed since treatment.

These patients were 41 out of our 440 cases (9.3%) of all tumors treated by radiation during this period.

Furthermore, they correspond to 25% of our 158 cases of malignant tumors of the head and neck.

The patients were grouped in a number of ways for analysis.

1. Classification by age

Fig. 1. Age Distribution of Malignant Lymphoma originated in Head & Neck.

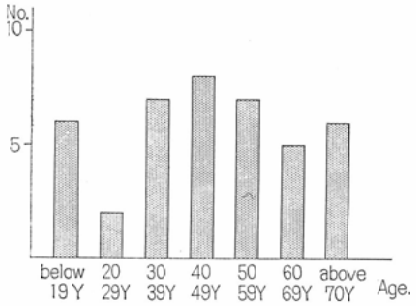


Table 1. Pathological classification of malignant Lymphoma.

Reticulum cell sarcoma.	36	No.
Lymphosarcoma.	2	
Hodgkin's disease.	2	
Giant follicular Lymphoma.	1	
Total.	41	No.

The patients were distributed over a wide age range, from a minimum of age 1 year to a maximum of 77 years, but as shown in figure 1, there was a peak at ages 40—49 which is in agreement with the report of Otake (6).

The fewer number of patients in the 20-year age group in comparison with children age 19 and less is the same as in the report of Kaneda (7).

2. Classification by sex

No difference was seen in frequency by sex with 21 males and 20 females, but other reports seem to indicate a slightly greater number among males.

3. Histological classification

As shown in table 1, reticulum-cell sarcoma predominated with 36 cases (87%).

Watanabe et al. (8) report that reticulum-cell sarcoma predominates in Japan which agrees with my results, but the statistics in various other countries (9) (10) show the majority to be Hodgkin's disease with very few cases of reticulum-cell sarcoma.

Although there may be regional or racial differences, one of the reasons suggested for this discrepancy is the difference among pathologists in different countries (11).

4. Classification by primary lesion

Table 2. Primary Focus of malignant Lymphoma.

Epipharynx.	9	No.
Mesopharynx.	18	
Nasal sinus.	4	
Oral cavity.	2	
Neck.	5	
Others.	3	
Total.	41	No.

As mentioned above, the author believes malignant lymphoma to be of unicentric origin, and the term primary lesion will be used. A classification of the primary lesion by site is shown in table 2.

Tumor originating in the middle larynx was the most frequent with 18 cases (43%). This was followed by nine cases (22%) of upper laryngeal tumor and five cases (12%) of primary tumor of the cervical lymph nodes. The greater majority originated in the upper and middle laryngeal region where in general most undifferentiated tumors occur.

The remaining patients were rare instances of tumor having primary lesions in the mandible, lacrimal gland or sphenoid sinus.

5. Classification by stage of disease

Any attempt to determine the extent of lymphoma and stage of the disease just by simple laboratory tests at time of initial examination is very dangerous from the standpoint of therapy, and may even lead to a mistake in the method of treatment.

Furthermore, at present when even the T.N.M. classification (12) has not yet been decided upon, the classification of malignant lymphoma by stage of disease is difficult. However, the author has used the method of Peters and Middlemiss (1) to classify the stage of malignant lymphoma of the head and neck as shown in table 3.

Table 3. Stage Distribution of malignant Lymphoma by Peters & Middlemiss.

Stage 1.	refers to disease localized to one region.
Stage 2.	to disease localized to two or more contiguous region.
Stage 3.	to generalized disease.

First, the findings of physical examination were recorded followed by lymphography from the dorsum of the hands and feet to determine the presence of any metastasis to the supra- and infra-clavicular, axillary, retroperiotoneal or pelvic lymph nodes. The classification of the stage of malignant lymphoma was based upon these findings.

Metastasis to such organs as the liver, spleen, etc. which are difficult to visualize were excluded from this consideration.

In table 4, the patients are classified by stage of disease according to the above method.

Table 4. Stage Distribution of malignant Lymphoma.

Stage 1.	9	No.
Stage 2.	22	
Stage 3.	10	
Total.	41	No.

It is seen that 22 cases (54%) were stage 2, followed by 10 cases (24%) in stage 3 and nine cases (22%) in stage 1.

In two or three patients, the findings of physical examination appeared to be stage 1 or 2, but their lymphograms revealed extensive metastasis to the retroperitoneal or pelvic lymph nodes, and thus were advanced to as far as stage 3.

Lymphography

As indicated in the report of Kaneda et al. (7), autopsies have shown that metastases to the mediasti-

nal, retroperitoneal and pelvic lymph nodes usually occur with progress of malignant lymphoma resulting finally in death, but these metastases to the lymph nodes are frequently difficult to diagnose.

Visualization of the condition of the retroperitoneal and pelvic lymph nodes had not been possible until the clinical application of lymphography by Kinmonth (13) and the development of oil contrast media.

Subsequently, many reports have been published on the lymphographic findings in malignant lymphoma, and detailed roentgenographic considerations have been made regarding the structure and size of lymph nodes by Schwary (14), Davidson et al. (15), Koehler (16) and Takahashi. (17)

The author (18) has obtained lymphograms from the dorsum of the hands and feet in malignant lymphoma originating in the head and neck to determine the presence of any metastasis to the supra and infra-clavicular, axillary, retroperitoneal and pelvic lymph nodes, and compute the proportion of metastases in each stage of the disease.

Stereoscopic radiograms at a film-focus distance of 1 meter were obtained of the axillary, pelvic and

Fig. 2. Lymphography of retroperitoneal & intra pelvic region.

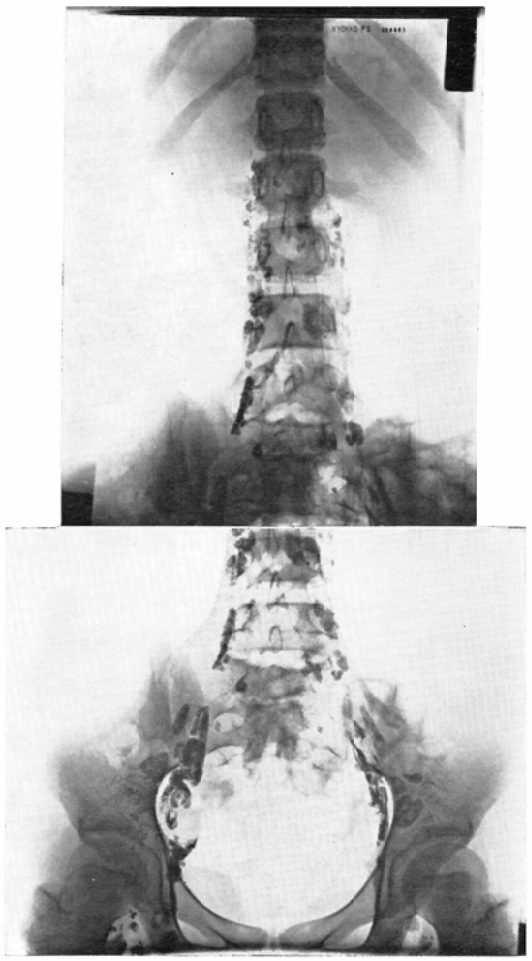
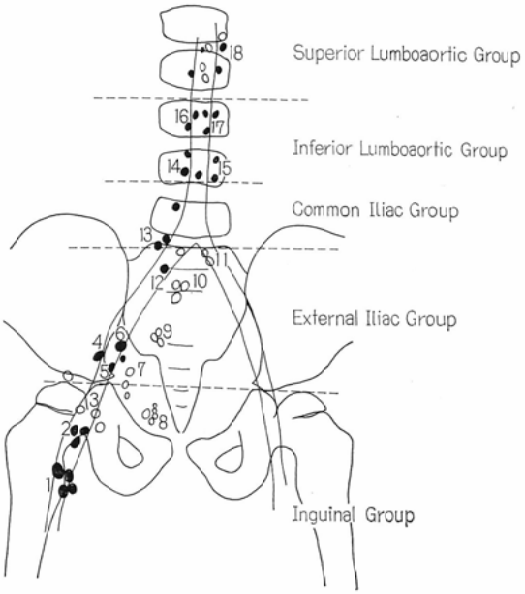


Fig. 3. Anatomical scheme of Lymphnode in Retropertoneal and pelvic region.



1 Lnn. inguinales superficiales inferiores. 2 Lnn. inguinales profundi. 3 Lnn. inguinales superficiales superiores. 4 Lnn. iliaci externi laterales superiores. 5 Lnn. iliaci externi laterales profundi. 6 Lnn. iliaci externi mediales. 7 Lnn. obturatorii. 8 Lnn. glutaei inferiores. 9 Lnn. glutaei superiores. 10 Lnn. sacrales 11 Lnn. subaortici. 12 Lnn. iliaci communes mediales. 13 Lnn. iliaci communes laterales. 14. Lnn. lateroaortici dextri. 15 Lnn. lateroaortici sinistri. 16 Lnn. praeaortici. 17 Lnn. retroaortici. 18 Lnn. aortici

lumbar regions for a stereoscopic examination of the individual lymphatic vessels and lymph nodes to confirm the state of overlapping and the relation in location of lymph nodes.

In addition, the area of each lymph node on the anterior views were measured with a planimeter to determine the size beyond which should be considered abnormal. The inner structures of the lymph nodes also were classified into a number of types and used in association with the size for the radiological evaluation of metastasis.

Lymphograms obtained for other reasons on non-malignant lymphoma patients were used as controls.

1. Lymphography of lower extremities

Lymphograms were obtained by the original method of Kinmonth using a needle devised by the author (18) to introduce 7 cc of Lipiodol Ultra fluid into the lymphatic vessels on the dorsum of each foot with an injection time of 1—1.5 hours. Radiograms of the pelvic, lumbar and thoracic regions were taken immediately after and 24 hours after injection at a focus-film-distance of 1 meter. In the pelvic and lumbar regions, stereoscopic views were obtained by moving the tube 10 cm.

The area of the lymph nodes on these radiograms were measured with a planimeter separately for the para-aortic, external iliac and inguinal groups.

Measurements were obtained on 1,188 nodes of 28 patients with malignant lymphoma and 689 nodes of 19 patients with non-malignant lymphoma.

The lymph nodes thus measured were classified according to 0.2 cm^2 steps. Table 5 shows the change in proportion of lymph nodes in each area size grouping among malignant lymphoma and non-malignant lymphoma patients.

Table 5. Percentage Distrtbution of Lymphnodes at retroperitoneal and pelvic region.

	Para Aortal Ly.		External iliac Ly.		Inguinal Ly.	
Sq. cm^2	Non malig Ly.	Malignant Ly.	Non malig Ly.	Malignant Ly.	Non malig Ly.	Malignant Ly.
0.00–0.20	33.3	26.7	39.1	19.2	30.3	18.6
0.21–0.40	25.2	18.3	20.2	15.1	16.7	17.3
0.41–0.60	18.1	15.2	19.0	13.6	17.4	10.9
0.61–0.80	9.3	12.9	10.9	9.7	7.5	12.2
0.81–1.00	4.2	8.2	7.2	9.7	5.3	7.6
1.01–1.20	3.8	6.5	4.8	6.7	5.3	4.2
1.21–1.40	2.5	3.9	4.4	6.0	3.8	2.1
1.41–1.60	1.3	2.8	2.0	3.0	3.8	3.0
1.61–1.80	0.6	1.9	2.4	3.9	2.2	2.5
1.81–2.00	0.3	1.2	2.8	2.4		2.1
2.01–2.20		0.2	1.0	1.0	1.5	4.6
2.21–2.40		0.6		0.6	1.5	7.1
2.41–2.60		0.2		0.8	1.5	1.3
2.61–2.80				0.63		1.7
2.81–3.00		0.2		0.21		0.4

Akisada (19), Takahashi (20) and others have measured the maximum diameter of each lymph node on lymphograms in the comparison of malignant lymphoma and normal patients, and from their results consider a maximum diameter of 2.4—2.5 cm or more to be positive for metastasis.

Since the lymph nodes on lymphograms are round or oval and even normal lymph nodes frequently

are oblong, I feel that the size of the lymph node cannot be expressed accurately just by the maximum diameter. Therefore, as mentioned above, the area of the nodes on the anterior views were measured with a planimeter.

Whenever the lymph nodes were difficult to distinguish because they overlapped each other in double or triple layers, stereoscopic films were examined under a stereoscopic viewer to delineate the margins of the lymph nodes.

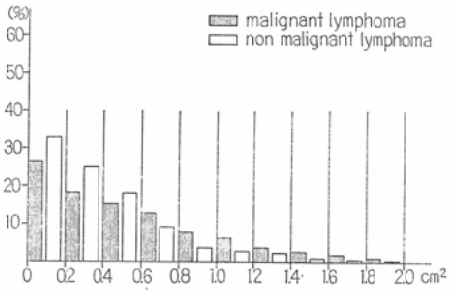
a) Para-aortic lymph nodes

The common iliac group located between the promontorium to the lower edge of the fourth lumbar vertebra, the inferior lumboaortic group extending to the upper edge of the third lumbar vertebra and the superior lumboaortic group which ascends further to the cisterna chyli were collectively considered as para-aortic lymph nodes.

Measurements were obtained in this region on 487 nodes of malignant lymphoma patients and 309 nodes of non-malignant lymphoma patients for a total of 796 nodes.

In the classification of the area of the lymph nodes shown in table 5 and figure 4, those 0.00—0.20 cm² in size accounted for about 30% in both groups of patients with slightly more in the non-malignant lymphoma group.

Fig. 4. Percentage Distribution of Lymphnode at Retroperitoneal Region



The number of lymph nodes gradually decreases with increase in size but the degree of decrease is more marked in the non-malignant lymphoma patients.

Thus, beyond 0.60 cm² the proportion seen in malignant lymphoma cases exceeds the non-malignant lymphoma group.

b) External iliac lymph nodes

These lymph nodes are distributed downwards from the promontorium and located midway along a line connecting the pubic tubercle with the anterior superior iliac spine. Measurements were obtained on 464 nodes of malignant lymphoma patients and 268 nodes of non-malignant lymphoma patients for a total of 732 nodes.

The proportion of nodes in each area size group is shown in table 5 and figure 5.

Except for the large lymph nodes of the lateral retrofemoral group, those 0.61 cm² or larger are more numerous among malignant lymphoma patients as noted previously in the para-aortic chain.

c) Inguinal lymph nodes

These lymph nodes are located below the line connecting the pubic tubercle with the anterior superior

Fig. 5. Percentage Distribution of Lymphnode at External iliac Region

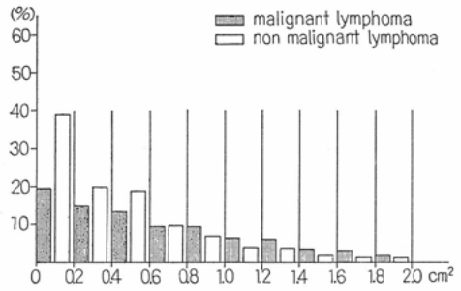
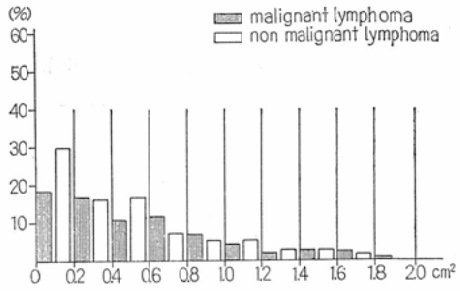


Fig. 6. Percentage Distribution of Lymphnode at Inguinal Region.



iliac spine. Measurements were obtained on 237 nodes of malignant lymphoma patients and on 132 nodes of the non-malignant lymphoma group for a total of 369 nodes.

The proportion of cases by classification of their area is shown in table 5 and figure 6.

In general, the lymph nodes are larger than in other areas because of the greater likelihood of repeated chronic inflammation in the lower extremities, but the proportion of those 0.61 cm^2 or larger is greater among the malignant lymphoma group as in the previous two areas.

From these observations on the classification of the lymph nodes in these three areas by size, it can be said that those 0.61 cm^2 or larger are more common among malignant lymphoma patients. In other words, lymph nodes 0.61 cm^2 or larger are more likely to be abnormal. However, this does not mean that lymph nodes 0.61 cm^2 or larger in size can be concluded as being positive for metastasis.

The determination of whether the node is abnormal or not requires a study of the internal structure.

On the other hand, lymph nodes less than 0.61 cm^2 size with no evidence of alteration of the internal structure may presumably be considered to be negative for metastasis.

Table 6. Classification of abnormal Lymphnode.

N; Normal Appearance.
F; Foamy Appearance.
- F1 foamy appearance slight.
- F2 foamy appearance moderate.
- F3 foamy appearance marked.

D; Filling Defect.
- D1 filling defects less than 1/3.
- D2 filling defects 1/3 to 2/3.
- D3 filling defects more than 2/3.

Among lymph nodes visualized on lymphograms, those 0.61 cm^2 or larger in size were classified by their internal structure in table 6. A typical case is illustrated in figure 7.

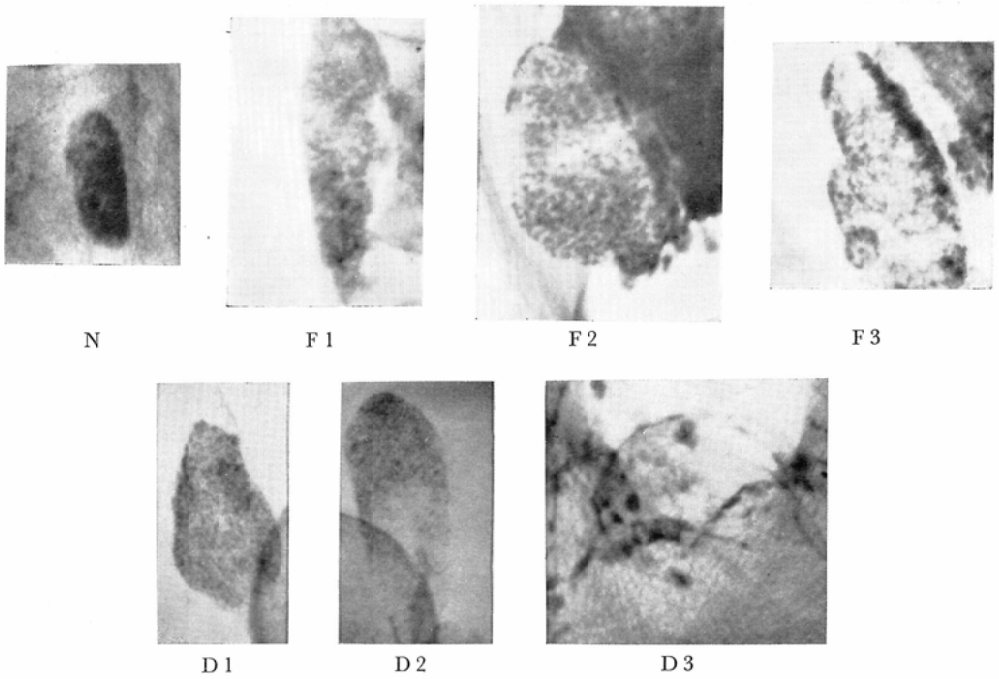
N: Normal appearance. Fine, dotted opacities of contrast media are seen uniformly distributed quite densely. This is the most typical pattern in normal lymph nodes.

F: Foamy appearance. Each contrast media opacity is slightly more coarse that in the above pattern, and the shape is irregular as well as the deposition with a foamy appearance.

These were further subdivided into types F1, F2 and F3 according to their degree.

D: Filling defect. In this condition, the contrast media opacity which should appear is absent in one part of the lymph node.

Fig. 7. Typical Roentgenograms for abnormal Lymphnodes.



This type was classified further into types D1, D2 and D3 according to the extent of the defect.

Of the above patterns, the author has considered N, F1 and D1 to be the normal types, and F2, F3, D2 and D3 as indicating abnormality (metastasis).

Lymph nodes 0.61 cm^2 or larger in size were selected and classified by this method for a total of 23 malignant lymphoma patients; 19 in stage 1 or 2, and 4 in stage 3.

The results are shown in table 7 with both the number and proportion in each class.

Table 7. Classification of Internal Architecture of Para Aortal & Pelvic Lymphnode above 0.6 cm^2

		N	F1	F2	F3	D1	D2	D3	
Stage 1 & 2	NO. of LY.	252	111	9	1	41	11	1	426
	(%)	59.0	26.1	2.1	0.2	9.6	2.6	0.2	100.0
Stage 3	NO. of LY.	40	52	40	39	11	9	7	198
	(%)	20.2	26.3	20.2	19.7	5.6	4.5	3.5	100.0

In stage 1 and 2, 59.0% presented the normal appearance, 26.1% were F1, and 9.6% D1. If F1 and D1 are assumed to be the normal pattern, 94.7% would be the so-called normal pattern.

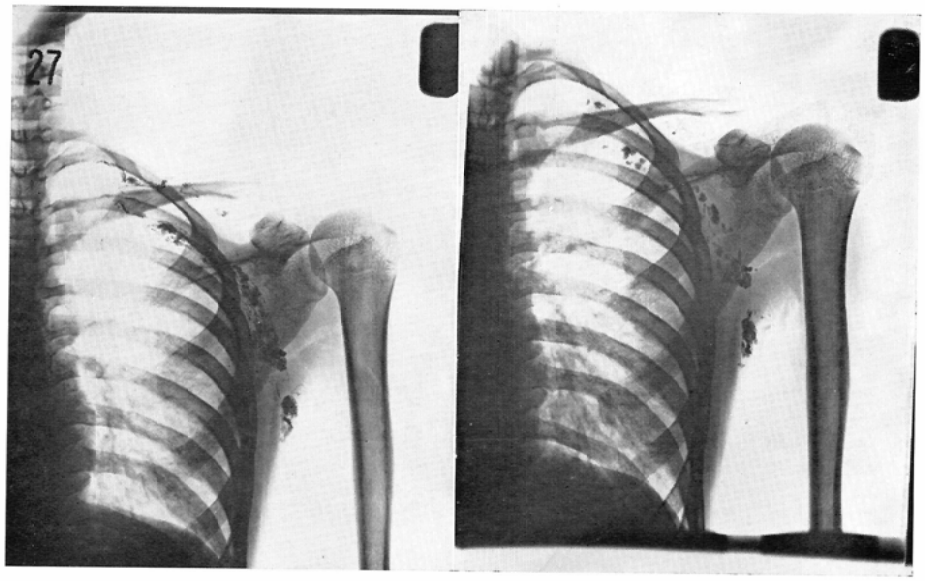
In contrast, lymph nodes of types F2, F3, D2 and D3 which are presumed to be positive for metastasis were very infrequent being found in 22/426 for a rate of 5.3%.

In stage 3, the presumably normal types N, F1 and D1 were noted at a rate of 52.1%, while types F2, F3, D2 and D3 with metastasis to the lymph node were seen in 47.9%. Thus, almost half of the cases seemed to have radiological evidence of metastasis to the lymph node.

2. Lymphography of upper extremity

By the same method as lymphography of the lower extremity, 4—5 cc of Lipiodol Ultra fluid was

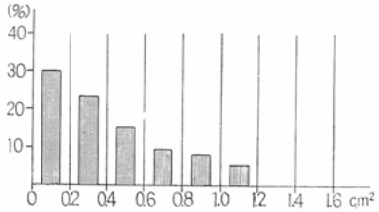
Fig. 8. Lymphography of axillar & infra clavicular region.



injected into the lymphatic vessel on the dorsum of the hand between the first and second fingers, with an injection time of 40—60 minutes to primarily visualize the axillary, supra- and infra-clavicular lymph nodes.

The author obtained lymphograms of the upper extremity by this method on nine cases of malignant lymphoma originating in the head and neck. Measurements of the area of 170 lymph nodes were obtained with a planimeter by the same method as for lymphograms of the lower extremity.

Fig. 9. Percentage Distribution of Lymphnode at Axilla & Supra-infraclavicular Region. (Stage 1. 2. Cases)



The results shown in figure 9 indicate that the proportion of lymph nodes decreases linearly with size up to 0.60 cm^2, but beyond 0.61 cm^2 the gradient of the rate of decrease changes and becomes more uniform.

In other words, lymph nodes 0.61 cm^2 or larger in size should be considered to be abnormal as in lymphograms of the lower extremity, but examination of the internal structure is needed. Under the assumption that types F2, F3, D2 and D3 have metastasis, 47 lymph nodes 0.61 cm^2 or larger in seven patients in stage 1 and 2 (for whom lymphograms were available) were classified by their internal structure according to the criteria in table 6, and the results are shown in table 8.

Types F2, F3, D2 and D3, the so-called metastasis positive types, were seen in 12 nodes, for a positive rate of 12/47 or 25.5%, which shows that metastasis may occur at a rate five times greater than in the re-

Table 8. Internal Arthitecture of Axillar & Infraclavicular Lymphnodes above 0.6 cm².
(Stage 1 & 2 Patients.)

Normal Appearance		Foamy Appearance		Filling Defects	
N	19	F2	6	D2	5
F1	6	F3	–	D3	1
D1	10				

troperitoneal or pelvic lymph nodes.

Summary

Lymphograms were obtained from the dorsum of the hand and feet in malignant lymphoma originating in the head and neck to determine the degree of metastasis to areas other than the primary site or adjacent lymph nodes.

In stage 1 and 2 patients, metastasis had occurred to 25.5% of the axillary, supra- and infra-clavicular nodes and to 5.3% of the retroperitoneal and pelvic lymph nodes. Thus, metastases to the contiguous lymph nodes and the supra- and infra-clavicular regions are likely to occur from the early stage, but the rate of metastasis to the lymph nodes of the infra diaphragm, in other words, the retroperitoneal and pelvic lymph nodes is low.

On the other hand, in stage 3 patients, metastasis had occurred to 47.5% or almost half of the nodes in the retroperitoneal and pelvic regions.

In view of these findings, the site of irradiation and size of field should be decided according to the stage of the disease.

Radiographic visualization of the mediastinal lymph nodes is of course invaluable, but very difficult to accomplish.

Ishida et al. (21) report that visualization is possible to some extent in animal experiments, but has not been applied clinically yet. We have not attempted their method since it apparently is not yet sufficiently developed for practical use.

Radiotherapeutic Procedures

As mentioned in the preliminary report of the author (5), malignant lymphoma is highly radiosensitive, and a very small dose can achieve tumor regression or disappearance.

Historically, in a review by Melville et al. (22), a dose of 1000 R or less had been used for malignant lymphoma during the first part of the 20th century.

This had resulted in temporary improvement in the tumor, but local recurrence was frequent.

From about 1950, with the availability of better radiotherapeutic equipment and improved techniques, irradiation by about 2000 R of X-rays became possible.

However, even this dosage was found to be insufficient for the complete control of the lesion.

Therefore, X-ray equipment had been replaced with the use of gamma rays from cobalt 60. This made possible a tumor dose of 2500—3500 R, and it has gradually been recognized that true recurrence as defined by Kaplan (2) can be prevented, in other words, reappearance of tumor at the treated area or lymph nodes involved in the initial course of radiotherapy does not occur.

However, the problem of marginal recurrences or extensions, in other words, the reappearance of tumor at or adjacent to the margins of the therapeutic field or the development of new lesions at a pre-

viously untreated site could not be solved by previous methods.

The author has given careful considerations to these points, and it is felt that in marginal recurrences the problem was the therapeutic field which had not been extensive enough to cover the entire primary foci, while in extensions a proper diagnosis of spread beyond the primary site had not been made.

Therefore, the method of irradiation described below has been devised.

In other words, the primary lesion is irradiated using a large field which covers the primary lesion and includes the contigous lymph nodes. In addition, lymphograms are obtained by the previously described method to determine the presence of lesions other than the primary lesion and systematic prophylactic irradiation is delivered to such involved areas.

A consideration will be given to how this method differs from previous methods.

1. Simple irradiation of primary lesion

This method was used during the earlier stage of treatment. In stage 1, a small radiation field centered on the primary lesion was used, while in stage 2 the primary lesion and metastasis to adjacent lymph nodes were irradiated separately with no connection between the two fields.

Except for a case that had received only 600 R due to an accident, irradiation had been continued until disappearance of the tumor so that some cases received only 1000—1250 R, but in other cases, 200—300% more irradiation had been given after tumor disappearance so that a maximum of 5000 R was received in certain cases.

The results are summarized in table 9.

The majority of cases in stages 1 and 2 given simple irradiation to only the primary lesion had tumors

Table 9. Radiation Therapy to Malignant Lymphoma of Stage 1 & 2 Cases.
(only irradiated cases to Primary Focus & regional metastasis)

Case Number	Primary Focus.	Total Dosis	Decrease in Tumor size.	Recurrence	Extension	Prognosis	Survival Month.
8	Epiph	3420R/17D	##		□	Dead	2
10	Epiph	3500 /17	##		□	Dead	4
17	Epiph	4600 /51	##		□	Dead	4
29	Mesoph. Nasal	4000 /24	#		□	Dead	6
35	Sinus	4000 /28	##		□	Dead	4
53	Mesoph	1000 /10	##	▲	□	Dead	10
85	Mesoph	1250 / 5	##	▲	□	Dead	8
101	Mesoph Nasal	4200 /20	##		□	Dead	9
141	Sinus	4000 /23	##			Alive	26
152	Mesoph	4000 /23	##		□	Dead	14
153	Epiph	5000 /14	##			Alive	26
177	Neck Nasal	3750 /22	##			Alive	24
259	Sinus Oral	3000 /15	##		□	Dead	6
301	Cavity	600 / 2	#	▲	□	Dead	2
320	Epiph	3000 /21	#	▲	□	Dead	6
352	Sphenoidal Sinus	2600 /19	##		□	Dead	6

of the upper and middle larynx.

The primary effect of radiation dose was evaluated by the degree of tumor regression. Tumor disappearance with 1000 R or less was classified as grade 2 (++) and disappearance with 1000—2000 R was expressed as grade 1 (+). In no case was more than 2000 R required for tumor disappearance.

Thus, tumor regression was marked even with a relatively small dose and almost all cases were grade 2.

Inspite of the rapid disappearance of tumor, the prognosis was poor and most patients died in half a year or at the longest one year after radiation therapy.

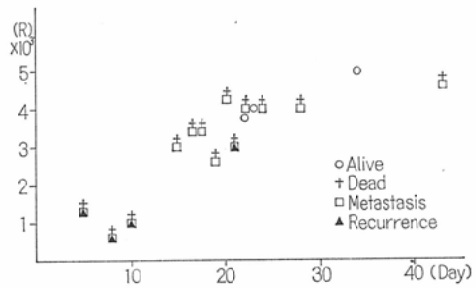
Only three patients with primary lesion in the neck, maxillary sinus and upper larynx, respectively, have survived asymptomatically and in good health for more than two years.

A detailed study was made of the cause of death.

Shown in figure 10 is the prognosis in relation to the therapeutic dose and duration.

Table 9 and figure 10 show that all 13 deaths had developed distant metastasis.

Fig. 10. Correlation between Dosis & Times in Stage 1 & 2 Cases of Malignant Lymphoma (Irradiated cases to only Primary Focus.)



Among patients exposed to 2600 R or more, except the one whose effect of treatment was evaluated as grade 1 (case number 320), no local recurrence was seen. In three patients with doses 1250 R or less, there was local recurrence as well as distant metastasis resulting in death.

This suggests that:

1) For local tumors, a radiation dose of 3000—4000 R/3 W is sufficient and effective;

2) The three patients who died with recurrence had been exposed to a low dose of 600—1250 R, and though tumor regression is possible with this level of irradiation complete local cure cannot be expected;

3) In the deaths among patients who were exposed to 3000—5000 R and developed distant metastasis without local recurrence, the local radiation dose had not been insufficient but rather the size of the radiation site had presumably been insufficient due to misclassification of the stage of the disease from the lack of accurate knowledge of the extent of involvement.

The majority of patients in this group had been treated in the earlier period when lymphography was infrequently done. Radiotherapy was performed after evaluating the stage of disease on the basis of physical examination and simple radiograms. Thus, although tumor regression had been possible as a primary effect, permanent cure could not be expected.

In other words, nearly 30% of the 13 patients had already advanced as far as stage 3 so that the radiation field probably should have been set up to include the supra- and infra-clavicular, mediastinal or retroperitoneal and pelvic lymph nodes.

The surviving three cases had received only simple irradiation to the primary lesion, but have all remained asymptomatic for over three years. In these cases, the tumor presumably had been localized without metastasis to other sites so that fortunately even irradiation to only the primary lesion was effective.

Lymphograms from the dorsum of the feet obtained after treatment on two of these three cases showed no metastatic lesion in the retroperitoneal or pelvic region.

2. Systematic prophylactic irradiation

The simple irradiation of the primary lesion described above had been limited to sites where tumor could be palpated from the surface of the body, but since the tumor in this disease is highly radiosensitive, even this alone has primary effect.

Eventually, however, extensive distant metastasis occurred in many cases, but nothing further was possible and finally terminated in death.

In other words, misdiagnosis of the case as being in the early stage of the disease had lead to an inappropriate decision on treatment, and irradiation was delivered to only the site presumed to be the primary lesion. Moreover, since tumor regression had been regarded as cure, no further treatment was provided, and the condition usually progressed to stage 2 and stage 3 within several months.

Historically, this fact had been recognized in 1939 by Gilbert (23) who felt that the radiation field should include not only the primary lesion but also the normal tissues in the periphery of the main lesion. He called this method segmental radiation therapy.

At that time, the classification of the stage of disease had been incomplete so that results of treatment were not sufficiently satisfactory.

Subsequently, Boden (24), Jellife et al. (25) and others suggested higher doses.

Their results were effective in producing tumor regression as a primary effect but did not accomplish permanent cure.

Later, Peters and Middlemiss (1), Kaplan (26), Kaplan and Saul (27) and others reported that prophylactic irradiation generously to the surrounding sites yielded incomparably better results than by previous methods.

The author has reviewed their methods and devised a further new method of irradiation which was attempted on stage 1 and 2 malignant lymphomas of the head and neck.

This method first takes into consideration the fact that malignant lymphoma is highly radiosensitive and requires a much lower dose than for other malignant tumors for almost complete tumor regression, and second that such a dose level produces hardly any physical disturbances. Therefore, the procedure was extended to include lymphatics where tumor may possibly develop later and areas where metastases may already have occurred though evidence of such is difficult to obtain by external examination. To these areas, systematic irradiation was delivered at a dose level adequate for prophylactic purposes but within the permissible range from the standpoint of radiation disturbances.

The author calls this method systematic prophylactic irradiation.

In systematic prophylactic irradiation for malignant lymphoma of the head and neck, first the irradiation to the primary site was by a field as large as possible, including the cervical lymph nodes and extending from the upper larynx to the supraclavicular fossa, with a dose of 2500—4000 R/3—4 W by opposed two-portal irradiation from both sides.

Second, in view of the finding of 25% metastasis to the infraclavicular and axillary regions by lym-

phography from the dorsum of the hands, single-portal irradiation of 2000—3000 R/2—3 W was delivered at the same time to the axillary-infraclavicular fossa.

Thirdly, because metastasis to the mediastinum cannot be determined accurately by lymphography or other examinations, an adequate prophylactic dose within the permissible range from the standpoint of disturbances, in other words, 2000—3000 R was delivered indiscriminately to the mediastinum by a large radiation field of 6 × 15 cm even in stage 1 and 2 patients.

Furthermore, exposure to the primary lesion, mediastinum, and axillary-infraclavicular fossa was not delivered on separate occasions but in succession.

Since metastasis to the retroperitoneal and pelvic lymph nodes had been noted radiologically at a frequency of about only 5.3% on lymphography as described before, no prophylactic irradiation was given to these regions in metastasis negative patients. They were followed by repeated lymphography for any change.

The sites irradiated are shown in figure 11. The volume dosage was limited to less than 20 MgR in systematic prophylactic irradiation and hardly any side effects were seen as will be described later.

Systematic prophylactic irradiation was performed for stage 1 and 2 malignant lymphomas of the head and neck, and followed for six months or more in 15 cases as shown in table 10. The primary site was the middle larynx in eight patients followed by the upper larynx in three.

Table 10. Radiation Therapy to Malignant Lymphoma of Stage 1 & 2 Cases.
(systematic prophylactic irradiated cases.)

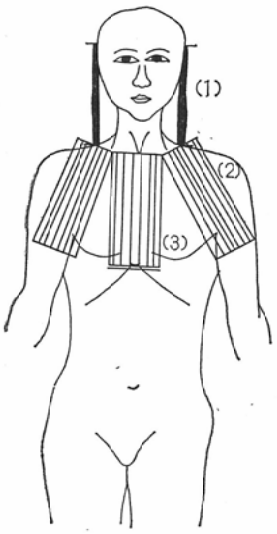
Case Number.	Primary Focus.	Total Dosis.	Decrease in Tumor size.	Prognosis.	Survival Month.
22	Epiph.	5000R/31D	++	Alive.	24 M.
41	Lac. Gl.	3000 /17	++	Dead.	7
34	Mesoph.	3000 /20	++	Alive.	34
142	Neck.	3000 /17	++	Alive.	26
223	Mesoph.	4000 /23	++	Alive.	19
280	Mesoph.	3000 /17	++	Alive.	14
291	Mesoph.	3000 /18	++	Alive.	14
343	Epiph.	4000 /22	++	Alive.	12
344	Epiph.	3750 /20	++	Alive.	12
405	Mesoph.	3000 /20	++	Alive.	7
455	Mesoph.	2750 /15	++	Alive.	6
172	Mesoph.	2750 /16	++	Alive.	24
250	Nasal Sinus.	3000 /15	++	Alive.	17
254	Mesoph.	4500 /27	++	Alive,	14
394	Nasal Sinus.	3000 /16	++	Alive,	7

The degree of tumor regression was marked in all cases and was grade 2 (++) according to the previous criteria. The prognosis was good and, except for one patient who died in an accident, all patients have survived asymptomatically with no evidence of recurrence or metastasis for as long as 34 months.

The relation between duration of treatment and dose for the 15 patients given systematic prophylactic irradiation and followed for over six months is shown in figure 12.

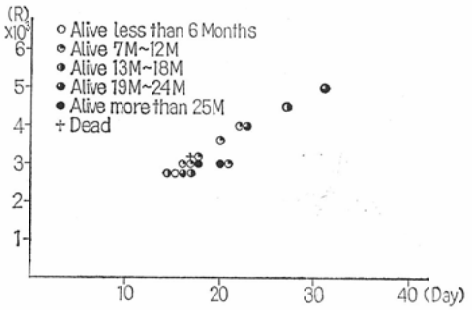
It is seen in table 10 and figure 11 that the prognosis is good in both those exposed to 2750—3500

Fig. 11. Irradiated Sites in systematic prophylactic Irradiation Malignant Lymphoma.



(1) Neck Fields size 8 × 15 cm.
(2) Axilla-Infra Clavicular Region. 10 × 15 cm.
(3) Mediastinum. 6 × 15 cm.

Fig. 12 Corralation between Dosis & Times in Stage 1 & 2 Cases of Malignant Lymphoma. (Systematic Prophylactic Irradiated Cases.)



R/2—3 W and those irradiated to 4500—5000/4—5 W, and though the duration of observation is short, no significant difference can be seen at present between these two groups.

Thus, a dose of 2750—3500 R/2—3 W may be sufficiently effective.

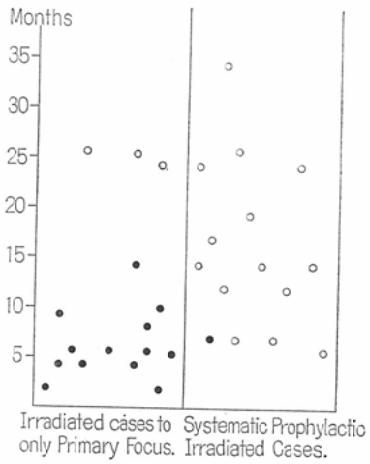
Furthermore, it is felt that prophylactic irradiation to the mediastinum and axillary-infraclavicular fossa is adequate for stage 1 and 2 patients with no need of irradiating the retroperitoneal and pelvic lymph nodes in all cases.

It was found that the survival time could be prolonged much more than with previous methods.

The difference in survival time between the group treated with simple irradiation of the primary lesion and that given systematic prophylactic irradiation is illustrated in figure 13.

The primary effect shown in tables 9 and 10 is good in both groups, but the majority of patients treated

Fig. 13. Survival after Radiation therapy of Malignant Lymphoma-Stage 1 & 2 originanted in Head & Neck.



with simple irradiation to the primary lesion develop distant metastasis, particularly metastases to the retroperitoneal lymph nodes and liver, within three to six months.

Contrarily, patients treated with systematic prophylactic irradiation have survived for six to 34 months and have lived and entirely normal life, indicating the great effect of this method.

3. Radiotherapy for stage 3

The prognosis of stage 3 patients is generally poor, and systemic treatment by chemotherapy frequently should be given more priority than local treatment by radiotherapy.

Table 11. Radiation Therapy to Malignant Lymphoma of Stage 3 Cases.

Case Number	Primary Focus	Total Dosis	Decrease in Tumor size	Recurrence	Extension	Prognosis	Survival Month
11	Mesoph. Nasal	4200R/27D	+		■	Dead	6
32	Sinus	3000 /16	++		■	Dead	2
44	Mesoph.	3000 /16	++		■	Dead	8
46	Mesoph.	3000 /20	++		■	Dead	2
163	Neck	3250 /21	++		■	Dead	5
205	Neck	2500 /17	++			Alive	21
346	Epiph.	3250 /20	++		■	Dead	3
391	Jaw	3000 /16	++		■	Dead	4
418	Mesoph.	4000 /25	++			Dead	6
421	Mesoph.	1500 / 9	+	▲	■	Dead	3

Stage 3 patients handled by the author are the 10 cases shown in table 11. This includes two or three patients who had been classified as stage 3 by the detection of metastatic lesions of the retroperitoneal and pelvic lymph nodes by lymphography.

In seven patients, 1500—4200 R had been irradiated to each tumor site in succession, giving priority to those areas at which the patient complained of such symptoms as pain.

Daily irradiation was performed with a daily tumor dose of 200—250 R.

This procedure resulted in temporary disappearance of tumor, but during the treatment of one site another new lesion would develop elsewhere so that lesions developed one after the other and all seven patients died within two to eight months.

Autopsy revealed swelling of untreated lymph nodes and marked metastases to the liver, spleen, etc. in these patients.

In the remaining three patients, the complaints of the patient were not taken into consideration and systematic irradiation was delivered to the primary lesion, and the cervical, mediastinal, axillary-infraclavicular, retroperitoneal and pelvic lymph nodes in sequence.

One of these three patients has survived and has been asymptomatic for 21 months after treatment.

The other two patients died within seven months after radiation treatment, but neither was due to recurrence of tumor or metastasis. Severe leukopenia and anemia had developed following treatment which finally developed into aplastic anemia with bleeding tendency and terminated in death.

The volume dosage in these two patients had been 41 and 35 MgR, respectively, which is two to three times larger than that in the previous stage 1 and 2 patients, so that the physical effects were large and hence the side effects were also large.

Fig. 14. Hand Lymphography of Stage 3 Case.

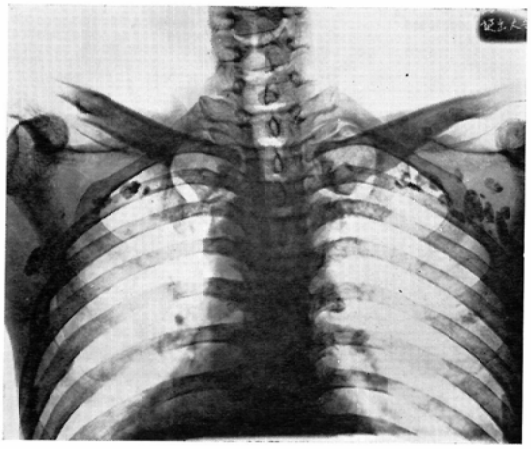


Fig. 15. Foot Lymphography of Stage 3 Case. (before irradiated state.)

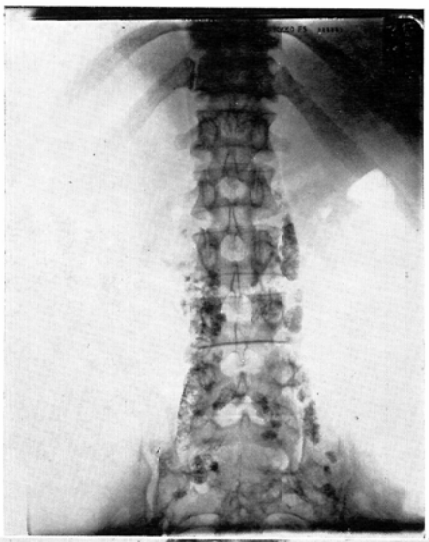
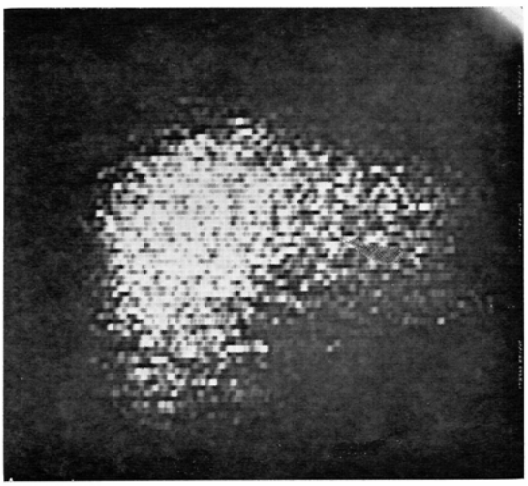
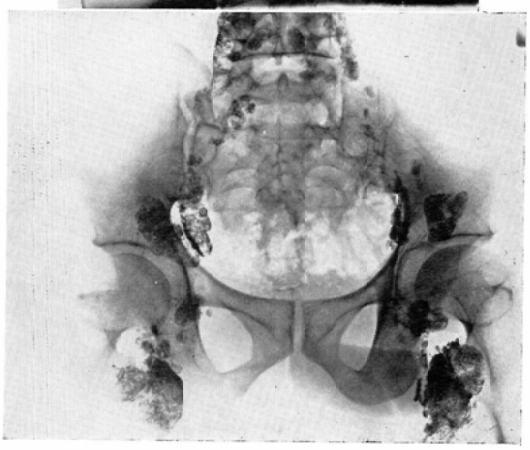


Fig. 16. Liver scintigramm of Stage 3 Case.





From the experience in these two patients, I feel that radiation therapy may very likely be extremely effective even in stage 3 patients if the weekly dosage were limited to about 800 R and the irradiation dose to a single site reduced to slightly less than that in stage 1 and 2 patients.

One of these patients will be presented here.

Case: 38-year-old male with tumor of middle larynx.

At initial examination, many swollen lymph nodes were felt in the right palatine tonsillar, bilateral cervical, axillary, bilateral inguinal and cubital regions. Lymphograms obtained from the dorsum of the hands and feet, as shown in figures 14 and 15, revealed the typical pattern of malignant lymphoma showing mainly a foamy appearance. Liver scintigrams with Au^{198} shown in figure 16 demonstrated no evidence of liver metastasis.

In the radiation therapy of this patient, the same radiation field and same dose as in systematic prophylactic irradiation for stage 1 and 2 patients were used for the primary lesion and mediastinum, while 2500—4000 R/3—4 W was delivered to the retroperitoneal, pelvic and inguinal regions.

Shown in figure 17 is the post-irradiation condition of the retroperitoneal and pelvic lymph nodes. There is reduction in size of each of these lymph nodes and the internal structure shows the normal reticular pattern.

From the sixth month, fever and bleeding tendency appeared, and a diagnosis of aplastic anemia was made by peripheral blood and bone marrow examinations. The patient ultimately died in the eighth month after treatment.

From the results in this patient, it is presumed that even in stage 3 patients, if there is no metastasis to the liver or other major organs and the sites of lesions are accurately determined, systematic irradiation performed in proper sequence along with careful observation of the general condition can result in completion of irradiation within the tolerable limits of radiation dosage and thus prevent the development of side effects and improve the survival rate.

Disturbances due to Systematic Prophylactic Irradiation

Although systematic prophylactic irradiation for stage 1 and 2 patients can be completed with a com-

Fig. 17. Foot Lymphography of Stage 3 Case (after irradiated state.)

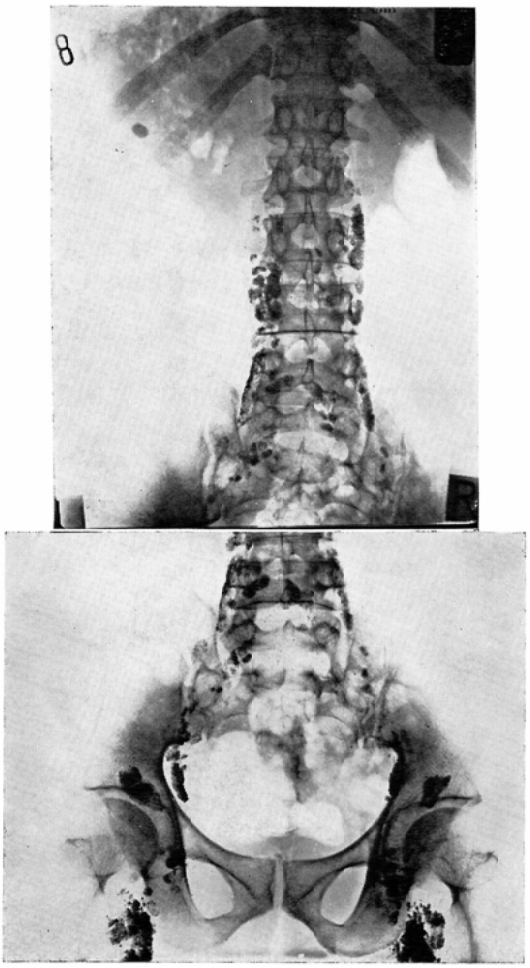


Fig. 18. Correlation between Volume Dosis & R.B.C. in Malignant Lymphoma. (Systematic prophylactic Irradiated Cases)

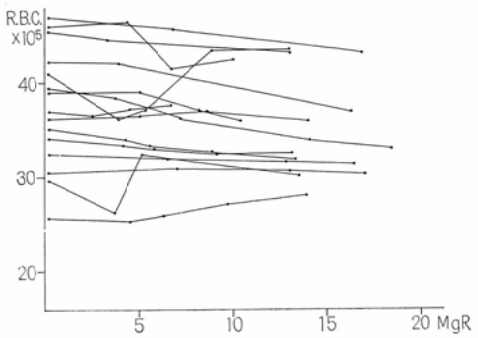
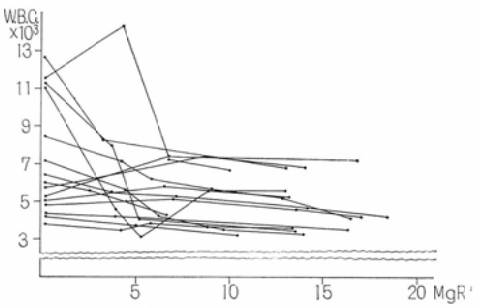


Fig. 19. Correlation between Volume Dosis & W.B.C. in Malignant Lymphoma. (systematic prophylactic Irradiated Cases)



paratively small dose, disturbances cannot be said to be completely absent.

To study the degree of disturbances, the results of various chemistry determinations were compared with the volume dose to see how much disturbance had been produced in patients by irradiation in order to determine if systematic prophylactic irradiation can be safely done.

The concept of volume dose had been reported by Ellis (28) and Happey (29). Mayneord (30) who used a unit of gramroentgen (MgR) has reported a simple method of calculating the volume dose.

The author has applied the integral dose factor of Scarpa to calculate the whole body volume dose of the patients.

In other words, the integral factor is calculated from the body thickness, and the volume dose computed from the formula:

$$\sum = F \cdot A \cdot D$$

Where F is the integral factor, A is the field size at entry surface, and D is the total air dose at entry surface.

In irradiation for stage 1 and 2 malignant lymphoma originating in the head and neck, in other words, primary lesion irradiation and systematic prophylactic irradiation to the primary lesion-cervical region, mediastinum and axillary-infraclavicular fossa, the volume dose varied from 6.7 to 17.0 MgR, but irradiation had mostly been completed at less than 10—13 MgR.

1. Hematological changes and volume dose

The relation between the erythrocyte count and volume dose is shown in figure 18.

Most patients had a pre-treatment count of $30 \times 10^5/mm^3$ to $50 \times 10^5/mm^3$ which tended to decrease in all cases with doses of 15 MgR or greater, but systematic prophylactic irradiation by lower doses apparently has no effect.

The relation of the leukocyte count to volume dose is shown in figure 19.

There is more marked effect than in the erythrocyte count, but with doses of 15 to 17 MgR or less, the leukocyte count does not decrease to less than $3000/mm^3$ and no case had effects severe enough to require discontinuation of irradiation.

In the three patients who had infection prior to commencement of treatment, a rapid decrease of leukocytes occurred with irradiation. The count dropped to 3500—4000/mm³ by irradiation of 4—6 MgR after which the counts remained constant.

This phenomenon may perhaps be one of the indicators of the improvement in general condition. In stage 1 and 2 patients, whose general condition is comparatively good, the effect upon the leukocytic series can be considered to be negligible.

The changes in hematocrit and hemoglobin are shown in figure 20, but these values are almost consistent before and after treatment like the erythrocyte count.

2. Biochemistry and volume dose

When the mediastinum is exposed as part of the systematic prophylactic irradiation, a portion of the liver may be included within the lower margin of the radiation field which could result in some change in biochemical tests. Therefore, a study of this possibility was done.

The total protein and A/G ratio before and after completion of irradiation are shown in figure 21. The total protein ranged within 6—8 g/dl, but all cases exhibited mild decrease after irradiation except for the four patients who showed a mild increase.

The A/G ratio showed a mild decrease in most patients including a decrease from 1.1 to 0.65 in a pa-

Fig. 20. The Effect of Irradiation on Hb (g/ld).

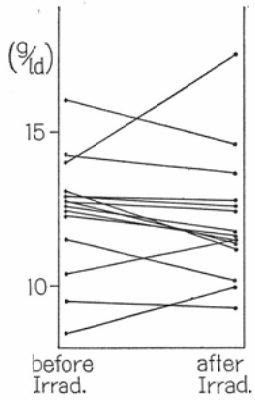
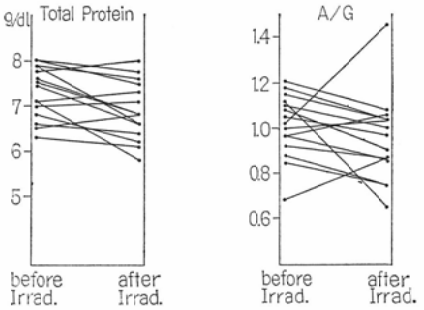


Fig. 21. The Effect of Irradiation on Total Protein & A/G ratio.



tient whose volume dose was 17 MgR, but the change was not severe enough to require discontinuation of irradiation.

The above total protein and A/G ratio did not indicate the presence of any factor which would make systematic prophylactic irradiation impossible.

The relation of serum cholesterol and volume dose is shown in figure 22.

The serum cholesterol was always increased, except in one patient receiving 13 MgR in whom it was decreased.

This phenomenon suggests that inclusion of one part of the liver within the radiation field in mediastinal irradiation had resulted in transient liver function disturbances, and in particular the marked elevation in the group receiving more than 13 MgR indicates that when a higher dose is to be used the daily dose should be reduced.

The GPT and GOT values before and after irradiation are shown in figure 23.

Fig. 22. Correlation between Volume Dosis & Total Cholesterol.

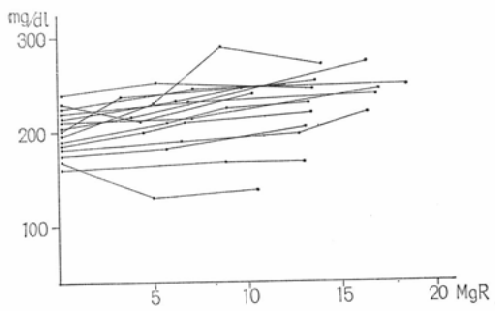
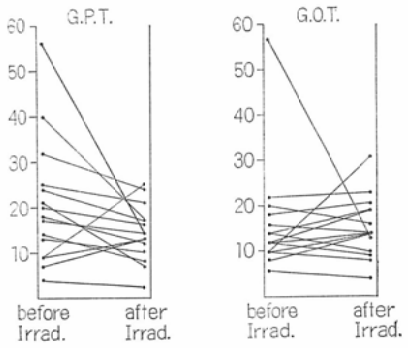


Fig. 23. The Effect of Irradiation on G.P.T. & G.O.T.

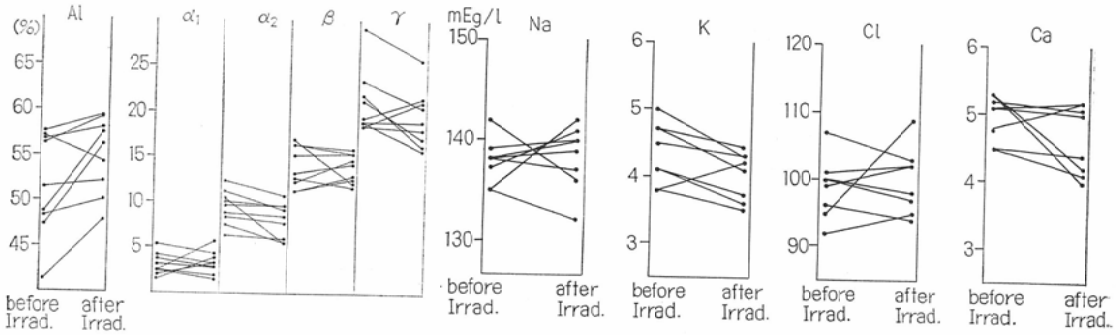


Both showed little difference before and after irradiation. In one patient, who had a high value before irradiation, a decrease occurred with commencement of treatment and the value was normal when the irradiation was completed. This patient is thought to have had a temporary change in liver function.

The serum protein fractions likewise do not seem to be affected by irradiation as shown in figure 24.

Fig. 24. The Effect of Irradiation on Protein Fraction.

Fig. 25. The Effect of Irradiation on Electrolyte.



3. Serum electrolytes and volume dose

As shown in figure 25, comparison of the sodium, potassium, chloride and calcium values before and after irradiation do not indicate any marked change by irradiation as in the other chemical tests, and irradiation was accomplished rather uneventfully.

4. Volume dose in systematic irradiation for stage 3 patients

Irradiation of 13—17 MgR for stage 1 and 2 patients was accompanied by only very mild disturbances as described above and no particular point needed to be considered in performing the irradiation. When the volume dose exceeded 20 MgR, however, physical effects were large and require adequate consideration.

The effects of irradiation on the previously described patient in stage 3 were studied by the relation

Fig. 26. 38y. male. Systematic irradiated case of stage 3 originated in tonsillar gland.

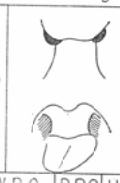
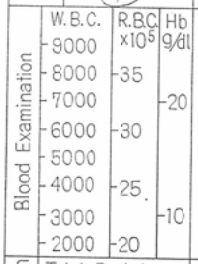
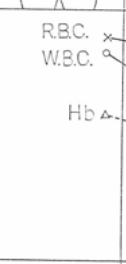
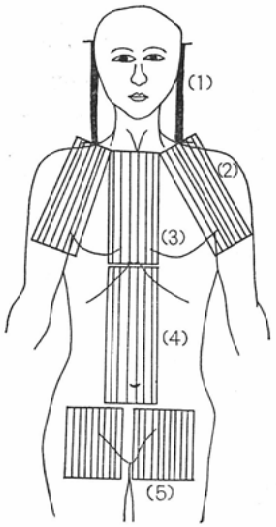
Weeks	before Irradiation	1 2 3 4	5 6 7	8 9	10 11 12 13 14	15 16
Irradiated Focus		Neck	Mediastinum	Supra-infra Clavicular Axilla	Retro-peritoneum	Pelric & Inguinal Region
Volume Dosis (MgR)		11.1	15.7	24.3	30.0	41.0
Clinical Findings					Petroperitoneal Lymphnodes were remarkably decrease in Size and appeared normal internal arthitecture.	
Blood Examination						
Liver Function: Total Protein		7.4 g/dl	5.6	5.8	6.4	5.6	4.6
Liver Function: Total Chlesterol		170 mg/dl	139.0	163.0	190.0	134.0	130.0
Liver Function: G.P.T.		3	12.0	4.0	3.0	18.0	10.0
Liver Function: G.O.T.		9	14.0	4.0	9.0	16.0	12.0

Fig. 27. Irradiated Field in Stage 3 Case.
(originated to Tonsillar Gland.)



(1) Neck Fields size 8×15 cm^2.
(2) Axilla-Infra Clavicular Region. 10×15 cm^2.
(3) Mediastinum. 6×15 cm^2.
(4) Para Aorta. 6×30 cm^2.
(5) Intra pelvic-Inguinal Region. 15×15 cm^2.

between various laboratory tests and volume dose. The results are shown in figure 26.

The radiation fields had been established for the sites shown in figure 27.

Before irradiation, there had been infection with elevated leukocyte count, but with commencement of irradiation the count decreased and remained at a level of 4000/mm^3 up to 15 MgR. When the volume dose exceeded this, a rapid decrease in leukocyte occurred and at the completion of 41 MgR an extreme reduction to 1200/mm^3 was seen.

The erythrocyte count also showed a marked decline from 409×10^5/mm^3 before irradiation to 239×10^5/mm^3 at time of completion of irradiation.

In biochemical tests, marked changes were noted beyond 15 MgR in total protein, A/G ratio, GPT and GOT. Therefore, amino acid preparations, reduced glutationine, B6, B12, etc. were administered. Subsequently, minimal improvement was seen and irradiation was completed uneventfully with a volume dose of 41 MgR.

Since anemia and leukopenia persisted for six months after discharge with bleeding tendency, the patient was readmitted for examination which revealed the picture of aplastic anemia in the peripheral blood and bone marrow.

Subsequently, fever and bleeding tendency increased in severity and the patient died in the eighth month.

Even at time of death, no swollen lymph nodes could be felt on external examination. Death had not been due to tumor, but aplastic anemia from loss of bone marrow function due to radiation exposure had been the cause of death.

Summary

The effects upon various chemistry tests were examined in stage 1 and 2 patients treated with 13—17 MgR and stage 3 patients treated with 35—41 MgR. Disturbances are few at 13—15 MgR or less, and irradiation can be completed without any supportive measures. Beyond 15 MgR, however, anemia,

leukopenia and decrease of total protein and A/G ratio occurs with elevation of total cholesterol, GPT and GOT.

Such changes require blood transfusions, fluid transfusions, and the administration of liver protective agents and other medication to promote improvement in the general condition.

The author (31) has previously reported that irradiation up to a volume dose of 30 MgR can be accomplished satisfactorily by the use of reduced glutationine.

Patients should be carefully followed for two to three months after irradiation in an effort to prevent infection.

Kaplan (2) has reported that in his extended field, intensive megavoltage radiotherapy for 31 patients in stage 3, blood disturbances were few though the bone marrow had been irradiated quite extensively. The leukocyte count had been in the range of 2000—3000/mm^3 and in exceptional cases been 1000/mm^3. Both of the two cases experienced by the author, however, had developed marked changes. Whenever 30—40 MgR is to be irradiated, the daily permissible dose must be computed and the exposure limited to within this range.

Discussion

Malignant lymphoma is highly radiosensitive but has the contradictory characteristic of having a poor prognosis, and various types of treatment have been reported by different workers.

Gordon Richards (32) has mentioned that "you never extinguish a fire by pouring water on the center of the fire" which indicates the difficulty in the treatment for this condition.

Historically, radiotherapy for Hodgkin's disease was first introduced in 1902 by Pusey (33). Until 1920, whole body irradiation by small doses or massive single exposure to the affected sites had been performed but with poor results and marked side effects, so that many workers discontinued this method.

Subsequently, a systematic review was made by Gilbert (23) on the methods of treatment that had been used. Gradually, more use of wide field irradiation was made and comments on the longterm results began to appear.

The methods at that time were mostly simply sectional or segmental therapy.

That is, Chaoul and Lange in 1923 divided the trunk of the body into a number of sections to which irradiation was delivered. Schwarz in 1935 irradiated the affected sites but not the normal lymphatic tissues.

In 1935, Gilbert who disagreed with the methods of Schwarz and of Chaoul and Lange devised a method in which other areas suspected to be involved by malignant lymphoma were irradiated in addition to the main lesion.

His primary argument was that with the method of Schwarz marginal recurrences were difficult to prevent though tumor regression is possible, while with the method of Chaoul and Lange the low energy units used during that period could not completely control malignant lymphoma.

Later, in 1945, Desjardins (34), Peters (35) and others reported a method of delivering systematic irradiation to the lesion and surrounding lymphatic tissues.

On the other hand, remarkable improvements in radiation equipment were made. In 1937—1953, 400 kv units had mainly been used, but from 1953 the use of Cobalt 60 teletherapy units has made possible higher tumor doses.

After 1960, it was reported that the radiation field of a single portal should be large enough to include the surrounding lymphatics which received the strong support of Kaplan (36).

The results of treatment by this wide field irradiation have been reported for stage 1 and 2 cases by Easson (37), Kaplan (26) and Salzman (38), and for stage 2 and 3 cases by Molander (39), Peters (1) and others. From the comparison of the five-year survival rate, prophylactic exposure has been found to be meaningful in stage 2 and 3.

Taking this point into consideration, the author has, for malignant lymphoma originating in the head and neck, irradiated the primary site using a field as large as possible by a single port which included the cervical lymph nodes to prevent marginal recurrence, and in addition, delivered prophylactic irradiation to the supra- and infra-clavicular fossa and axillary region where metastases have been noted at a rate of 25% by lymphography, along with further prophylactic irradiation with as large a dose as permitted by whole body tolerance for possible metastasis to the mediastinum, for which there is as yet no method of determining the presence of metastasis.

These three exposures were delivered in succession, and I have called this systematic prophylactic irradiation.

Since the possibility of metastasis to the retroperitoneal and pelvic lymph nodes has been found to be only 5.3% by lymphography, systematic irradiation to these regions was not performed.

From the results of systematic prophylactic radiation therapy to the socalled supra-diaphragmatic region for stage 1 and 2 malignant lymphoma originating in the head and neck, the following conclusions were derived.

Conclusions

1. Retrospection on previous methods

With the previous method of simple irradiation to the primary lesion for malignant lymphoma originating in the head and neck, even early cases in stage 1 or 2 usually eventually progressed to stage 3 and took a fatal course.

True recurrences were likely to occur with local doses less than 1250 R, while marginal recurrences and progress to stage 3 occurred with a small radiation field confined to only the tumor site.

The author considers the optimal local dose to be 2500—3500 R/2—3 W, and has made the radiation field as large as possible.

2. Systematic prophylactic irradiation

Even though tumor regression is possible with irradiation to only the tumor, recurrences and metastasis occur as mentioned above. Therefore, the irradiation techniques proposed by Kaplan, et al. were reviewed. For patients in stage 1 and 2, irradiation to the primary site and systematic prophylactic irradiation including the mediastinum were performed, while for patients in stage 3, systematic irradiation was further extended to also include the retroperitoneal and pelvic lymph nodes. The long-term results of this procedure was found to be superior to that of previous methods.

3. Rate of metastasis to respective lymph nodes

On lymphograms obtained from the dorsum of the hands and feet, patients in stage 1 and 2 showed radiographic evidence of metastasis in 25.5% of the supra and infraclavicular and axillary lymph nodes, and in 5.3% of the retroperitoneal and pelvic lymph nodes.

Stage 3 patients were found to have metastasis in 47.5% of the retroperitoneal and pelvic lymph nodes.

However, there are still many problems yet in the accurate determination of the presence of metastasis by lymphography so that comparative studies on the future course of the patients and the histological changes are necessary.

4. Disturbances due to systematic prophylactic irradiation

In stage 1 and 2 patients, irradiation to the primary site and systematic prophylactic irradiation could be completed with a volume dose of 13—17 MgR or less.

A volume dose less than this did not produce effects upon the various chemistry tests severe enough to discontinue irradiation.

A patient in stage 3, who had required irradiation including the retroperitoneal and pelvic lymph nodes, was given a volume dose of 41 MgR, but he died with aplastic anemia in the eighth month after treatment. From this experience, it is felt that if systematic irradiation to all lesions were to be made with a dose of 2000 R/2 W for each lesion and the course completed within a volume dose of 30—35 MgR, along with the administration of various amino acid preparations and anti-leukopenia drugs to promote improvement of the general condition, irradiation could prove to be adequately effective even for stage 3 patients.

In conclusion appreciation is expressed to Professor Tsuyoshi Koyama for the constant helpful guidance and review of the manuscript. I also am grateful for the assistance of Professor Shizuyuki Kurozumi of the Department of Otolaryngology.

(The outline of this study was presented at the 25th, 26th and 27th general meetings of the Japan Medical Radiology Society and at the 5th general meeting of the Japan Cancer Treatment Society.)

Reference

1) Peters, Middlemiss: A Study of Hodgkins Disease. Treated by Irradiation Am. J. Roentgenol and Radium Therapy, 79, 114. 1958.
2) Henry, S, Kaplan: Role of Intensive Radiotherapy in the Management of Hodgkins Disease. Cancer, 19, 356, 1966.
3) Miyazi: Rinshobyorigaku. Kyorin Shoin in Japan.
4) Custer and Bernhard: Am. J. M. Sc, 216, 625, 1948.
5) Miyazaki: Studies on Systemic Prophylactic Irradiation of Malignant Lymphoma originated to Head and Neck Region. Japanese J. of Cancer Clinics, 12, 98, 1967.
6) Ohtake: Radiation Therapy of Malignant Lymphoma. Rinsho Hoshasen, 12, 98, 1967.
7) Kaneda: Results of Radiation Treatment of Reticulum Cell Sarcoma, Lymphosarcoma, Giant Follicular Lymphoma and Hodgkins Disease. Nippon Acta Radiologica, 23, 741, 1963.
8) Watanabe: Radiation Therapy on Malignant Lymphomas. Nippon Acta Radiologica, 25, 1100, 1965.
9) Jackson: Hodgkins Disease and Allied Disorder. Oxford Univ. Press, 1947.
10) Lumb, Tumorsof. Lymphoid Tissues. Livingston, Edinburgh and London. 1954.
11) Textbook of Radiology, 928, 1959. Igakushoin in Japan.
12) Yamashita: Lymphadenoma-Hodgkins Disease. Japanese Journal of Cancer Clinics, 13, 408, 1967.
13) Kinmonth: Lymphangiography, A Technique for Its Clinical Use in the Lower Limb. Brith. Med. J, 1, 940, 1955.
14) Schwary: Lymphography, Cavography, Urography in The Evaluation of Malignant Lymphoma. Acta Radiol, 3, 138, 1965.
15) Davidson: et al. Lymphography in Lymphoma, with Particular Referrence to Hodgkins Disease. Radiology, 88, 281, 1967.
16) Koehler: et al. Lymphographic Patterns in Lymphoma, with Emphasis on The Atypical Forms. Radiology, 87, 623, 1966.
17) Takahashi. et al.: The Accurecy of Lymphangiographic Diagnosis in Malignant Lymphoma. Radiology,

89, 448, 1967.
18) Miyazaki. et al.: Sudies on Lymphangiography. (Clinical Reports) Journal of The Hiroshima Medical Association, 21, 653, 1968.
19) Akisada: Lymphography. Rinsho Hoshasen, 11, 221, 1966.
20) Takahashi: Lymphography in The Diagnosis of Malignant Lymphoma. Nippon Acta Radiologica, 27, 1361, 1968.
21) Ishida: Lymphangiography of Lung and Mediastinum. Nippon Acta Radiologica, 26, 623, 1966.
22) Melville. et al.: Lymphomas, Relationship between Dosage and Recurrence. Radiology, 83, 106, 1964.
23) Gilbert: Radiotherapy in Hodgkins Disease. Am. J. Roentgenol and Radium Terapy, 41, 198, 1939.
24) Boden: Result of X-Ray Treatment of Reticulosis. Brit. J. Radiol, 24, 494, 1951.
25) Jelliffe. et al.: Prognosis in Hodgkins Disease. Brit. J. Cancer, 9, 21, 1955.
26) Kaplan: Radical Radiotherapy of Regionally Localized Hodgkins Disease. Radiology, 78, 553, 1962.
27) Kaplan. and Saul.: Extended-Field Radical Radiotherapy in Advanced Hodgkins Disease. Cancer Research, 26, 1268, 1966.
28) Ellis: Brith. J. Radiol, 15, 174, 1942.
29) Happey: F. Nature, 145, 668, 1940.
30) Mayneord: Energy Absorption. Brith. J. Radiol, 13, 235, 1940.
31) Miyazaki. et al.: Radiation Protects of Tathion. Rinsho Hoshasen, 12, 624, 1967.
32) Paters: Prophylactic Treatment of Adjacent Areas in Hodgkins Disease. Cancer Research, 26, 1232, 1966.
33) Pusey: Case of Sarcoma and of Hodgkins Disease Treated by Exposures to X-Rays-A Preliminary Report. Am. J. Roentgenol and Radium Therapy, 63, 299, 1950.
34) Desjardins: Salient Factors in The Treatment of Hodgkins Disease and Lymphosarcoma with Roentgen Ray. Am. J. Roentgenol and Radium Therapy, 54, 707, 1945.
35) Peters: A Study of Survivals in Hodgkins Disease Treated Radiologically. Am. J. Roentgenol and Radium Therapy, 63, 299, 1950.
36) Kaplan: The Radical Radiotherapy of Regionally Localized Hodgkins Disease. Radiology, 78, 553, 1962.
37) Easson: The Cure of Hodgkins Disease. Brith. Med. J, 13, 170, 1994.
38) Salzman: Wide Field Irradiation of Lymphoma. Am. J. Roentgenol and Radium Therapy, 92, 124, 1964.
39) Molander: Management and Survival of 883 Patients with Malignant Lymphoma. Am. J. Roentgenol and Radium Therapy, 93, 154, 1965.
40) Fridman: Hodgkins Disease, Tumor Lethal Dose and Iso-Effect Recovery Curve. Am. J. Roentgenol and Radium Therapy, 99, 843, 1967.
41) Molander: Hepatic Gammascanning as An Aid in The Management of Patients with Malignant Lymphomas. Am. J. Roentgenol and Radium Therapy, 99, 851, 1967.
42) Suit: Prognostic Singnificance of Extent of Tumor Regression at Completion of Radiation Therapy. Radiology, 84, 1100, 1965.
43) Segi: Statistics of Malignant Lymphoma. The Saisin Igaku, 19, 1788, 1964.
44) Hilton: Malignant Lymphoma, Classification, Prognosis and Treatment. Lancet, 2, 283, 1962.
45) Akazaki. et al.: Akusei Linpasyusyo No Kenkyu. Annual Report of The Co-Operative Research, Ministry of Education. 259, 1957. 301, 1958. 161, 1959.
46) Aisenberg: Hodgkins Disease-Prognosis, Treatment, Etiology and Immunologic Considerations. New Engl. J. Med, 270, 508, 565, 617, 1964.
47) Lukes: The American Concept of Malignant Lymphoma. The Saisin Igaku, 19, 1931, 1964.
48) Akazaki: Monaikei No Gainen. Nippon Ketsuekigaku Zensho, 1, 630, 1963.
49) Akazaki: Monaikei Syuyo. Nippon Ketsuekigaku Zensho. 5, 386, 1962.
50) Miller: Patterns of Immunological Deficiency in Lymphomas and Leukemia. Ann. Int. Med, 57, 703, 1962.